

# Potential modification of the UKPDS risk engine and evaluation of macrovascular event rates in controlled clinical trials

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**Background:** The aim of this study was to evaluate a modified UKPDS risk engine in order to establish a risk prediction benchmark for the general diabetes population.

**Methods:** Data sources were summary demographic and risk factor data from the major type 2 diabetes mellitus outcomes studies, including ACCORD, ADVANCE, VADT, RECORD, PROactive, ADOPT, and BARI 2D. Patients in these studies spanned a wide spectrum of disease, from drug-naïve to insulin-dependent. Cardiovascular events/major adverse coronary events (CVE/MACE) were primary or safety end points. Overall observed rates for cardiovascular events/MACE were summarized, and the observed annualized event rates were calculated using linear approximation. Simulation studies were then conducted using original (cardiovascular history excluded) and modified (cardiovascular history included) United Kingdom Prospective Diabetes Study (UKPDS) models; the predicted event rates were then compared with the observed event rates for all studies. The consistency of the predicted rates derived from each model was then evaluated using descriptive statistics and linear regression.

**Results:** The original UKPDS model tended to overestimate event rates across studies. The ratio of predicted events versus observed MACE ranged from 0.9 to 2.0, with mean of  $1.5 \pm 0.4$  and a coefficient of variation of 26% ( $R^2 = 0.80$ ). However, cardiovascular risk predictions were more precise using a modified UKPDS model; the ratio of predicted versus observed MACE events ranged from 1.8 to 2.4, with a mean of  $2.1 \pm 0.25$  and a coefficient of variation of 13% ( $R^2 = 0.94$ ).

**Conclusion:** A modified UKPDS model which includes adjustments for prior cardiovascular history has the potential for use as a tool for benchmarking and may be useful for predicting cardiovascular rates in clinical studies. This modification could be further evaluated, recalibrated, and validated using patient-level information derived from prospective clinical studies to yield greater predictability.

**Keywords:** type 2 diabetes mellitus, macrovascular disease, outcomes, United Kingdom Prospective Diabetes Study, modeling

## Introduction

Type 2 diabetes mellitus (T2DM) confers a 2–4-fold increased risk of macrovascular disease relative to nondiabetic individuals.<sup>1,2</sup> Accordingly, the goals of lifestyle modification, and therapeutic intervention when required, are to improve those risk factors known to be important in improving macrovascular outcomes. Several recently published outcomes studies have evaluated macrovascular events for various treatment options.<sup>3–12</sup> Further, various regulatory agencies, including the United States Food and Drug Administration, have generated guidelines for the development of novel medications in the treatment of T2DM to ensure that these agents, in addition to improving

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indices of glycemic control, provide adequate evidence for cardiovascular safety.<sup>13</sup>

Predictive measures of macrovascular risk for use in prospectively designed studies have been generated based on cardiovascular risk models developed from epidemiologic studies, such as the Framingham Heart,<sup>14</sup> Hoorn,<sup>15</sup> DECODE (Diabetes Epidemiology: Collaborative analysis of Diagnostic criteria in Europe),<sup>16</sup> and Fremantle Diabetes<sup>17</sup> studies, as well as from prospectively designed outcomes studies. The United Kingdom Prospective Diabetes Study (UKPDS) was the first to examine cardiovascular risk in subjects with T2DM. The UKPDS risk engine has been considered a useful tool for assessing cardiovascular risk and identifying high-risk individuals among newly diagnosed patients having no previous history of cardiovascular disease.<sup>18,19</sup> However, the generalizability of the UKPDS model for use in the broader population of subjects with T2DM may be limited, because utilization of the UKPDS risk engine, when applied to other individual outcomes studies, tended to overestimate the macrovascular event rate.<sup>15</sup> Furthermore, overestimation of rates tended to vary between outcomes studies, rendering prospective risk prediction modeling a challenge.<sup>20</sup>

While the inconsistency of prediction of the UKPDS model has been observed within individual studies, the pattern of prediction across different studies including a broader spectrum of patient populations has not been evaluated. Accordingly, the purpose of the present study was to explore the hypothesis that the UKPDS risk engine, when applied across a broad population of subjects with T2DM derived from several major outcomes studies, would generate a more consistent prediction of event rates. A model modification strategy for improving the predictability of the UKPDS risk engine to allow for differences in duration of diabetes and risk factors for cardiovascular disease was also evaluated. The results provided herein suggest that event rate prediction based on the modified UKPDS model could be used as a benchmark for more accurate prediction of event rates in prospectively designed clinical trials.

