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Short running title: CVD risk estimates in type 2 diabetes

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Accurate cardiovascular disease (CVD) risk estimates can inform choice of therapeutic strategies for individuals, provided that they have been validated appropriately [1]. Risk calculators are of particular relevance in diabetes given the 2-4 times higher CVD risk compared with non-diabetic people [2]. Framingham Study [3] risk equations for coronary heart disease (CHD) and CVD, based on age, gender, blood pressure, cholesterol (total and HDL) and smoking, with diabetic status as a categorical variable, have been validated prospectively in the general population [4, 5] but not in diabetic subjects [6]. Systematic Coronary Risk Evaluation (SCORE) project risk scores for fatal CHD and CVD [7] appear to overestimate risk in the general population [8] and have not been evaluated in diabetes. Following recognition of glycemia as a CVD risk factor [9], the DECODE study group developed a fatal CVD risk equation incorporating glucose tolerance status and fasting plasma glucose (FPG) [10]. We have evaluated these three risk equations in patients with type 2 diabetes (T2DM) using data from the United Kingdom Prospective Diabetes Study (UKPDS) [11].

Research Design and Methods

The UKPDS [11,12] recruited 5,102 of 7,616 people with newly-diagnosed type 2 diabetes in 23 UK centres and followed them for median 10.4 years (range 6 to 20). Exclusion criteria included severe vascular disease, myocardial infarction or stroke within the previous year, and major systemic illness. The study received ethical committee approval, conformed to the Declaration of Helsinki guidelines (1975 and 1983) and all patients gave informed consent. Analyses were restricted to 3898 patients with complete baseline risk factor data who were mean (SD) age 53 (9) years, systolic blood pressure 135 (19) mmHg, total cholesterol 5.4 (1.1) mmol/l, HDL cholesterol 1.07 (0.24) mmol/l, and HbA1c 7.2 (1.8) % with 59% male and 30% current smokers. Observed 10-year fatal CHD (fatal MI or sudden death) and fatal CVD (fatal MI, sudden death, fatal stroke or fatal peripheral vascular disease) event rates were derived from Kaplan Meier survival curves, and Framingham, SCORE and DECODE 10-year risk scores for fatal CVD and fatal CHD (except DECODE) calculated for each patient.

Estimated event rates were deemed acceptable if within the 95% confidence interval of the observed rates. Risk equations were evaluated also for different durations of diabetes by selecting patients for analysis at random times between 1 and 10 years after their diabetes had been diagnosed. This analysis excluded 779 patients because of a fatal CVD event or censoring prior to their chosen start time, or missing risk factor data. Risk equation sensitivity and specificity were examined by comparing

areas under the receiver operating characteristic (aROC) curve using actual survival times, where possible.

Results

The 10-year fatal CVD event rate (95%CI) observed in UKPDS was 7.4% (6.5–8.3). Framingham underestimated this by 32% with an Absolute Risk (AR) of 5.0% (Figure 1a). SCORE overestimated risk by 18% (AR 8.7%) whereas DECODE (AR 6.6%) yielded an acceptable estimate. For males, only SCORE provided a reasonable estimate. In females, only Framingham performed well. For Caucasians (n=3207), the 7.9% (6.7-9.0) observed event rate was underestimated by 34% using Framingham (AR 5.2%), overestimated by 19% using SCORE (AR 9.4%) and estimated appropriately by DECODE (AR 7.1%). The 5-year fatal CVD event rate (95%CI) observed in UKPDS for those selected with diabetes for median 5 (IQR 3 to 7) years was 4.5% (3.7-5.3). Framingham underestimated this by 56% (AR 2.0%) whereas both SCORE (AR 5.6%) and DECODE (AR 15.6%) yielded overestimates (Figure 1b). SCORE and DECODE estimated fatal CVD appropriately in males but not in females.

