

Evidence Tables

RISK 1 Which arterial risk tables, equations or engines for calculation of arterial risk are most predictive of arterial disease in people with type 2 diabetes?

Reference	Study type Evidence level	Number of patients	Patient characteristics	Intervention		Outcome measures	Effect size	Source of funding
Guzder RN, Gatling W, Mullee MA, Mehta RL, Byrne CD. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed Type 2 diabetes: results from a United Kingdom study. Diabetic Medicine 2005; 22(5):554-562. Ref ID: 3447	Observational Cohort study 2++	N=428 (241 male, 187 female) From 24 GP practices in the Poole area (UK)	Inclusion criteria: All newly diagnosed T2D individuals. Exclusion criteria: patients aged <30 years or >74 years, pre-existing CV disease, registered outside Dorset Health Authority	Final outcomes in the Cohort: Forty (9.3%) participants died during the course of the study. The death certificate recorded cardiovascular disease as the underlying cause in 18 (45%) of these individuals. Ninety-eight primary cardiovascular events were identified during the course of the study. Of these, 37 were episodes of angina/unstable angina, 11 were fatal and non-fatal MI, 21 were cerebrovascular disease (strokes 9, TIAs 12), 17 were cases of peripheral vascular disease, and 12 of heart failure. Recording only primary CHD events,	Follow-up 4.2 years (median)	Distribution of predictive 10-year CHD scores using both risk calculation methods.	<p>Distribution of predictive 10-year CHD scores</p> <p>Using both risk calculation methods, similar proportions were assigned 10-years scores less than 15% (Framingham 27.3% and UKPDS 25.7%). However, the UKPDS risk engine assigned a 10-year score over 30% to 187 (43.7%) of the study participants as compared with only 88 (20.5%) when derived from Framingham.</p> <p>The 15%, 10-year CHD risk threshold with both the Framingham and UKPDS risk engines had similar sensitivity for primary CVD as the lipid level threshold¹ [85.7 and 89.8% vs. 93.9% (p=0.21 and 0.34) and both had greater specificity [33.0 and 30.3% vs. 12.1% (p<0.001 and p<0.001)]</p> <p>Framingham risk function (FRF) & UKPDS</p> <p>At the level of the entire cohort, the number of events predicted by the FRF underestimates both true CVD</p>	Diabetes UK

¹ ADA lipid threshold (LDL ≥2.6 mmol/L or triglycerides ≥4.5 mmol/L)

						<p>and CHD events by 33% and 32%, respectively, as opposed to the statistically non-significant 13% of CHD events in the case of the UKPDS risk engine.</p> <p>The Framingham results suggest a tendency towards a greater degree of underestimation of CHD events in men than women (41% vs. 26%) and for pre-treated rather than untreated blood pressure (42 vs. 31%).</p> <p>The UKPDS risk engine confirms the trend in relation to anti-hypertensive therapy (21 vs. 8%) but differs in relation to gender (men 16% vs. women 10%).</p> <p>However, in relation to prognostic values on an individual basis, both risk assessment methods show moderate discrimination and poor calibration. The secondary analyses, and specifically those relating to pre-treatment with anti-hypertensives and gender show similar discrimination. The exclusion of LVH does not have a detrimental effect on the discrimination measurement.</p>	
Coleman R, Stevens R, Renakaran R, Holam RR. Framington, SCORE and DECODE do not provide reliable	Historical case series Level 3	N=3,898 participants with complete baseline risk factor data	Inclusion: newly-diagnosed type 2 diabetes, mean age 53years, SBP 135 (19) mmHg, total cholesterol 5.4 (1.1) mmol/l, HbA1c	Framingham Score Systematic Coronary Risk Evaluation (SCORE). The SCORE project assembled a pooled dataset of cohort studies from 12 European countries (total N=205,178), the	Comparison of Framingham, SCORE and DECODE risk estimates	<p>*10-year fatal CVD event rate (95% CI) The 10-year fatal CVD event rate observed in the UKPDS was 7.4% (6.5 to 8.3). Framingham underestimated this by</p>	Oxford University