## Materials and methods

### UKPDS and selected outcome studies: harmonization of event definitions

The UKPDS risk engine included two risk equations for coronary heart disease<sup>19</sup> and stroke<sup>18</sup> (Appendix 2A). Coronary heart disease was defined as the occurrence of fatal or nonfatal myocardial infarction (MI) or sudden death, verified by two independent clinical assessors. The definition of stroke included fatal and nonfatal stroke.

Several recently completed and published large outcome studies were included in this analysis, namely ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation),<sup>10,21</sup> VADT (Veterans Affairs Diabetes Trial),<sup>4,9</sup> ACCORD (Action to Control Cardiovascular Risk in Diabetes),<sup>3,6</sup> RECORD (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes),<sup>8</sup> PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events),<sup>22,23</sup> and BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes).<sup>5,11</sup> In each of these studies, specific cardiovascular outcomes were combined into a common descriptor as major adverse cardiac events (MACE), either as the primary safety end point or key safety end point. MACE generally included nonfatal MI, stroke, and cardiovascular death (including acute MI, heart failure, stroke, pulmonary embolism, and cardiovascular procedure-related); the definition of MACE is essentially equivalent to the UKPDS definition of coronary heart disease (which includes nonfatal MI, and death from MI, heart failure, and others) and stroke (Appendix 1). For modeling purposes in this study, only the first event was considered in patients experiencing multiple events. Hence, the event rate predictions for the composite end point (MACE) were approximated as the sum of event rates for the UKPDS coronary heart disease and stroke models.

### UKPDS risk factors: models of coronary heart disease and stroke

The baseline risk factor estimates for the coronary heart disease and stroke models, along with their corresponding risk equations, are provided in Appendices 2–4.

### Model evaluation using data from outcome studies

To apply the UKPDS model to each of the outcome studies, the following analytical procedures were performed: the population means (standard deviation) of the demographics and risk factor data were summarized and subsequently used for model evaluation using simulation (patient-level data were not used as source data for this analysis); the overall observed rates for cardiovascular events/MACE were summarized, and the observed annualized event rates were calculated using linear approximation (given the observation that the overall event rate was low); and simulation studies were conducted using both the original and modified UKPDS models (see below). Predicted event rates were compared with observed event rates for each of the outcome studies.

## Model assumptions

In the original UKPDS model, risk factors including glycosylated hemoglobin (HbA<sub>1c</sub>), systolic blood pressure (BP), total cholesterol, high-density lipoprotein, and age in years at diagnosis of diabetes were measured within 1–2 years of patient diagnosis; these risk factors may have changed over the course of the study as a consequence of disease progression or treatment intervention. In contrast, the T2DM subjects included in the selected outcome studies were 7 to more than 11 years post-diagnosis, with risk factors measured at study initiation as a baseline measure. Accordingly, for the purpose of model development, it was assumed that the values for HbA<sub>1c</sub>, systolic BP, total cholesterol, and high-density lipoprotein did not change from the time of diagnosis for the study duration, and were used as model inputs. Age at diagnosis was obtained by subtracting the duration of disease from the current age. Event rate for the duration of studies (3 to about 5 years, depending on the study) was obtained by risk equations using the following model inputs: R (t = 3 to approximately 5, T = duration of disease, risk factors, including HbA<sub>1c</sub>, systolic BP, total cholesterol, high-density lipoprotein at baseline, age in years at diagnosis of diabetes minus duration of disease).

