

Validation of QRISK2 (2014) in patients with diabetes

Authors

Julia Hippisley-Cox Professor of Clinical Epidemiology & General Practice¹
Carol Coupland Associate Professor and Reader in Medical Statistics¹
Peter Brindle Research and Development Programme Director²

Institutions

¹Division of Primary Care, 13th floor, Tower Building, University Park, Nottingham, NG2 7RD.

²Avon Primary Care Research Collaborative, Bristol Clinical Commissioning Group, South Plaza, Marlborough Street, Bristol BS1 3NX.

Guarantor & Author for correspondence - Julia Hippisley-Cox

Email: Julia.hippisley-cox@nottingham.ac.uk

Telephone: 0115 8466915

Fax: 0115 8466904

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1 Purpose of document

The NICE draft lipid modification guidelines, published in February 2014[1], recommend QRISK2[2] is used to assess cardiovascular risk. There are two exceptions to this. One is where the patient has chronic kidney disease. The other exception is when the patient has diabetes where the guideline recommends the use of the UKPDS for type 2 diabetes[3] and no risk assessment for patients with type 1 diabetes. This paper summarises the evidence for the use of UKPDS in patients with diabetes and presents new information on the validation of QRISK2 in the subset of patients with diabetes.

2 Background

UKPDS Risk Engine (<http://www.dtu.ox.ac.uk/riskengine/>) is a type 2 diabetes-specific risk calculator for estimating the 10-year risk of CHD (fatal and non-fatal MI, and sudden cardiac death) and stroke (both fatal and non-fatal). The original paper for predicting CHD published in 2001 by Stevens et al[3] identified a number of limitations of UKPDS since the model was derived from patients recruited for a randomised controlled trial and so was limited to patients aged 25 to 65 years. Stevens et al also concluded that “ideally, the model would be derived from a large-scale epidemiological study of diabetic patients”.

The draft lipid guideline prefers the UKPDS because it has been validated specifically in patients with diabetes whereas QRISK2 has been validated in populations which include diabetics but not in the subset alone. This paper reviews aspects of the lipid guidance in relation to this decision. Specifically it

- compares the populations used to derive the current version of QRISK2 vs UKPDS.
- reviews the evidence from the validation studies cited in the lipid guidance.
- presents original results for the performance of QRISK2 specifically in the subset of patients with diabetes so that the results can be compared with the published literature.

3 Comparison of development and use of QRISK2 & UKPDS

Table 1 compares the populations used to derive QRISK (2014) and UKPDS (2001). The salient points are:

1. **Cohort definition:** UKPDS is based on 4,540 newly diagnosed patients with diabetes referred to hospital clinics between 1977 to 1991 whereas QRISK2 (2014) was developed using a cohort of 3.6 million patients of which 48,889 patients with prevalent type 2 diabetes within primary care. Since the purpose of the risk assessment is not limited to newly diagnosed patients, and will mainly take place within primary care, the population used for QRISK2 is likely to be more suitable.
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2. **Update:** The UKPDS has not been updated for 15 years (data capture until 1997) whereas QRISK2 is updated annually (currently on data captured until 2013). This is important since the population has changed significantly over that time both in terms of the incidence of CVD but also the prevalence of risk factors relevant to CVD risk assessment.
3. **Outcomes:** QRISK2 predicts absolute risk of CVD which is the key outcome of interest. In contrast the version of UKPDS included in the draft recommendation by NICE (p75) recommends calculating the risk of CHD and stroke separately and then adding them together[1]. This results in double counting as the outcomes are not mutually exclusive and the CHD and Stroke models include different predictor variables. This will result in inaccurate predictions and overestimation of risk compared with a score designed to predict risk of the relevant outcome. The UKPDS website itself states “Summing the coronary heart disease (CHD) and stroke risk estimates from the Risk Engine is not recommended”
4. **Age range:** QRISK2 has been developed and can be applied to patients aged 25-84 years. UKPDS was developed in patients aged 25-65 so doesn't apply to the relevant age range. The draft guideline doesn't make this clear.
5. **Predictors:** UKPDS does not include some well-established predictors such as deprivation, family history, body mass index, rheumatoid arthritis, chronic renal disease or treated hypertension. UKPDS will tend to under-estimate risk in patients with these factors. Recent updates of QRISK2 include both type 1 and type 2 diabetes as predictor variables [ref].