<p>cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007. Ref ID: 3619</p>		<p>from the UKPDS. N=779 excluded because of a fatal CVD event or censoring prior to their chosen start time, or missing risk factor data.</p> <p>23 UK centres</p>	<p>7.2 (1.8) %, 59% male, 30% female – these were reflective of the whole cohort.</p> <p>Exclusion: included severe vascular disease, MI or stroke within 1 year, major systemic illness</p>	<p>aim was to develop a system of risk estimation for clinical practice in Europe and involved 3 phases. First, the development of simple paper-based risk charts for high-risk and low-risk European populations; secondly, the development of methods for creating national or regional risk charts based on published mortality data; finally, the integration of risk estimation into a computer-based risk factor management application.</p> <p>DECODE study, this cohort (N=24,413 from 14 European studies) considered risk factors, specifically including glucose, to inform cardiovascular risk prediction.</p>		<p>32% (AR 5.0%), SCORE overestimated risk by 18% (AR 8.7%), DECODE underestimated by 11% (AR 6.6%), considered acceptable by the authors.</p> <p>*5-year fatal CVD event rate (95% CI) The 5-year fatal CVD event rate observed in the UKPDS was 4.5% (3.7 to 5.3). Framingham underestimated this by 56% (AR 2.0%), SCORE overestimated by 24% (AR 5.6%), DECODE also considerably overestimated (AR 15.6%).</p> <p>*10-year fatal CHD event rate (95% CI) The 10-year fatal CHD event rate observed in the UKPDS was 6.3% (5.5 to 7.1). Framingham underestimated (AR 4.3%), while SCORE provided a reasonable estimate (AR 5.7%).</p> <p>*5-year fatal CHD event rate (95% CI) The 5-year fatal CHD event rate observed in the UKPDS was 3.9% (3.1 to 4.6). Framington underestimated (AR 2.0%), while SCORE provided a reasonable estimate (AR 3.6%).</p> <p>*aROC The aROC analysis was used to</p>	
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						<p>compare risk equation sensitivity and specificity, using actual survival times, where possible.</p> <p>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).</p> <p>The authors concluded that Framingham, SCORE and DECODE models do not provide reliable fatal CVD and CHD risk estimates in T2D.</p>	
<p>Eddy DM, Schlessinger L. Validation of the Archimedes diabetes model. Diabetes Care 2003; 26(11):3102-3110. Ref ID: 3621</p>	<p>External Validation study Level 3</p>	<p>Population from 18 Clinical trials</p>	<p>The study simulated a variety of randomized controlled trials by repeating in the model the steps taken for the real trials and comparing the results calculated by the model with the results of the trial. Eighteen trials were chosen by an independent advisory committee. Half the trials had been used to help build the model ("internal" or "dependent" validations); the other half had not. Those trials comprise external" or "independent" validations</p>	<p>The full Archimedes model is designed to be comprehensive and includes not only individual people (patients) but also other important aspects of a health care system, such as health care personnel, facilities, equipment, supplies, policies and procedures, regulations, utilities and costs.</p> <p>The model includes the pertinent organ systems, more than 50 continuously interacting biological variables, and the major symptoms, tests, treatments, and outcomes. The model is continuous in time and represents biological variables continuously. The equations on which is model is built can simulate a variety of clinical trials and reproduce their results with good accuracy. The Archimedes is a model which attempts to address what happens underneath the clinical states, between the annual jumps, and inside the transition probabilities.</p>	<p>Validation</p>	<p>A total of 74 validation exercises were conducted involving different treatments and outcomes in the 18 trials. For 71 of the 74 exercises there were no statistically significant differences between the results calculated by the model and the results observed in the trial.</p> <p><u>The results for the 10 trials that explicitly included patients with diabetes are summarized in Table 1. The results of the other trials that are pertinent to the cardiovascular complications of diabetes are summarized in Table 2. Trials not used to build the model are marked.</u></p> <p>The correlation coefficient for all 74 exercises is $r = 0.99$</p> <p>If the outcomes in the control group and the absolute differences</p>	<p>Kaiser Permanente Southern California and the Care Management Institute of Kaiser Permanente</p>