## Model modification: inclusion of cardiovascular history

The UKPDS risk engine was based on newly diagnosed, drug-naïve patients without a previous history of cardiovascular disease; however, history of disease is considered one of the most important predictive factors for cardiovascular outcomes in subjects with T2DM. To address the potential impact of previous cardiovascular history on the estimation and/or prediction of cardiovascular event rate using the original UKPDS model, several outcome studies of patients

with previous cardiovascular history were included in model development and analysis. The relative risk for patients with previous cardiovascular history versus those without cardiovascular history was calculated by meta-analysis, which weighted relative risk of the individual study by total patient-years (Appendix 5). The relative risk ranged from 1.5 to 2.2, with an overall estimated relative risk of 2.0 for these studies (Table 1). In addition, a recently published combined analysis, which included ACCORD, ADVANCE, UKPDS, and VADT data, summarized the pooled number of MACE events for subjects with and without a cardiovascular history. The relative risk of MACE for subjects with a cardiovascular history for this combined study was calculated as 2.1,<sup>24</sup> which is very close to the estimated value from meta-analysis. Accordingly, the value of 2.0 was incorporated into the modified UKPDS model to adjust for prior cardiovascular history (Appendix 2B).

## Results

### Subject demographics

Summary data from the ACCORD, ADVANCE, VADT, RECORD, PROactive, ADOPT (A Diabetes Outcome Progression Trial), and BARI 2D studies were used for model development (Table 2). Collectively, the total population used for this analysis included 39,585 subjects, primarily from North America, Europe, and Asia. The patient population ranged from 52% (RECORD) to 97% male (VADT), and mean age ranged from 57 years (ADOPT) to 62.4 years (BARI 2D). The average body mass index across the studies ranged from 28 to 32.2 (considered obese). Importantly, in this analysis the composite study population showed a wide variation in duration of diabetes (<3 years [ADOPT] to 11.5 years [VADT]), baseline HbA<sub>1c</sub> levels (7.4% [ADOPT] to 9.4% [VADT]), and history of cardiovascular disease

**Table 1** Relative risk of cardiovascular events for patients with versus without cardiovascular history: meta-analysis

Study	Subjects (n)	With CV history (MACE events/subjects [n])	Without CV history (MACE events/subjects [n])	Calculated RR of CV history
<b>Individual study results</b>				
ACCORD <sup>3</sup>	10,251	393/3608	330/6643	2.2
ADVANCE <sup>21</sup>	11,140	742/3590	1057/7550	1.5
RECORD <sup>8</sup>	4447	193/772	451/3675	2.0
Finnish study <sup>1</sup>	1059	109/169	271/890	2.1
Overall relative risk via meta-analysis				2.0
<b>Combined analysis<sup>24</sup></b>				
ACCORD/ADVANCE/UKPDS/VADT	27,049	1099/7921	1271/19,128	2.1

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation; CV, cardiovascular; MACE, major acute coronary events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial; RR, relative risk.