Regarding ethnicity, while UKPDS risk engine at first sight appears to have three options (White, Afro-Caribbean and Asian-Indian) as these were used in the initial modelling, the resulting algorithm in fact only uses two for the CHD outcomes and none for the Stroke outcome[4] Entering White or Asian-Indian give the same answers for CHD and changing the ethnicity drop down makes no difference at all for Stroke. There is no 'black African' category – a group that nowadays makes up a large proportion of some practices and who do not fit with the binary category for ethnicity included in the UKPDS CHD model. It is well known that CVD risk and the prevalence of risk factors for CHD and Stroke vary considerably between ethnic groups and a risk score should reflect these differences[5]. QRISK2, however, includes an ethnicity variable with 9 categories[2].

6. **HBA1C:** HBA1C was included as a predictor in the UKPDS CHD model[3] but it was not significant for stroke and so wasn't included[4]. In the UKPDS CHD model, HBA1C is entered as a % whereas now it is measured in mmol/l so a conversion would be needed. Further evidence from other studies has found that the addition of HBA1c to a version of Framingham is marginally better than Framingham alone for predicting CHD but this was only a small statistically significant improvement in discrimination in men but not women and without improvement in reclassification of risk category[6].
 7. QRISK2 is integrated within GP systems so that the risk score can be automatically calculated and recorded in the record for patients without the need to do separate data entry. The UKPDS risk engine requires separate data entry making CVD risk assessment more time consuming and error prone.
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Table 1 Comparison of QRISK2 and UKPDS derivation cohorts and model inputs

| | QRISK2 2014 | UKPDS (Stevens 2001) |
|-----------------------------------|--|--|
| Derivation cohort | Total of 3.6 million patients (1998-2013) including 58,613 patients with prevalent diabetes (48,889 cases with type 2 diabetes) | 4540 newly diagnosed, hospital-referred patients with type2 diabetes for CHD model 4549 patients included in the stroke model |
| Time period for follow-up | 1998-2013 | 1977-1997 |
| Date last updated | Jan 2014 | Published 2001 |
| outcome | CVD | 2 separate outcomes: CHD & Stroke To get CVD risk then add CHD and stroke risks (not recommended by Stevens et al) |
| Outcome numbers | 795 CVD events (in type 1) 10,643 CVD events(in type 2) | Not reported for CHD There were 188 strokes |
| Age range | 25-84 years | 25-65 years |
| ethnicity | 9 levels: White/not recorded, Indian, Pakistani, Bangladeshi, other Asian, black African, black Caribbean, Chinese, other including mixed | 2 levels for CHD model - Afro Caribbean vs other. Ethnicity was not included in the stroke model |
| deprivation | Townsend score | - |
| sex | M/F | M/F |
| smoking status | 5 levels: Non-smoker, ex-smoker, current – light, current – moderate, current-heavy | current smoker vs other |
| Family history CHD under 60 years | Yes/no | - |
| atrial fibrillation | Yes/no | Yes/no but only included in the stroke model |
| Chronic renal disease | Yes/no | - |
| Rheumatoid arthritis | Yes/no | - |
| Treated hypertension | Yes/no | - |
| Type 1 diabetes | Yes/no | - |
| Type2 diabetes | Yes/no | - |
| Body mass index | Continuous | |
| systolic blood pressure | Continuous | Continuous |
| total cholesterol & HDL | Ratio of total/HDL | Ratio of total/HDL |
| HBA1c | - | Yes but only included in the CHD model, not in stroke in CHD, no in Stroke |

| | | |
|-------------------|---|-----|
| Duration diabetes | - | Yes |
|-------------------|---|-----|

3.1 Validation studies of UKPDS

The draft lipid guideline refers to a number of validation studies of UKPDS compared with Framingham in patients with diabetes. None of these studies tested the modification of the UKPDS suggested by NICE – namely the arithmetic addition of the risk of CHD plus the risk of stroke determined by two separately modelled equations with different parameters.

