Validating the UKDS 82 risk equations to contemporary outcomes studies in type 2 diabetes

Authors: David Grant [1], Volker Foos [2], and Phil McEwan [3]

1 IMS Health, London, United Kingdom; 2 IMS Health, Basel, Switzerland; 3 Centre for Health Economics, Swansea University, United Kingdom;

Introduction

IMS CORE Diabetes Model (CDM) is a widely published and previously validated decision support tool (1,2). The default model uses the UKPDS 68 risk equations (REs) (3) to predict cardiovascular events and recent studies have demonstrated the model's validity to predict event rates consistent with those reported in contemporary type 2 diabetes mellitus (T2DM) outcomes studies (4).

The UKPDS group have recently published a new set of risk equations, the UKPDS 82 REs (5); these are based on longer follow-up data compared to the 68 REs (median follow-up of 17.6 years) and capture more outcomes (primary and secondary myocardial infarction stroke and amputations plus the addition of ulcer as an endpoint). These equations have now been coded into the CDM and are available to use alongside the CDMs existing risk equation base.

Objectives

The objective of this study was to compare the event rate predictions from the UKPDS 82 and 68 REs within the CDM when compared to the observed event rates from contemporary T2DM outcomes studies.

Methods

Simulation cohorts mirroring baseline characteristics of each of the trials included in this study were generated and intensive (INT) and conventional (CON) treatment arms were modeled for the relevant study specific follow-up.

A total of 82 validation simulations were performed to data from UKPDS 33(6); UKPDS 80 (7), the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) (8); the Veterans Affairs Diabetes Trial (VADT) (9); the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) 10; the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (11,12). Validation endpoints were aligned to those reported in each study and included: all-cause mortality (ACM); congestive heart failure (CHF); cardiovascular disease (CVD); myocardial infarction (MI); stroke, micro-vascular disease (MVD) and study defined primary endpoints (PE).

Table 1 details the validation studies, cohort size, average follow-up period and the observed number of events. Goodness of fit was assessed the coefficient of determination (R2) and mean absolute percentage error (MAPE).

Table 1) Observed events for each T2DM validation study together with predicted events obtained from the IMS CDM using either UKPDS 68 and UKPDS 82 risk equations

Study	Total N	Mean follow-up (years)	Outcome	Trial (INT)	Trial (CON)	CDM - UKPDS 68		CDM - UKPDS 82	
						INT	CON	INT	CON
UKPDS	3,867	10	MI	387	186	290	135	234	110
			STROKE	148	55	107	51	83	39
			CHF	80	36	85	40	48	21
			ESRD	16	9	6	6	4	3
			Cataracts	149	80	108	55	104	55
			ACM	489	213	367	167	284	124
UKPDS 80 (SU/INS)	3,867	16.8	MI	678	319	553	255	448	208
			Stroke	260	116	254	118	209	97
			ACM	1162	537	798	362	706	312
			MVD	429	222	414	286	320	239
UKPDS 80 (MET)	3,867	16.8	MI	81	126	74	98	60	81
			Stroke	34	42	35	46	29	39
			ACM	152	217	110	143	98	125
			MVD	66	78	58	115	45	97
ACCORD (BP)	10,251	4.7	PE	208	237	140	157	226	242
			MI (NF)	126	146	40	44	72	74
			Stroke (NF)	34	55	50	59	53	63
			CHF	83	90	70	76	71	68
			CV Death	60	58	50	54	100	104
ACCORD (GL)	10,251	4.7	PE	352	371	258	294	383	405
			MI (NF)	186	235	80	89	125	132
			Stroke (NF)	67	61	94	102	93	100
			CHF	152	124	112	122	110	110
			CV Death	135	94	85	103	165	173
ADVANCE	11,140	4.9	PE	620	654	686	700	787	804
			MI (NF)	153	156	198	202	254	260
			Stroke (NF)	214	209	251	251	227	233
			CV Death	253	289	237	247	306	311
			CHF	220	231	199	203	152	150
ASPEN PP	2,410	4	MI	28	34	27	36	29	34
			Stroke	27	29	23	22	20	22
			CV Death	24	19	19	23	19	21
ASPEN SP	2,410	4	MI	21	32	17	20	23	26
			Stroke	7	9	12	14	10	11
			CV Death	14	18	12	13	20	22
VADT	1,791	5.6	PE	235	264	191	225	210	233
			MI	64	78	42	49	50	58
			CHF	76	82	17	19	16	16
			Stroke	28	36	33	35	26	29
			Amputation	11	17	27	30	20	20
			CV Death	40	33	26	34	39	43