The 10-year fatal CHD event rate (95%CI) observed in UKPDS was 6.3% (5.5–7.1). Framingham underestimated this (AR 4.3%) while SCORE provided a reasonable estimate (AR 5.7%). Both equations provided reliable estimates for females but not males. For Caucasians, the observed rate of 7.2% (6.3–8.1) was underestimated by both Framingham (4.6%) and SCORE (6.2%). The 5-year fatal CHD event rate (95%CI) observed in UKPDS for those with a prior period of diabetes was 3.9% (3.1–4.6). Framingham underestimated this (AR 2.0%) while SCORE provided a reasonable estimate (AR 3.6%). Both models performed well in females but only SCORE provided a reasonable estimate in males.

The aROC analysis for fatal CVD revealed similar discriminative capacity for Framingham (c=0.76), and SCORE (c=0.77) while DECODE, which required times rounded to 5 or 10 years, did less well (c=0.67)

To determine the degree to which absence of glycaemia as a risk factor contributed to poor risk equation performance, we estimated CHD risk using the UKPDS Risk Engine [13, 14], a T2DM-specific model that has been validated in a diabetic cohort [15], with HbA1c values set to a non-diabetic value (5%). Under these artificial conditions, 10-year fatal CHD risks were underestimated to the same extent as the Framingham model (4.2%).

Conclusions

Framingham, SCORE and DECODE models do not provide reliable fatal CVD and CHD risk estimates in T2DM. The underestimate seen with Framingham is consistent with previous reports [15-17] and not surprising given that there were only 337 diabetic individuals in the Framingham cohort. Also, diabetes is incorporated as a categorical variable implying that diabetes increases risk similarly regardless of glycaemic control or diabetes duration. This limitation pertains also to SCORE which simply doubles risk estimates for diabetic men and quadruples them for diabetic women. DECODE, which included over 2000 subjects with diabetes, incorporated FPG in a categorical fashion and so does not adequately consider the effect of different levels of glycaemia.

The aROC analysis showed better discrimination for the Framingham equation than reported previously in diabetic cohorts [15]. The DECODE value may be lower than might be expected given the limitation of using 10-year or 5-year estimates only.

The similar underestimation of CVD risk seen with the Framingham equations when using the UKPDS Risk Engine with HbA1c levels set artificially to a non-diabetic value highlights the importance of glycaemia to CVD risk estimation in T2DM. This report emphasizes the need for validated diabetes-specific risk calculators that can estimate CVD risk reliably in people with T2DM.

Figure Legend

1a) Ten-year fatal cardiovascular disease (CVD) risks estimated using Framingham, SCORE and DECODE equations, relative to that observed (95% CI) in UKPDS patients with newly-diagnosed diabetes.

1b) Five-year fatal cardiovascular disease (CVD) risks estimated using Framingham, SCORE and DECODE equations, relative to that observed (95% CI) in UKPDS patients with diabetes diagnosed for between one and ten years.