				<p>The model differs in many ways from other clinical models. In addition to including behaviours, care processes, logistics, resources, and costs, the most obvious differences are that the Archimedes model is written at a fairly deep level of biology. It is continuous in time, and it preserves the continuous nature and simultaneous interactions of biological variables.</p> <p>Structurally, it is written with differential equations and is programmed in an object-oriented language called Smalltalk. Another difference is the fairly extensive comparisons to empirical studies</p> <p>The trials Ten trials explicitly included people with diabetes. These are the U.K. Prospective Diabetes Study (UKPDS), the Diabetes Prevention Program (DPP), the Heart Protection Study (HPS), the Health Outcomes Prevention Evaluation (HOPE), Micro-HOPE (the diabetic subpopulation of the HOPE trial), Cholesterol and Recurrent Events (CARE), the ACE Inhibitors and Diabetic Nephropathy Trial (Lewis), the IRMA-2 trial , the Diabetes Control and Complications Trial (DCCT), and the Irbesartan Diabetic Nephropathy Trial (IDNT) .</p> <p>Eight more trials were chosen by the committee to test the model's realism for representing coronary artery disease (CAD). They are the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial, the Helsinki Heart Study (HHS), the Systolic Hypertension in the Elderly Study (SHEP)</p>		<p>between the control and treated groups are compared for model and trial, the correlation coefficient is $r=0.99$.</p> <p>Focusing specifically on the absolute differences in the outcomes, which determines the number needed to treat, the correlation coefficient is $r=0.97$.</p> <p>For the 10 trials that were not used to build the model, the correlation coefficient is also $r=0.99$.</p> <p>Methodology For the disease-determined outcomes, we use Kaplan-Meier curves to compare the results calculated by the model with the actual results of the trial. Kaplan-Meier curves provide the most complete information about the outcomes over the entire time course of the trial in all the arms of a trial.</p>	
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				<p>, the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), the Medical Research Council (MRC) hypertension trial, the West of Scotland Coronary Prevention Study (WOSCOPS), the Veterans Affairs High-Density Lipoprotein Cholesterol interventions Trial (VA-HIT) , and the Scandinavian simvastatin Survival Study (4S)</p> <p>Use of trial data to build the model. Ten of the trials (DPP, HPS, MICROHOPE, LIPID, HHS, SHEP, LRC-CPPT, MRC, VA-HIT, and WOSCOPS) were not used at all to build the physiology model; they provided external or independent validations of the model. The remaining eight trials (UKPDS, HOPE, CARE, Lewis, IRMA-2, DCCT, IDNT, and 4-S) provided internal or dependent validations.</p> <p>In general, between 10 and 30 equations are needed to represent the pathophysiology of the disease and to calculate the effect of a specific treatment on a specific outcome in a specific population (i.e., not including the equations for behaviours, care processes, logistics, and other nonbiological aspects of the model). When a piece of information from a trial is used, it is used to help write only one of those 10–30 equations.</p>			
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<p>Song SH, Brown PM. Coronary heart disease risk assessment in diabetes mellitus: comparison of UKPDS risk engine with Framingham risk assessment function and its clinical implications.² Diabet Med 2004; 21(3):238-245. Ref ID: 3456</p>	<p>Historical case series Level 3</p>	<p>N= 700</p>	<p>Inclusion criteria: patients without arterial disease (no history of ischaemic heart disease, cerebrovascular disease and peripheral vascular disease recorded in general practice computer databases), aged between 30 and 74 years, who were not prescribed any statin therapy and who fulfilled the criteria for both the UKPDS risk engine and JBS method were included in the analysis.</p> <p>As the general practice registers did not record the type of diabetes, patients aged < 30 years who were on insulin treatment were excluded on the assumption that these patients were likely to have T1D.</p>	<p>JBS risk calculator utilizes <u>eight</u> risk factors [age, sex, systolic or diastolic blood pressure, smoking status, presence of absence of DM and left ventricular hypertrophy (LVH) and total and HDL cholesterol] to calculate absolute CHD risk in those patients aged between 30 and 74 years.³</p> <p>The UKPDS risk engine model utilizes <u>nine</u> risk factors (age at diagnosis, duration of diabetes, sex, ethnicity, smoking status, systolic blood pressure, HbA1c, total and HDL cholesterol) to calculate CHD risk.</p> <p>The differences between the two models are as follows: the UKPDS model recognizes glycaemic control as a continuous risk factor rather than a dichotomous variable such as absence or presence of diabetes. Furthermore, age is replaced by two diabetes-specific variables; age at diagnosis and duration of diabetes. Ethnicity is also included as a risk factor in the UKPDS equation but no in the Framingham equation.</p> <p>The absolute CHD risk was expressed as the percentage over 10 years</p> <p>Following calculation of the absolute 10-year</p>	<p>Comparison of JBS risk calculator and UKPDS risk engine.</p> <p>Implications on clinical practice of CHD primary prevention.</p>	<p>Comparison of JBS risk calculator and UKPDS risk engine</p> <p>* General difference The correlation between UKPDS risk engine and JBS calculator follows a curvilinear pattern ($r^2 = 0.70$, $p < 0.001$) (see graphic).</p> <p>Overall, the UKPDS risk engine calculated a significantly higher mean CHD 10-year risk (UKPDS vs JBS, 21.5 vs 18.3% $p < 0.0001$) with the mean difference of 3.2% (95% CI, 2.7 – 3.8).</p> <p>As for gender differences, there is a bias towards men to have a much higher CHD risk with the UKDPS risk engine. The mean difference in risk score between men and woman was approximately 8.4% with the UKPDS risk engine in comparison with 1.7% with the JBS calculator. For men, the UKPDS risk engine calculated CHD risk approximately 6% higher than the JBS calculator.</p> <p>* CHD risk score categorization To determine the distribution of patients into the different risk</p>	<p>Scarborough Primary Care Trust.</p>
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² The purpose of this study is to address the following questions: (i) to assess the difference between CHD risks calculated by the Joint British Societies (JBS) risk calculator based on the Framingham equation with those calculated by the UKPDS risk engine in patients with T2D; (ii) to determine the significance of the differences between these two risk assessment methods on the clinical practice of CHD primary prevention based on JBS and NICE guidelines; (iii) to examine the impact of CHD risk threshold reduction from 30 to 15% (as proposed by NICE guidelines) on the additional number of patients who would be treated with statin and the subsequent cost of statin prescription, and (iv) to examine the impact of HPS findings on the number of patients who would be treated with statin and the subsequent cost of statin prescription in CHD primary prevention.