**Table 2** Baseline characteristics for the UKPDS and outcome studies

	UKPDS	ACCORD	ADVANCE	VADT	RECORD	PROactive	ADOPT	BARI 2D
Population	UK	North America	Europe/Asia	United States	Europe/Australia	Europe	North America/Europe	America/Europe
Participants (n)	5102	10,251	11,140	1791	4437	5238	4360	2368
Male	59%	62%	58%	97%	52%	66.1%	57.7%	70.4%
Age group (years)	25–65	40–79	>55	>40	40–75	35–75	30–75	>25
Mean age (years)	52	62.2	66	60.5	58.5	61.8	57	62.4
Ethnicity	83% Caucasian	27% Hispanic, African-American	37% Asian	38% Hispanic, African-American, Native American	99% white	98.5% white	88.5% white	70.4% white
Weight (kg)		93.5	78	97.2	89	88.0	NA	NA
BMI	27.7	32.2	28	31	31.4	30.9	32.2	31.7
Duration of T2DM (years)	<1	10	8	11.5	7	9.5	<3	10.4
Baseline HbA <sub>1c</sub>	6.7	8.3	7.5	9.4	7.9	8.1	7.4	7.7
Smoker	31%	14%	15%	17%	16%	13.8%	14.6%	12.5%
Prior CVD	0%	35%	32%	40%	21%	100%	0%	100%
Systolic BP (mmHg)	135	136.4	145	132	138.5	143.4	133	131.7
TC (mmol/L)	5.4	4.7	5.2	4.7	4.9	4.6	5.2	4.4
HDL (mmol/L)	1.11	1.1	1.3	0.92	1.2	1.16	1.2	0.98
TG (mmol/L)	NA	1.74	NA	2.39	2.3	2.24	1.9	1.67
Statin use	NA	59.3%	28%	NA	NA	40.8%	NA	74.9%
Key inclusion criteria	Age 25–65, no recent history of MI, angina, or heart failure	Age 40–79 with CV disease or 55–79 with 2+ CV risk factors	Age > 55 with history of major macro/microvascular disease or 2+ risk factors	Age ≥ 41 with no CV events within 6 months	Age 40–75 with no major CV events in last 3 months	Age 35–75 with history of CV disease	Age 30–75 without unstable or severe angina, CHF, or uncontrolled hypertension	Age > 25 with diagnosis of CHD
Protocol-specified CV end points	Fatal or nonfatal MI or sudden death, stroke	CV death, nonfatal MI/stroke	CV death, nonfatal MI/stroke, macrovascular event	CV death, nonfatal MI/stroke, CHF, macrovascular event	CV death, nonfatal MI/stroke, CHF, macrovascular event	Composite of all-cause mortality, nonfatal MI/stroke, others	MI/stroke, CV death, confirmed heart failure, new angina, and revascularization procedures	Composite of death, MI/stroke

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADOPT, A Diabetes Outcome Progression Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; HbA<sub>1c</sub>, glycated hemoglobin; CV, cardiovascular disease; HDL, high-density lipoprotein; MI, myocardial infarction; NA, not available; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

(0% for ADOPT and 100% for PROactive and BARI 2D). Inclusion of the studies enabled approximation of cardiovascular risk across a wide range of observed cardiovascular rates by regression. By comparison, there are important differences in the baseline characteristics of the aforementioned studies from that of the UKPDS cohort. In addition to having a negative history of cardiovascular disease, the UKPDS cohort were of lower mean age, lower body mass index, lower HbA<sub>1c</sub>, shorter duration of type 2 diabetes, with a higher percentage of smokers.

## Risk assessment using the original UKPDS model

When using the original UKPDS model to predict annualized MACE event rates from the aforementioned outcomes studies, there is an apparent overestimation of risk across studies; with the exception of PROactive, the ratio of predicted versus observed event rates was higher than 1.2 (Table 3A and Figure 1). Importantly, the magnitude of the overestimate was not consistent across studies: the ratio of predicted versus observed event rates ranged from 0.9 to 2.0, with a mean of  $1.5 \pm 0.4$  and a coefficient of variation of 26% ( $R^2 = 0.80$ ).

Two studies deserve specific mention. In PROactive, the estimated event rate with the original UKPDS model was lower than the observed event rate. In BARI 2D, in which all subjects had a previous cardiovascular history, the magnitude of the difference between observed and predicted event rates was much smaller compared with the other studies, even though the predicted event rate was somewhat larger than the observed event rate.

## Risk assessment using a modified UKPDS model

The UKPDS risk equations provide estimates for probability of coronary heart disease complications and stroke and the

relative risk associated with potential risk factors. However, the risk equations may not be directly applicable to data from patients with a long history of diabetes and a previous cardiovascular history because they were derived from drug-naïve patients without a cardiovascular history. The results from this modified UKPDS model analysis demonstrate that when the risk equations were adjusted for prior cardiovascular history, the predictions for MACE were more consistent between studies (Table 3B) and closer to the mean regression line (Figure 2). The ratio of predicted versus observed event rates ranged from 1.8 to 2.4, with a mean of  $2.1 \pm 0.25$  and a coefficient of variation of 13% ( $R^2 = 0.94$ ).