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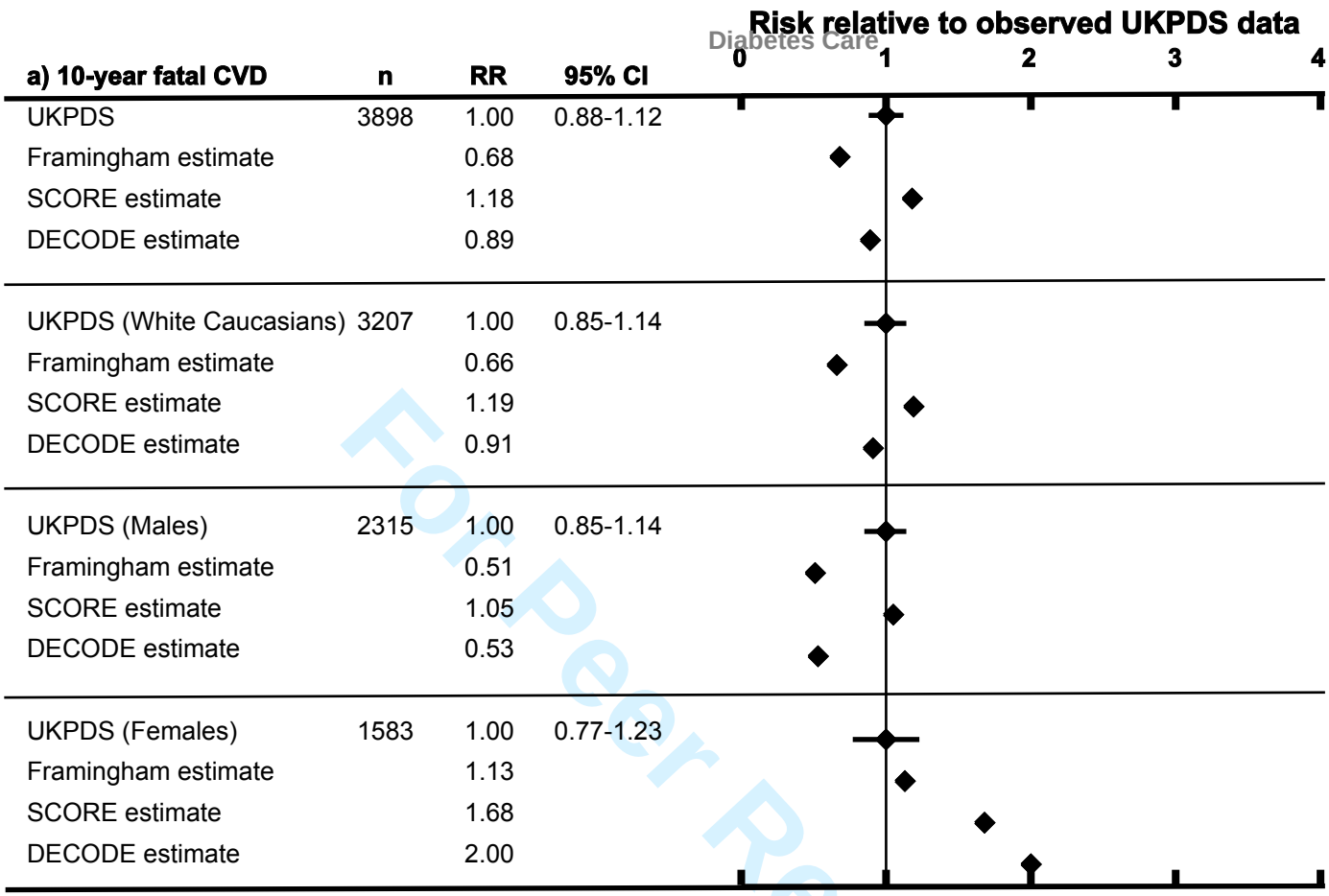
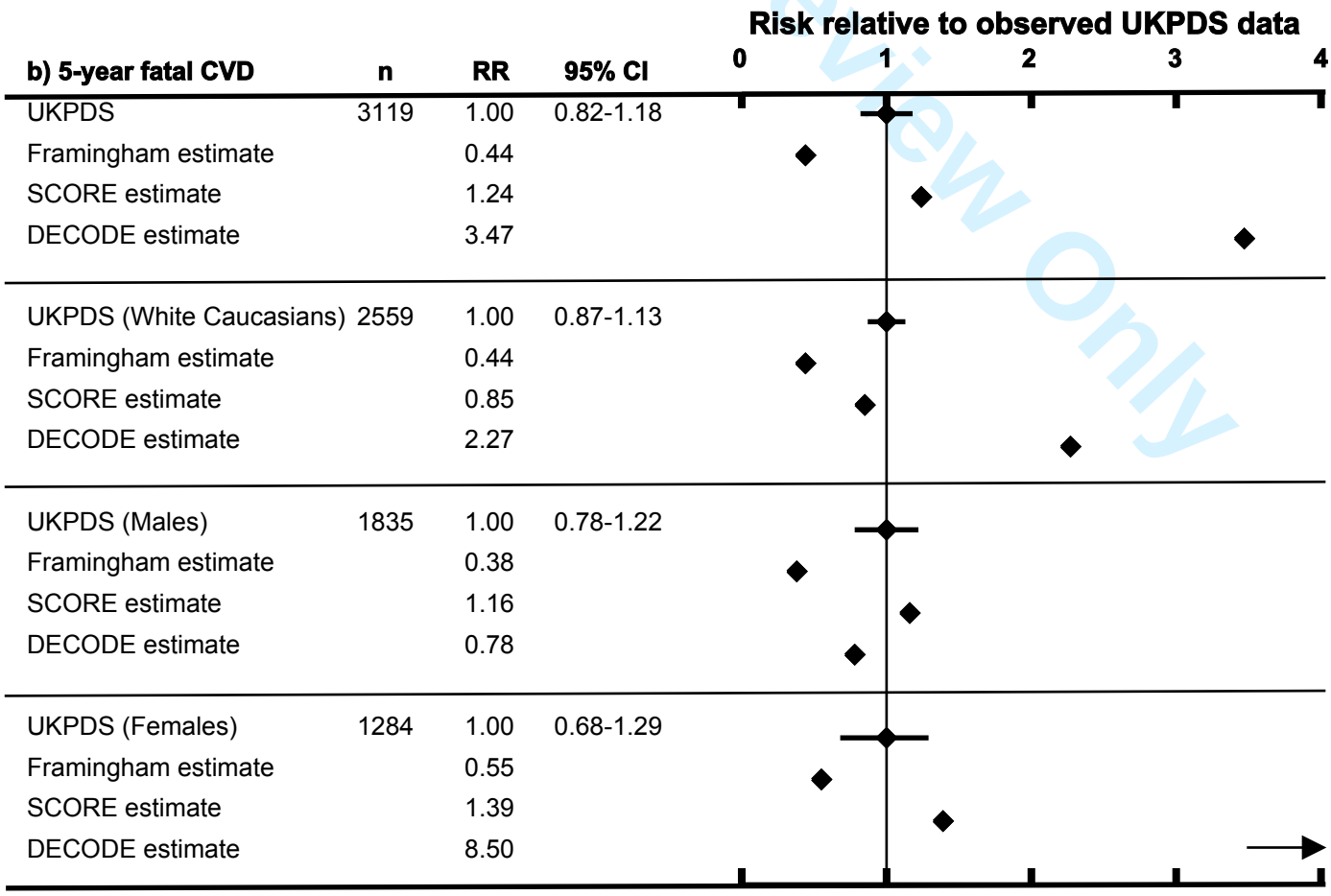


