All cause mortality validation of the IMS CORE diabetes model against predictions of the Charlson Comorbidity Index

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Introduction

Previous validation studies of the IMS CORE Diabetes Model (CDM) (1-2) have confirmed the model as a credible tool for predicting both the absolute number of clinical events and future treatment consequences associated with the management of diabetes patients.

The CDM has recently undergone a single "all cause mortality" (ACM) validation exercise including internal validation and external validation against a number of contemporary outcome studies (3-6) which has shown a below average fit with a R^2-statistic of 0.651 (Figure 1 (A)). This compares to an overall R -statistic of 0.90 as obtained in the 2014 CDM revalidation exercise including 112 micro-vascular, macro-vascular and mortality validation endpoints (2). Lack of fit was associated with a considerable overestimation of ACM when the model was compared to contemporary outcome studies such as ACCORD, ADVANCE, VADT and ASPEN in which mortality incidence was notably low.

It is generally understood that these studies reported low mortality incidence, likely because patients were managed under controlled clinical trial (RCT) conditions. As the overall intention of diabetes simulation models is to predict the implications of new technologies in clinical practice, the above findings were compared to a number of ACM validation exercises that included data from external settings that are more eligible to represent practical, real-life conditions.

Objectives

The objective of this study was to compare CDM ACM validations that focused on (A) controlled clinical trial data versus (B) non-controlled, real-world observations.

Methods

The CDM is a lifetime simulation model designed to assess the health outcomes and economic consequences of interventions in T1DM or T2DM. A total of 37 validation endpoints were simulated across 3 datasets (Table 1).

Charlson Comorbidity Index (CCI)
The CCI (7) is a widely utilized index tool to measure the burden of disease and predict mortality in various disease subgroups including cancer, renal disease, liver disease and diabetes. Since its first publication in 1987 the index has been validated extensively to demonstrate its ability to predict mortality risk in real world practice. The CCI was applied to predict the 10 year mortality risk for diabetes patients with four age strata (50, 60, 70 and 80 years). For each age strata, risk scores were generated for five different baseline co-morbidity levels: no complications (NC), myocardial infarction (MI), MI and stroke (MI+S), MI+S and heart failure (MI+S+HF) and MI+S+HF and end stage renal disease (MI+S+HF+ESRD). For the resulting 20 cohort profiles CCI mortality scores were calculated and compared to corresponding 10 year ACM predictions from the CDM.

The UK General Practice Research Database (GPRD)
The CDM was validated to data from a retrospective cohort study (8) from the UK General Practice Research Database (GPRD). The study compared ACM across five glucose-lowering regimens: metformin monotherapy, sulfonylurea monotherapy, insulin monotherapy, metformin plus sulfonylurea combination therapy, and insulin plus metformin combination therapy. Baseline characteristics and treatment effects as published for the five glucose lowering regimens were reproduced in the CDM and projected over mean follow up of three years.

Life expectancy calculator based on administrative dataset from Western Australia (WA-LEC)
The external validity of the CDM was tested against a life expectancy online calculator (9) that utilizes diabetes specific mortality risk equations derived from 13,884 Western Australian hospital and mortality records (10).

Life expectancy after diabetes related myocardial infarction (a) and stroke (b) was predicted for male and female sex in three age strata (40-64 years; 65- 84 years; and 85+ years) and compared to respective predictions of the CDM.