- a. **Validation study by Stephens (2004)**: The study by Stephens et al [7] compared UKPDS with Framingham in a selected sample of 798 patients from a London hospital clinic with 358 CVD events during follow-up. The study included a mixture of patients with type 1 and type 2 diabetes. The results showed Framingham performed substantially better than UKPDS with ROC values of 0.80 for Framingham compared with 0.74 for UKPDS[7]. The calibration of both UKPDS & Framingham was poor with significant under-prediction which the authors think could be related to the selection of hospital patients likely to be at higher risk than patients in primary care. Stephens et al also suggest that inclusion of BMI (which is not included in UKPDS) may improve risk prediction.
 - b. **Validation study by Guzder (2005)[8]**: This study examined 428 newly diagnosed type 2 diabetics from an affluent predominantly white population in Dorset. There were 98 CVD events. Discrimination for UKPDS was 0.67 compared with 0.66 for Framingham. Calibration of both models was reported to be poor.
 - c. **Validation study by Elkeles (2008) [9]**: this study examined 576 patients with type 2 diabetes recruited from a London hospital clinic. They excluded black people. There were 66 CVD events with a ROC value of 0.63 for version 3 of UKPDS (which was the same as the value of 0.63 reported for Framingham). Calibration was not reported.
 - d. **Validation study by Simmons (2009) [10]**: this study validated both UKPDS and Framingham in 272 patients with type 1 & type 2 diabetes from Norfolk. The analysis was restricted to patients with complete data and those aged 40-79 years. All patients were white. There were 69 CVD events. The study found UKPDS was well calibrated and better than Framingham. However more patients were correctly classified with Framingham than Framingham and there was no statistically significant difference with UKPDS (ROC value for Framingham was 0.73 compared with 0.72 for UKPDS). The authors concluded that further testing of UKPDS is needed before it can replace Framingham[10] though there are no more recent papers cited providing evidence of further testing.
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Table 2 Summary of UKPDS validation information included in draft lipid guidance (2014)[1].

| Source | Validation cohort | Number of CVD events | End point measured | Version UKPDS tested* | AUROC | Calibration/reclassification |
|------------------|---|----------------------|--------------------|-----------------------|------------------|--|
| Stephens 2004[7] | 798 patients with type 1 & type 2 diabetes 1990-2001 London Hospital Diabetes clinic 35-74 years | 358 | CVD + PVD | Version 1 | 0.74 (0.70-0.78) | Poor calibration with significant under prediction. |
| Guzder 2005 [8] | 428 newly diagnosed type 2 diabetics 30-74 years from Poole 1996-1998. Affluent white population. | 98 | CHD events | Version 1 | 0.67 | Poor calibration. Discrimination & calibration no better than Framingham |
| Elkeles 2008[9] | 576 patients type 2 diabetes recruited from outpatient clinics, central & west London aged 50-75 years; excluded black people. Median follow-up 4 years | 66 | CVD | Version 3 | 0.63 (0.56-0.71) | Not reported |
| Simmons 2009[10] | 272 type 1 & 2 diabetes, white patients from Norfolk. Analysis restricted to patients with complete data. Aged 40-79 recruited 1993-8. Followed up until 2007 | 69 | CVD | Version 3 | 0.72 (0.65-0.78) | UKPDS no significant difference in reclassification or discrimination c.f. Framingham. |

*Version 1 of UKPDS predicts CHD and stroke risks separately. Version 3 UKPDS predicts combined CVD outcome. There are no validation studies of the NICE modified version of UKPDS which sums CHD and stroke risk.

4 Methods for validation of QRISK2 (2014):

In light of the draft lipid guideline, we have undertaken a validation of the latest version of QRISK2 (2014) in the subset of patients with diabetes using version 36 of the QResearch database (updated until 01 Aug 2013). QRISK2-2014 was derived using an open cohort of patients aged 25 to 84 registered with the practices from 01 Jan 1998 until 01 Aug 2013. We tested the performance of QRISK2(2014) in the validation cohort in patients with type 1 diabetes and patients with type 2 diabetes

We calculated the ROC values, D statistics and R^2 values, and assessed calibration by comparing observed risks with mean predicted risks across tenths of predicted risks. We used multiple imputation in the derivation and the validation cohorts to impute missing values for systolic blood pressure, cholesterol/HDL ratio, smoking status, and body mass index and combined results across the imputed datasets in the analyses.

We also derived a separate model based on the subset of patients with a diagnosis of diabetes and including HBA1C as a continuous variable and duration of diabetes as a categorical variable (<1; 1-4; 5-9; 10+ years) as well as the usual variables already in QRISK2 but found no significant improvement in the validation statistics.

5 Results of QRISK2 validation

5.1 Baseline characteristics

Table 3 shows the baseline characteristics of patients with either type 1 or type 2 diabetes in the derivation and validation cohorts.