## Discussion

The generalizability of the original UKPDS risk engine for use in the broader population of subjects with T2DM is limited, since utilization of the UKPDS risk engine, when applied to other individual outcomes studies, tended to generate inconsistent and more often overestimate the macrovascular cardiovascular event rate. The analysis in this paper provides a quantitative summary of the extent of overestimation and inconsistency of the original UKPDS risk engine using summary risk factor data from the ACCORD, ADVANCE, VADT, RECORD, PROactive, ADOPT, and BARI 2D studies to the UKPDS risk engine results in an inconsistent overestimation of MACE rates by a factor of 1.5 (range 0.9–2.0), with a high degree of variability (coefficient of variation, 26%).

However, with the proposed inclusion of cardiovascular history in the UKPDS risk engine (using an adjustment factor of 2.0 derived from risk estimates from the individual studies and from a recently reported meta-analysis), this modified UKPDS model provides a more consistent (although still overestimated) event rate, with a lower degree of variability (coefficient of variation, 13%). Therefore, by including

**Table 3A** Comparison of predicted/observed annualized MACE outcomes using original UKPDS model

	ACCORD	ADVANCE	VADT	RECORD	PROactive	ADOPT	BARI 2D
Observed MACE	~2.2	~2.1	~4.2	~1.45	~3.6	~0.81	~4.69
Predicted CHD	2.6	2.7	4.3	1.7	2.4	1.2	3.6
Predicted stroke	1.1	1.1	1.3	0.5	0.9	0.4	1.8
UKPDS predicted MACE (stroke + CHD)	3.7	3.8	5.6	2.2	3.3	1.6	5.4
Ratio of predicted versus observed event rates	1.7	1.8	1.3	1.5	0.9	2.0	1.2

**Notes:** MACE includes cardiovascular death, nonfatal MI, nonfatal stroke; study data were simulated based on mean and standard deviation from published reports.

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADOPT, A Diabetes Outcome Progression Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; MACE, major acute coronary events; CHD, coronary heart disease.

**Table 3B** Comparison of predicted/observed MACE outcomes using modified UKPDS model

	ACCORD	ADVANCE	VADT	RECORD	PROactive	ADOPT	BARI 2D
Observed MACE	~2.2	~2.1	~4.2	~1.45	~3.6	~0.81	~4.69
MACE predicted by original UKPDS	3.7	3.8	5.6	2.2	3.3	1.6	5.4
CV history-adjusted MACE prediction with revised UKPDS model	5.0	5.0	7.8	2.5	6.6	1.6	10.8
Ratio of predicted versus observed event rates	2.3	2.4	1.9	1.8	1.8	2.0	2.4

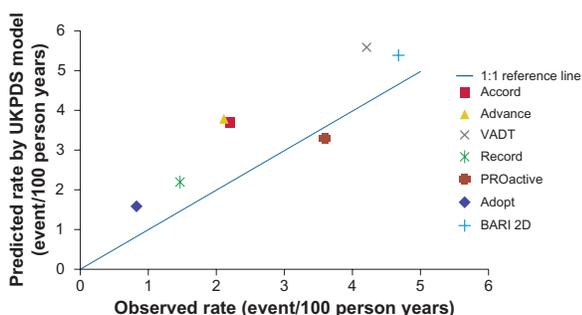
**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADOPT, A Diabetes Outcome Progression Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; UKPDS, United Kingdom Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; MACE, major acute coronary events; CV, cardiovascular.

cardiovascular history in the UKPDS risk engine, variability is reduced by 50%, thereby enhancing the general precision of assessment of the event rate.