The CDM was applied using two alternative sets of risk equations (RE):

Base Case: using UKPDS 82 risk equations (RE) to asses CV and mortality risk

SA: using UKPDS 68 RE to assess CV and mortality risk

Table 1) Study outcomes vs. CDM

CCI (10 year survival (%))	Age	CCI	CDM-UK82	CDM-UK68
No Complication	40	95.90%	97.20%	96.80%
	50	90.10%	92.80%	92.50%
	60	77.50%	82.30%	84.80%
	70	53.40%	62.40%	71.10%
	80	21.40%	34.40%	53.50%
MI	50	77.50%	72.10%	78.90%
	60	53.40%	60.10%	59.70%
	70	21.40%	46.00%	34.20%
	80	2.20%	27.70%	13.90%
MI and stroke	50	53.40%	67.70%	74.40%
	60	21.40%	50.70%	54.50%
	70	2.20%	31.50%	30.40%
	80	0.00%	13.50%	11.70%
Mi and stroke and CHF	50	21.40%	59.70%	75.10%
	60	2.20%	40.10%	54.90%
	70	0.00%	19.80%	30.90%
	80	0.00%	5.20%	12.00%
Mi and stroke and CHF and ESRD	50	2.20%	37.10%	45.40%
	60	0.00%	17.40%	16.70%
	70	0.00%	4.20%	2.60%
	80	0.00%	0.30%	0.10%

GPRD (event rate per 1000 person-years)		GPRD	CDM-UK82	CDM-UK68
GPRD SU		50.7	37.7	32.1
GPRD Insulin		46	24.8	20.2
GPRD MET + SU		17.6	23.9	18.8
GPRD Insulin + MET		15.7	15	15.1
GPRD MET		14.9	20.5	17.5

Administrative dataset from Western Australia (years survived)			WA-LEC	CDM-UK82	CDM-UK68
Post MI	Female	< 65 yrs	10.7	10.77	9.31
		65-84 yrs	3.8	4.37	2.919
		85+ yrs	1.3	1.64	1.124
	Male	< 65 yrs	9	10.22	8.349
		65-84 yrs	3.5	4.09	2.536
		85+ yrs	1.3	1.53	0.965
Post Stroke	Female	< 65 yrs	10.8	11.43	15.902
		65-84 yrs	4.3	4.83	7.057
		85+ yrs	1.7	2.08	3.292
	Male	< 65 yrs	9.7	10.47	13.678
		65-84 yrs	4.1	4.45	5.676
		85+ yrs	1.7	1.93	2.614

CCI=Charlson Comorbidity Index; MI=myocardial infarction; CHF=congestive heart failure; ESRD=end stage renal disease; GPRD=General Practice Research Database; MET=metformin; SU=sulfonylurea; INS=insulin; WA=Western Australia

Results

The outcomes of the individual validations are presented in Figure 2 (B-D). The coefficient of determination (R^2) goodness of fit measure was evaluated separately for the individual datasets. In the base case analysis, R^2 scores of 0.85, 0.81 and 0.99 were obtained when the CDM was compared to predictions from the CCI, GPRD and the WA life expectancy calculator. This compared to R^2 scores of 0.76, 0.82 and 0.84 in sensitivity analysis utilizing UKPDS 68 RE. The overall R including all real-life datasets (CCI, GPRD and WA) amounted to 0.92 in the base case analysis and 0.92 in sensitivity analysis.

Conclusions

In contrast to the validations against contemporary outcome studies where ACM was overestimated, the CDM exhibited a more balanced prediction with a trend towards ACM underestimation when compared to real-life datasets.

- In **CCI** validations, mortality was generally underestimated in projections UK82 and UK68 RE. This trend increased with age and rising co-morbidity level.
- **GPRD** validations demonstrated a more balanced picture with ACM being overestimated in two glucose lowering regimens (MET, MET+SU), underestimated in two regimens (SU, INS), and match for MET+INS.
- The CDM closely reflected the trends of the **WA-LEC** with UK82 RE. When UK68 RE were applied the CDM exhibited a slight overestimation of mortality in "post MI" validations and underestimation of mortality in "post stroke" validations.

It is important to acknowledge that expectations towards universally valid models that match arbitrarily selected external data sources are not realistic.

Model validations must be regarded in context and should include a broad range of data sources to enable assessments of the models predictive ability.

This validation exercise outlines the observed discrepancy when the CDM is compared data from RCTs or to data from non-controlled, real-world observations.

Including evidence from real-world settings is imperative to assess the external validity of disease simulation models.

