Assessing the Consistency of Absolute Cardiovascular Risk Prediction and Relative Risk Reduction in Type 2 Diabetes Mellitus.

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Objectives

- Accurate estimation of baseline cardiovascular (CV) risk and relative risk reduction (RRR) is crucial to ensure that economic evaluations of new health technologies for the treatment of type 2 diabetes (T2DM) are robust.
- Many economic models (such as the IMS CORE Diabetes Model [1]) use risk equations (RE) derived from UKPDS and concerns persist regarding their validity; particularly as new equations are published.
- The potential choice of risk equations is large; a recent review [2] identified twelve cardiovascular disease risk equations derived from cohorts with T2DM.
- The objective of this study was to compare the consistency of predicted CV risk using RE derived from various T2DM populations.

Methods

- All CV risk equations identified from a recent systematic review [2], derived from populations with T2DM, were coded and validated in Microsoft Excel. Equations from ADVANCE [3]; Australia, (Fremantle) [4]; New Zealand, Diabetes Cohort Study (DCS) [5]; Sweden, National Diabetes Registry (SNDR) [6]; Hong Kong, Diabetes Registry (HKDR) [7,8], Scotland, Diabetes Audit and Research in Tayside (DARTS) [9]; USA, Atherosclerosis Risk in Communities (ARIC) [10] and UK, United Kingdom Prospective Diabetes Study (UKPDS) [11,12,13] were included.
- To aid comparative analysis, UKPDS myocardial infarction (MI) and stroke risk were combined additively.
- Predicted 5-year CV risk was obtained using baseline cohort characteristics taken from ACCORD [14] (Table 1). Absolute and percentage risk reductions were obtained by applying a 10% reduction to HbA1c, total cholesterol (TC) and systolic blood pressure (SBP) both individually and in combination.
- Where risk equations required predictor variables not reported in Table 1, mean values from the risk equation population were imputed.

Results

- Mean 5-year predicted risk of CVD was 11.0% (SE 1.9%); minimum of 3.4% (ARIC) and maximum 20.7% (DARTS), Figure 1.
- A 10% reduction in HbA1c, TC and SBP resulted in a mean RRR of 6.4%(SE 0.7%), 6.8% (SE 1.5%)and 9.8% (SE 2.3%) respectively, Figure 2.
- The DCS equation predicted the lowest percentage reduction in risk for change in total cholesterol (1%);the HKDR stroke equation lowest for SBP (3.5%) and the UKPDS RE lowest for HbA1c change (4.1%).

Table 1: Baseline characteristics from ACCORD [14] utilised to obtain 5-year predicted risk

Risk factor	Mean (SD)	Low Risk	High Risk
Age (Years)	62.2 (6.8)	55.4	69
Sex (% female)	38.7	30.96	46.44
Duration of diabetes(Years)	10	8	12
Current smoker (%)	14.3	11.44	17.16
Previous smoker (%)	44.4	35.52	53.28
SBP (mm Hg)	136.2 (17.0)	119.2	153.2
DBP (mm Hg)	74.8 (10.6)	64.2	85.4
HbA1c (%)	8.3 (1.1)	7.2	9.4
Total cholesterol (mg/dl)	183.3 (42.1)	141.2	225.4
HDL cholesterol (mg/dl)	47.2 (13.0)	60.2	34.2
TC:HDL ratio	3.88	2.35	6.59
BMI (kg/m^2)	32.5 (5.5)	27	38

SD = Standard deviation; SBP=systolic blood pressure; DBP=diastolic blood pressure; TC=total cholesterol; BMI=Body Mass Index; Low and high risk derived from mean +/- 1 SD (or 10% if no SD reported)

- The largest percentage reduction in risk for HbA1c change was UKPDS 68 (9.1%) and the DARTS equation for TC and SBP (10.3% and 18.9%, respectively), Figure 2.
- Figure 3 shows absolute change in five year risk for each equation associated with a 10% reduction in HbA1c, lipids and SBP (individually and combined). The UKPDS 68 equations were associated with the largest absolute reduction in risk (1%) for a 10% change in HbA1c with the the DARTS equation providing the greatest change for TC and SBP (2.2% and 4.0%, respectively).

Conclusion

- The difference in absolute risk across these equations does not appear dependent on geographical location or study recruitment period.
- Generally, the UKPDS equations produced consistent absolute CV risk estimates close to group averages.
- Not all equations were capable of assessing the RRR associated with changes to SBP, cholesterol and HbA1c; furthermore, endpoints modelled across studies were not consistent. The results should, therefore, be interpreted with these caveats in mind.
- SBP modification results in greater variability in RRR than HbA1c and cholesterol.
- Where possible, economic evaluations in type 2 diabetes should conduct sensitivity analysis across multiple equations; particularly where changes in SBP are modelled.