The consistency of the proposed modifications of the UKPDS risk engine has the potential for use in benchmarking to calculate the risk of MACE in subjects enrolled in current clinical studies. This analysis should be considered exploratory, and further validation of these findings will be achieved through prospective analyses of ongoing clinical studies. The predicted event rate should be interpreted within the context of the relative relationship between predicted and observed event rates across all studies, using the regression line accordingly. For example, using the regression line, if the modified UKPDS model-predicted MACE event rate is 3%, then the likely observed event rate would be approximately 1.4.

There are several limitations to this study. First, the UKPDS model inputs of years 1 and 2 for HbA<sub>1c</sub>, systolic BP, total cholesterol, high-density lipoprotein, and age in years at diagnosis of diabetes are not available. For comparison purposes,

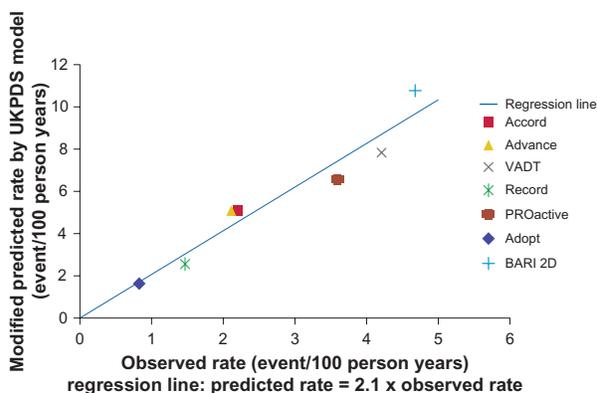
event rates were estimated based on the assumption that all subjects had similar HbA<sub>1c</sub>, systolic BP, total cholesterol, and high-density lipoprotein levels at the time of their initial diagnosis, adjusting age for the duration of T2DM. This may have affected prediction of the event rate. Second, modification of the UKPDS model to include a cardiovascular risk estimate of 2 for subjects with previous cardiovascular history, while based on published information on cardiovascular risk, requires validation (ie, patient-level data from specific studies). Third, systematic analysis needs to be performed to understand the physiologic basis for the overestimation of risk observed in this (and other) studies. Fourth, in this analysis, the comparison of MACE events was examined only with regard to baseline characteristics. In fact, in recent analyses conducted by Lu et al and others, UKPDS modeling was not appropriate for predicting specific short-term risk of coronary heart disease events



**Figure 1** Predicted and observed annualized MACE event rates in outcome studies using the original UKPDS model.

**Notes:** The duration of the outcome studies varied from 3 to 6 years. The predicted event rate was based on the length of the corresponding outcome study.

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADOPT, A Diabetes Outcome Progression Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; VADT, Veterans Affairs Diabetes Trial; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; MACE, major acute coronary events; UKPDS, United Kingdom Prospective Diabetes Study.



**Figure 2** Predicted versus observed MACE rates with a regression line using the modified UKPDS model.

**Notes:** A regression line was fitted with predicted rates as the dependent variable and observed rates as the independent variable. The estimated ratio of predicted rate versus observed rate is 2.1 (95% confidence interval 1.8–2.3).

**Abbreviations:** ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADOPT, A Diabetes Outcome Progression Trial; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified-Release Controlled Evaluation; BARI 2D, Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; VADT, Veterans Affairs Diabetes Trial; PROactive, Prospective Pioglitazone Clinical Trial in Macrovascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; MACE, major acute coronary events; UKPDS, United Kingdom Prospective Diabetes Study.

in patients with long-standing type 2 diabetes or metabolic syndrome, partly because of changes in medications used by patients with diabetes and other clinical care since the UKPDS studies were conducted.<sup>25,26</sup>

Further evaluation of dynamic prediction is needed based on individual patient data, and this is an area for future exploration. Therefore, its use should be considered for examination of population risks, and should not be considered as a tool for prediction of risk in individual patients.