a) 10-year fatal CVD	n	RR	95% CI
UKPDS	3898	1.00	0.88-1.12
Framingham estimate		0.68	
SCORE estimate		1.18	
DECODE estimate		0.89	
UKPDS (White Caucasians)	3207	1.00	0.85-1.14
Framingham estimate		0.66	
SCORE estimate		1.19	
DECODE estimate		0.91	
UKPDS (Males)	2315	1.00	0.85-1.14
Framingham estimate		0.51	
SCORE estimate		1.05	
DECODE estimate		0.53	
UKPDS (Females)	1583	1.00	0.77-1.23
Framingham estimate		1.13	
SCORE estimate		1.68	
DECODE estimate		2.00	



b) 5-year fatal CVD	n	RR	95% CI
UKPDS	3119	1.00	0.82-1.18
Framingham estimate		0.44	
SCORE estimate		1.24	
DECODE estimate		3.47	
UKPDS (White Caucasians)	2559	1.00	0.87-1.13
Framingham estimate		0.44	
SCORE estimate		0.85	
DECODE estimate		2.27	
UKPDS (Males)	1835	1.00	0.78-1.22
Framingham estimate		0.38	
SCORE estimate		1.16	
DECODE estimate		0.78	
UKPDS (Females)	1284	1.00	0.68-1.29
Framingham estimate		0.55	
SCORE estimate		1.39	
DECODE estimate		8.50	