References

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Table 2: Overview of the cardiovascular risk equations used in the study, geographic region, equation type and predictor variables included

Reference	Population	Events/Total N	Type of Model	Endpoint	Predictor Variables
[3] Kengne (2011); ADVANCE	20 countries	47//7168	Cox	F/NF MI; F/NF Stroke or CV death	Age at diagnosis, sex, duration of DM, pulse pressure, retinopathy, atrial fibrillation, HbA1c, Ln(urinary albumin/creatinine), non-HDL cholesterol, treated hypertension
[4] Davis (2010); Fremantle	Australia	185/1240	Logistic	F/NF MI; F/NF Stroke or CV death	Age, sex, prior CVD, Ln(urinary albumin/creatinine), Ln(HbA1c), Ln(serum HDL Cholesterol), southern European ethnicity, aboriginality
[5] Elley (2010); DCS	New Zealand	6479/36127	Cox	F/NF CVD	Age at diagnosis, diabetes duration, sex, systolic blood pressure, smoking status, total cholesterol to HDL ratio, ethnicity, HbA1c, urine albumin:creatinine ratio
[6] Cederholm (2008); SNDR	Sweden	1482/11646	Cox	F/NF MI; unstable angina; PCI; CABG; IHD; F/NF stroke	Onset age of diabetes, sex, duration of DM, BMI, Smoking, systolic blood pressure, HbA1c, antihypertensive therapies, lipid lowering agents
[7] Yang (2008); HKDR	China	351/7067	Cox	CHD	Age, sex, smoking status, duration of DM, Ln(estimated GFR), Ln(spot urine albumin:creatinine), non-HDL cholesterol
[8] Yang (2007); HKDR	China	332/7209	Cox	F/NF stroke	Age, HbA1c, spot urine albumin:creatinine ratio (ACR), history of CHD
[9] Donnan (2006); DARTS	Scotland	243/4569	Weibull	F/NF MI; CHD death	Age at diagnosis, duration of DM, HbA1c, smoking (current,past,never), sex, systolic blood pressure, treated hypertension, total cholesterol, height
[10] Folsom (2003); ARIC	USA	128/1273	Cox	CHD	Age, race, total cholesterol, HDL cholesterol, systolic blood pressure, use of anti-hypertensive medication, smoking status
[11] Stevens (2001) UKPDS risk engine [RE]	UK	NR/4540	Gompertz	F/NF MI; sudden death	Age, sex, ethnicity, duration of DM, smoking, HbA1c, systolic blood pressure,total cholesterol:HDL cholesterol ratio
[12] Kothari (2002) UKPDS risk engine [RE]	UK	188/4549	Gompertz	F/NF stroke	Age, sex, duration of diabetes, smoking, systolic blood pressure, total cholesterol to HDL ratio, presence of atrial fibrillation
[13] Clarke (2004); UKPDS 68	UK	652/3642	Weibull	F/NF MI; F/NF Stroke or CV death	Age at diagnosis of diabetes, age in years at first diabetes related event, duration of diabetes, sex, smoking,HbA1c, SBP, total cholesterol:HDL cholesterol ratio, presence of atrial fibrillation,IHD, CHF

F=fatal; NF=non-fatal; CV=cardiovascular; MI=myocardial infarction; PCI=percutaneous coronary implant; CABG; coronary artery bypass graft; CHD=corinary heart disease; Ln=natural logarithm; HDL=high density lipoprotein; GFR=glomerular filtration rate; IHD=ischaemic heart disease; CHF=congestive heart failure

Figure 1: Five year predicted risk (low and high intervals) by risk equation using baseline characteristics reported in Table 1

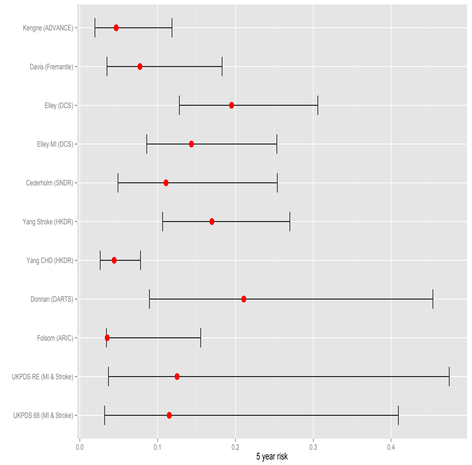


Figure 2: Percentage change in five year risk for each equation associated with a 10% reduction in HbA1c, lipids and SBP (individually and combined)

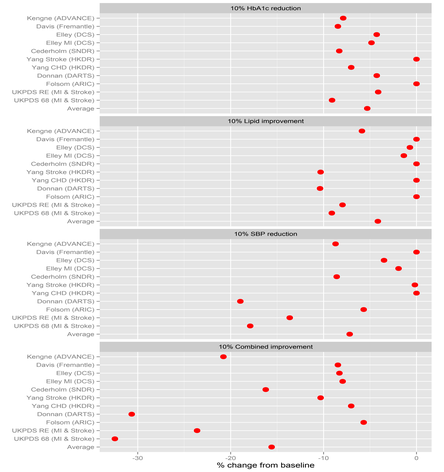
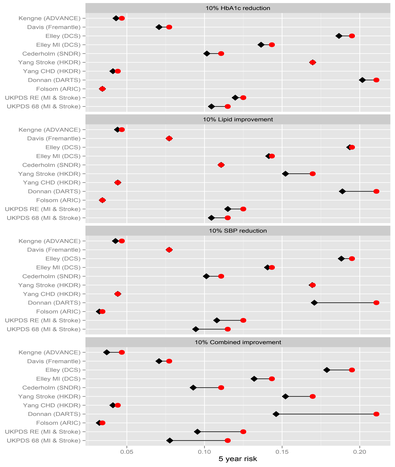


Figure 3: Absolute change in five year risk for each equation associated with a 10% reduction in HbA1c, lipids and SBP individually and combined (red circles show baseline risk, black triangles show risk after change)



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