Taken together, the results of this analysis assume significance because the sample population included over 39,000 subjects across the wide spectrum of duration of T2DM, age, and cardiovascular history. In this context, this overall population is more representative of the population likely to be seen in clinical practice. Thus, risk predictions based on this study population have relevance when establishing baseline MACE risk in populations to be evaluated in prospectively designed clinical studies. Accordingly, minimization of variation becomes essential to establish risk prediction in order to design and power clinical studies to meet the new United States Food and Drug Administration guidance protocols for determination of cardiovascular safety.

The observations presented in this study are consistent with those reported by Kengne et al, who found that the UKPDS model overestimated cardiovascular risk in the ADVANCE study by a similar magnitude. These investigators suggest that differences in baseline profiles, similarities in patient population characteristics, and use of concomitant medications that may modify the natural course of cardiovascular disease may provide in part an explanation for the overestimation of cardiovascular risk using the UKPDS risk engine.<sup>20</sup> Similar findings were reported by Song and Brown in a population from Scarborough, UK<sup>27</sup> and by Simmons et al in the EPIC-Norfolk cohort.<sup>28</sup> Finally, in restricted populations, the UKPDS and Framingham risk engines may not be highly predictive.<sup>7,29</sup> Collectively, these data suggest that the UKPDS risk engine may have general applicability, but should probably be used with caution when key demographic, ethnic, or cardiovascular risk factors in the population to be studied differ significantly from those of the UKPDS cohort. In addition, contributors to sources of environmental bias may be mitigated when analyzing large-scale, globally conducted clinical studies.

## Conclusion

As patients with an increased background of cardiovascular risk become more common in clinical trials, it is essential to assess the prediction of future cardiovascular events to ensure

that studies are adequately powered and yield enough events to determine the cardiovascular safety of new diabetes agents. Notwithstanding the limitations of the current study, the proposed modifications to the UKPDS risk engine may provide a more useful (albeit overestimated) measure of cardiovascular risk that can be used as a benchmark for more precise prediction of event rates in prospectively designed clinical trials. Furthermore, these can be subsequently recalibrated and validated using patient-level information derived from the clinical studies to yield greater predictability.

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FY conceived the study, participated in its design, interpreted the data, and helped to draft the manuscript. JY was responsible for performing the data acquisition and modeling, and contributed the methods section of the manuscript. KP served as scientific consultant to provide scientific input and was responsible for early drafts of the manuscript and for coordination of the drafting of the overall manuscript. MS contributed to the conception of the study, and providing medical input into the analyses. All authors contributed to the development and approval of the manuscript, and assume responsibility for the direction and content.

## Disclosure

FY, JY, and MS are employees of GlaxoSmithKline. Each of the authors own stock in GlaxoSmithKline. KP was an employee of GlaxoSmithKline within Medical Communications Quality and Practices, under the Chief Medical Officer, at the time of development of this manuscript. Editorial support was provided by Michelle Evans, LeeAnn Pastorello, and Brett Scott at MediTech Media, Hamilton, NJ, with funding by GlaxoSmithKline. Editorial assistance was also provided by Douglas L Wicks of GlaxoSmithKline. This study was presented at the 70th Scientific Meeting of the American Diabetes Association, Orlando, FL, June 25–29, 2010, and the 46th Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, September 20–24, 2010.

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# Appendices

## Appendix 1 Comparison of cardiovascular safety event definitions

	UKPDS definition	MACE
Nonfatal MI	CHD	X
Stroke	Stroke	X
<b>Cardiovascular death</b>		
Stroke	Stroke	X
MI	CHD	X
Heart failure	CHD*	X
Others	CHD*	X

**Notes:** X, event included in MACE definition; \*sudden death is generally cardiovascular-related.

**Abbreviations:** CHD, coronary heart disease; MACE, major adverse cardiac events; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study.