Notes: F=fatal; NF=non-fatal; BP=blood pressure lowering; GL=glucose lowering; PP=primary prevention; SP=secondary prevention; ACM=all cause mortality; MVD=microvascular disease; MI=myocardial infarction; CHF=congestive heart failure; ESRD=end stage renal disease; CV=cardiovascular

Figure 1) Observed versus predicted endpoints obtained using the UKPDS 68 and 82 risk equations

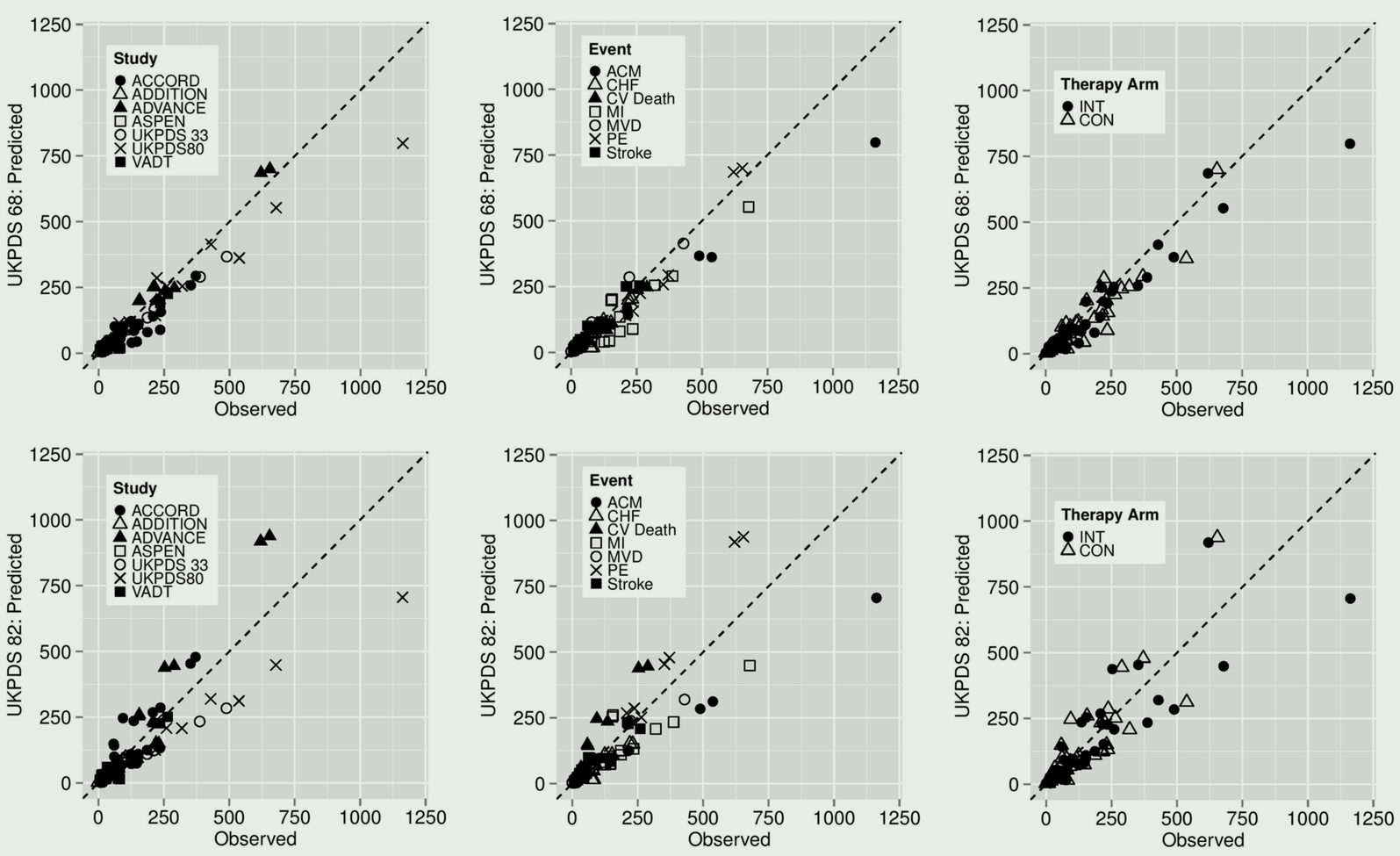

Table 2) Summary measures of goodness of fit of the CDM (UKPDS 68 and 82 equations) to validation studies and endpoints

	UKPDS 68		UKPDS 82	
	MAPE	R^2	MAPE	R^2
Variable				
Overall	28.2%	0.91	38.1%	0.82
INT	30.2%	0.93	39.4%	0.84
CON	26.3%	0.88	36.8%	0.82
Endpoint				
ACM	21.4%	0.99	28.5%	0.99
CHF	25.3%	0.87	38.6%	0.85
CV Death	17.0%	0.97	74.9%	0.95
CVD	38.3%	0.88	74.0%	0.84
MI	27.9%	0.89	28.8%	0.79
MVD	38.3%	0.95	35.8%	0.92
PE	19.0%	0.98	23.3%	0.99
Stroke	30.4%	0.94	31.7%	0.89
Study				
ACCORD	33.1%	0.73	52.90%	0.79
ADVANCE	15.6%	0.97	43.50%	0.92
ASPEN	26.3%	0.64	32.75%	0.73
UKPDS 33	25.5%	0.99	43.92%	0.99
UKPDS 80	19.0%	0.96	27.25%	0.97
VADT	45.0%	0.90	39.42%	0.91

MAPE=Mean Absolute Percentage Error; ACM=all cause mortality; CHF=congestive heart failure; CV=cardiovascular; CVD=cardiovascular disease; MI=myocardial infarction; MVD=microvascular disease; PE=primary endpoint; INT=intensive treatment arm; CON=conventional treatment arm.

Results

Across all validation studies the analysis of predicted events from the CDM contrasted with observed study events produced an R2 statistics of 0.91 and 0.82 for the UKPDS 68 and 82 risk equations respectively with corresponding MAPE of 28.2% (68 REs) and 38.1% (82 REs); see Table 1.