³ Because HDL cholesterol was not routinely checked, its level was assumed to be 1.2 mmol/l. This value is now recognized to be the average HDL level for patients with diabetes in the UK. The presence or absence of LVH was not recorded on the general practice computer databases and the assumption was made that LVH was absent in CHD risk calculation by JBS method

			<p>The reasons for exclusion were history of pre-existing arterial disease, existing statin therapy and age <30 or >74 years.</p> <p>Baseline characteristics: of the 1,782 patients identified from nine general practice databases, 1249 (70%) did not have any history of arterial disease and therefore were eligible for CHD primary prevention intervention. From this cohort, 700 (56.1%) fulfilled the criteria for risk assessment by both UKPDS risk engine and JBS calculator.</p>	<p>CHD risk, patients were divided into three categories, namely <15%, 15-30% and >30% risk groups. The proportion of those categorized into these risk groups by the two risk methods was compared.</p>		<p>categories, each patient's risk score was stratified into <15%, 15-30% and >20% risk groups.</p> <p><15%, Both methods identified similar proportion (~65%) of patients with CHD risk of at least 15% over 10 years.</p> <p>15-30% the JBS calculator categorized a higher proportion of patients into the 15-30% risk group (JBS vs. UKPDS, 58.3 vs 43.0%, p<0.001),</p> <p>>30% The UKPDS risk engine categorized a significantly higher proportion into the >30% risk group (JBS vs. UKPDS, 7.3 vs. 22.6%, p<0.001).</p> <p>When the cohort categorized into the 15-30% risk group by the JBS calculator had their risk calculated by the UKPDS risk engine, 114 out of 408 patients (27.9%) were classified as >30% risk by the UKPDS risk engine. (show table 2)</p> <p>There was a difference of 107 in the 15-30% risk group as calculated by the two methods. All these were classified as high risk (>30%) by the UKPDS risk engine, which accounted for the difference in the number observed between the two methods in the >30% risk group.</p>	
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					<p>Hence, the main differential feature between the two methods in their risk stratification function is the tendency of the UDPDS risk engine to identify more patients in the high risk category (>30%) in comparison with JBS. This can be explained by the tendency of the UKPDS risk engine to estimate higher CHD risk in comparison with the JBS calculator at higher mean CHD risk level.</p> <p>Implications on clinical practice of CHD primary prevention.</p> <p>* Overall proportion of patients eligible for CHD primary prevention (CHD> 15%)</p> <p>Both methods identified approx 65% of patients with T2D who require primary prevention intervention and therefore have comparable accuracy in identifying these high risk patients.</p> <p><u>Aspirin treatment (CHD>15% with NICE and JBS guidelines)</u> Both methods identified a similar proportion (~65%) who would qualify for this treatment.</p> <p><u>Statin treatment (CHD risk >15% with NICE and >30% with JBS guidelines)</u> At a risk threshold of 30% for statin initiation and total cholesterol >5mmol/L, UKPDS risk engine identified 2.5-fold more who would</p>	
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						<p>be eligible for this treatment in comparison with JBS calculator [UKPDS vs. JBS, 125/700 (17.8%) vs. 50/700 (7.1%)].</p> <p>However, both methods identified a similar proportion of eligible patients for statin at risk threshold of 15% and total cholesterol >5mmol/L [UKPDS vs. JBS, 328/700 (46.8%) vs. 344/700 (49.1%)]</p> <p>Gender differences For aspirin treatment, more men than women would be eligible with UKPDS risk engine assessment whilst where was no gender difference with the JBS calculator.</p> <p>For statin treatment more men than women would be eligible at a risk threshold of 30% with UKPDS risk engine assessment. The JBS calculator identified a similar proportion of men and women for statin at both risk thresholds.</p>	
<p>Stephens JW, Ambler G, Vallance P, Betteridge DJ, Humphries SE, Hurel SJ. Cardiovascular risk and diabetes. Are the methods of risk prediction satisfactory? Eur J Cardiovasc Prev Rehabil 2004; 11(6):521-528. Ref ID: 3457</p>	<p>Historical case series Level 3</p>	N= 798	<p>The study was performed within the diabetes clinic at UCL Hospital NHS Trust (UCLH) using the computerised clinic database. This contains demographic and clinical information on patients who have attended the diabetes clinic since 1983.</p>	<p>Risk prediction:</p> <p>Ten-year risk prediction was calculated using the JBSRC, CRM, PROCAM and the UKPDS risk engine.</p> <p>The JBSRC provides three risk categories for future CHD: low (<15%, intermediate (15-30%) and high (>30%).</p> <p>The CRM provides a discrete percentage risk derived from the original Framingham equation.</p>	Risk prediction	<p>* Risk prediction</p> <p>All tests (except PROCAM) demonstrated acceptable discrimination with respect to CHD/CVD, however, all underestimated the risk of future events.</p> <p>* Joint British Societies Coronary Risk Chart (JBSRC) With respect to CVD, disease</p>	British Heart Foundation