References

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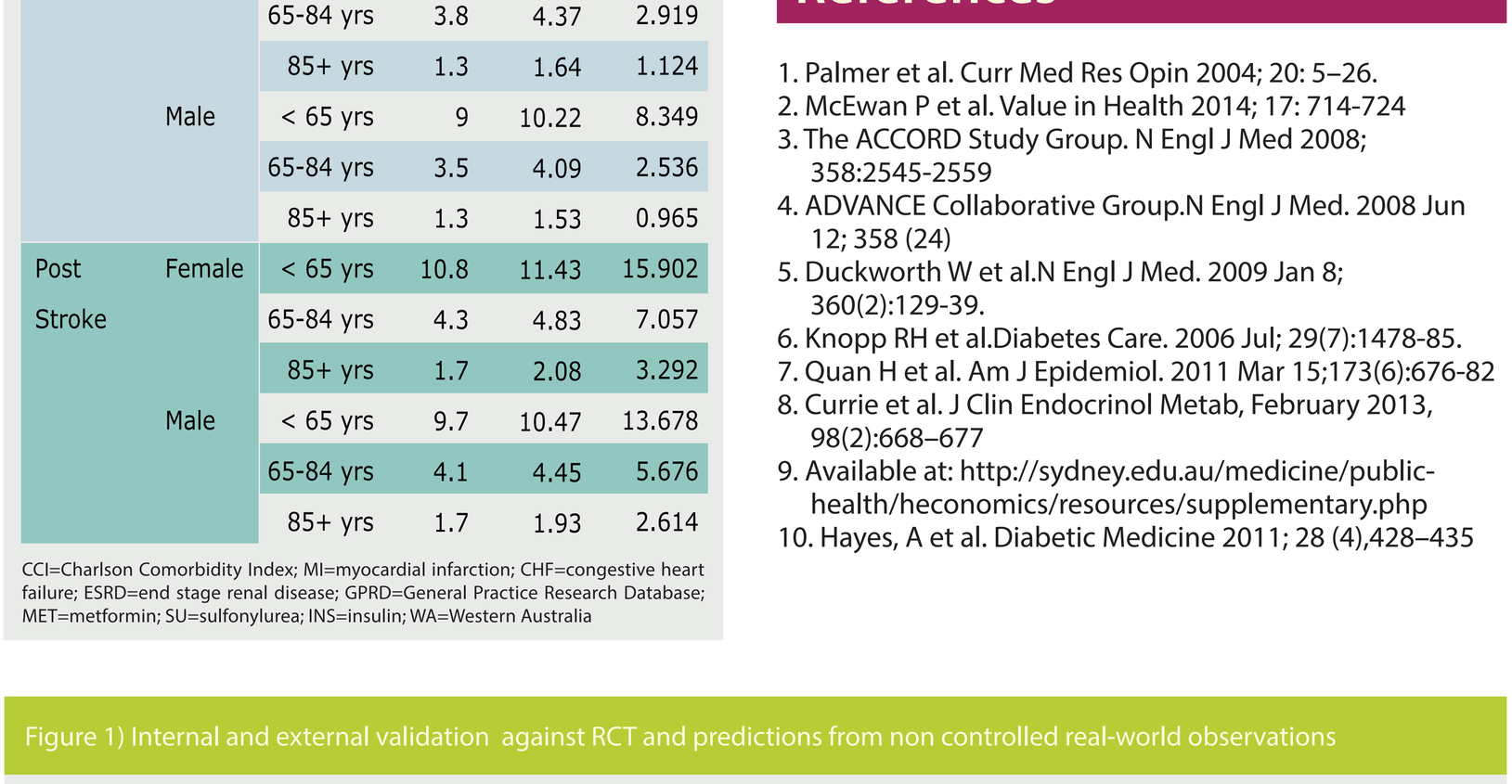
Figure 1) Internal and external validation against RCT and predictions from non controlled real-world observations



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