Across predicted endpoints both sets of equations produced a similar and consistent range of R2 statistics, with the exception of myocardial infarction (MIs): R2 of 0.79 (82 REs) versus 0.89 (68 REs). The UKPDS 82 equations exhibited a greater lack of fit to fatal and non-fatal cardiovascular disease compared to the UKPDS 68 equations.

Across validation studies, the UKPDS 82 predictions were generally associated with a less favourable goodness of fit compared to UKPDS 68 as indicated by the larger reported MAPE (Table 2); although R2 statistics were more consistent between the sets of risk equations.

Figure 1 illustrates the relationship between observed and predicted endpoints for the UKPDS 82 and 68 risk equation predictions in relation to validation study, endpoint and therapy arms.

Conclusions

The CDM model has been extensively validated using the UKPDS 68 risk equations and shown to have good predictive validity. Validation using the UKPDS 82 equations showed an improved fit to the UKPDS data with less accurate external validation results.

As diabetes modelling groups gain experience of working with these new equations their advantages and potential limitations will become better understood. Further validation research using these new equations, particularly from other diabetes modelling groups, is required.

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FOR FURTHER INFORMATION: Please contact Phil McEwan (phil.mcewan@heor.co.uk) or Volker Foos (vfoos@ch.imshealth.com)
IMS HEALTH | 210 PENTONVILLE ROAD, LONDON N1 9JY, UNITED KINGDOM