## Appendix 2 UKPDS equations used in this study

### A. Original UKPDS equations<sup>18,19</sup>

For a patient who has had no CHD/stroke in the first T years of diagnosed diabetes, the probability of a CHD/stroke event in the next t years is

$$R(t) = 1 - \exp(-qd^T(1 - d^t)/(1 - d))$$

For CHD risk model:

$$q = q_0 \beta_1^{AGE-55} \beta_2^{SEX} \beta_3^{AC} \beta_4^{SMOK} \beta_5^{H-6.72} \beta_6^{(SBP-135.7)/10} \beta_7^{LN(LR)-1.59}$$

For stroke risk model:

$$q = q_0 \beta_1^{AGE-55} \beta_2^{SEX} \beta_3^{AF} \beta_4^{SMOK} \beta_6^{(SBP-135.7)/10} \beta_7^{(LR)-5.11}$$

### B. Modified UKPDS equation

$$R(t) = 2^{precv} * (1 - \exp(-qd^T(1 - d^t)/(1 - d)))$$

Where precv = 1 if subject has previous CV history; otherwise, precv = 0

**Abbreviations:** CHD, coronary heart disease; CV, cardiovascular disease; UKPDS, United Kingdom Prospective Diabetes Study.

## Appendix 3 Risk factors in the UKPDS coronary heart disease and stroke models<sup>18,19</sup>

Abbreviation	Definitions/values (for both CHD model and stroke model)
AGE	Age in years at diagnosis of diabetes
SEX	1 for female; 0 for male
SMOK	1 for current smoker; 0 otherwise
SBP	Systolic blood pressure (mmHg), mean value for years 1 and 2
LR	TC/HDL (ratio, mean of values for years 1 and 2)
<b>Risk factor for CHD model only</b>	
AC	1 for Afro-Caribbean; 0 for Caucasian or Asian Indian
H	HbA <sub>1c</sub> mean values for years 1 and 2
<b>Risk factor for stroke model only</b>	
AF	Atrial fibrillation, detected by ECG at diagnosis of diabetes (1 for yes, 0 for no)

**Abbreviations:** CHD, coronary heart disease; UKPDS, United Kingdom Prospective Diabetes Study; TC, total cholesterol; HDL, high-density lipoprotein; HbA<sub>1c</sub>, glycated hemoglobin; ECG, electrocardiogram.

## Appendix 4 Parameter estimates for coronary heart disease model<sup>19</sup>

Parameter	Interpretation	Estimate
q <sub>0</sub>	Intercept	0.0112
β <sub>1</sub>	Risk ratio for 1 year of age at diagnosis of diabetes	1.059
β <sub>2</sub>	Risk ratio for female gender	0.525
β <sub>3</sub>	Risk ratio for Afro-Caribbean	0.390
β <sub>4</sub>	Risk ratio for smoking	1.350
β <sub>5</sub>	Risk ratio for 1% increase in HbA <sub>1c</sub>	1.183
β <sub>6</sub>	Risk ratio for 10 mmHg increase in systolic BP	1.088
β <sub>7</sub>	Risk ratio for unit increase in logarithm of lipid ratio	3.845
d	Risk ratio for each year increase in duration of diagnosed diabetes	1.078

**Abbreviations:** CHD, coronary heart disease; BP, blood pressure; HbA<sub>1c</sub>, glycated hemoglobin.

## Appendix 5 Parameter estimates for stroke model<sup>18</sup>

Parameter	Interpretation	Estimate
q <sub>0</sub>	Intercept	0.00186
β <sub>1</sub>	Risk ratio for 1 year of age at diagnosis of diabetes	1.092
β <sub>2</sub>	Risk ratio for female gender	0.7
β <sub>3</sub>	Risk ratio for atrial fibrillation	8.554
β <sub>4</sub>	Risk ratio for smoking	1.547
β <sub>6</sub>	Risk ratio for 10 mmHg increase in systolic BP	1.122
β <sub>7</sub>	Risk ratio for unit increase in lipid ratio	1.138
d	Risk ratio for each year increase in duration of diagnosed diabetes	1.145

**Abbreviation:** BP, blood pressure.

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