			<p>Inclusion criteria / Exclusion criteria: Patients were identified who had attended in 1990-1991 and continued under follow-up in 2000-2001. Only patients in the age range 35-74 years were included. All patients with pre-existing CVD, renal failure and a family history of dyslipidaemia were excluded. All subjects had diabetes diagnosed as defined by the WHO criteria.</p> <p>Analysis was performed on 798 (504 males, 294 females) patients with the available follow-up data. These were made up of 69% White, 23% Indian, 5% Afro-Caribbean and 3% Chinese. Of these 358 had CVD (269 had CHD) and 440 no CVD (529 no CHD)</p>	<p>The PROCAM gives a discrete percentage risk up to 30% and thereafter a risk of >30% for men, and up to 7.5% for women and a risk of >7.5% thereafter.</p> <p>The UKPDS risk engine provides a discrete percentage risk over 10 years.</p> <p>Identification and classification of endpoints</p> <p>From the database, patients were categorised by the presence/absence of clinically manifest CVD at follow-up (2000-2001). This was determined from the past medical history by the presence of CHD, pulmonary vascular disease, or cerebrovascular disease.</p>		<p>developed in 44 (14%) of 316 at low, 181 (60%) of 302 at intermediate, and 107 (85%) of 125 at high risk. The C-index was 0.80 indicating good discrimination</p> <p>With respect to CHD, disease developed in 28 (9%) of 316 at low, 142 (47%) of 302 at intermediate, and 83 (66%) of 125 at high risk. The C-index was lower at 0.77 but still indicating good discrimination.</p> <p>The calibration was however poor ($p < 0.001$) with reference to the predicted risk categories.</p> <p>* Cardio Risk Management (CRM) With respect to CVD and CHD, CRM had a C-index of 0.76 and 0.73 respectively, indicating good discrimination.</p> <p>The study also grouped the predicted risk estimates from CRM into the high, intermediate and low risk groups of the JBSRC. When this was done there was no significant difference in the number of patients with/without CVD/CHD in the three groups when compared to the JBSRC, indicating that both measures (being derived from the Framingham equation) are essentially the same, except that CRM can be used to give a discrete risk.</p>	
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						<p>PROCAM calculation With respect to CVD and CHD, PROCAM had a lower level of discrimination with a C-index of 0.67 and 0.65 respectively. Again the calibration is poor ($p < 0.0001$) with the observed risk being systematically higher than the predicted risk.</p> <p>UKPDS Risk Engine The C-index was 0.74 and 0.76 for CVD and CHD respectively. Again the calibration is poor ($p < 0.001$) although the method does not over-predict as much as the other methods.</p>	
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