Table 3 characteristics of all patients aged 25-84 years in the QRISK2 derivation and validation cohorts with either type 1 or type 2 diabetes.

| | Derivation cohort | | Validation cohort | |
|---------------------------------------|-------------------|--------------|-------------------|--------------|
| | Type 2 | Type1 | Type 2 | Type 1 |
| total | 48889 (100.0) | 9724 (100.0) | 26759 (100.0) | 5588 (100.0) |
| female | 22128 (45.3) | 4453 (45.8) | 12267 (45.8) | 2546 (45.6) |
| male | 26761 (54.7) | 5271 (54.2) | 14492 (54.2) | 3042 (54.4) |
| 25-34 years | 1201 (2.5) | 4522 (46.5) | 777 (2.9) | 2750 (49.2) |
| 35-44 years | 4832 (9.9) | 3169 (32.6) | 2818 (10.5) | 1763 (31.5) |
| 45-54 years | 9051 (18.5) | 1323 (13.6) | 4981 (18.6) | 699 (12.5) |
| 55-64 years | 12237 (25.0) | 501 (5.2) | 6495 (24.3) | 252 (4.5) |
| 65-74 years | 13004 (26.6) | 170 (1.7) | 7090 (26.5) | 99 (1.8) |
| 75+ years | 8564 (17.5) | 39 (0.4) | 4598 (17.2) | 25 (0.4) |
| Age (mean, SD) | 61.2 (13.1) | 37.6 (10.1) | 60.8 (13.3) | 37.1 (10.0) |
| Townsend deprivation score (mean, SD) | 0.5 (3.5) | 0.2 (3.5) | .8 (3.8) | .5 (3.7) |

| | | | | |
|-------------------------------------|--------------|--------------|--------------|--------------|
| ethnicity | | | | |
| ethnicity recorded | 31662 (64.8) | 6844 (70.4) | 17229 (64.4) | 3941 (70.5) |
| White or not recorded | 40987 (83.8) | 8975 (92.3) | 22361 (83.6) | 5107 (91.4) |
| Indian | 1676 (3.4) | 135 (1.4) | 907 (3.4) | 79 (1.4) |
| Pakistani | 1002 (2.0) | 98 (1.0) | 389 (1.5) | 38 (0.7) |
| Bangladeshi | 704 (1.4) | 80 (0.8) | 633 (2.4) | 59 (1.1) |
| Other Asian | 672 (1.4) | 54 (0.6) | 437 (1.6) | 40 (0.7) |
| Caribbean | 1399 (2.9) | 91 (0.9) | 665 (2.5) | 53 (0.9) |
| Black African | 1209 (2.5) | 132 (1.4) | 700 (2.6) | 112 (2.0) |
| Chinese | 200 (0.4) | 15 (0.2) | 116 (0.4) | 13 (0.2) |
| Other | 1040 (2.1) | 144 (1.5) | 551 (2.1) | 87 (1.6) |
| smoking status | | | | |
| smoking status recorded | 47415 (97.0) | 9559 (98.3) | 25933 (96.9) | 5492 (98.3) |
| non smoker | 27390 (56.0) | 5469 (56.2) | 15035 (56.2) | 3140 (56.2) |
| Ex-smoker | 11364 (23.2) | 1545 (15.9) | 6018 (22.5) | 880 (15.7) |
| light smoker | 4861 (9.9) | 1401 (14.4) | 2777 (10.4) | 776 (13.9) |
| moderate smoker | 1940 (4.0) | 647 (6.7) | 1093 (4.1) | 400 (7.2) |
| heavy smoker | 1860 (3.8) | 497 (5.1) | 1010 (3.8) | 296 (5.3) |
| medical history & values | | | | |
| family history CHD under 60 years | 4839 (9.9) | 1100 (11.3) | 2745 (10.3) | 636 (11.4) |
| rheumatoid arthritis | 954 (2.0) | 110 (1.1) | 517 (1.9) | 46 (0.8) |
| chronic renal disease | 810 (1.7) | 103 (1.1) | 548 (2.0) | 72 (1.3) |
| treated hypertension | 13094 (26.8) | 740 (7.6) | 7008 (26.2) | 367 (6.6) |
| atrial fibrillation | 1048 (2.1) | 17 (0.2) | 578 (2.2) | 8 (0.1) |
| BMI recorded | 45256 (92.6) | 9307 (95.7) | 24827 (92.8) | 5346 (95.7) |
| SBP recorded | 47939 (98.1) | 9598 (98.7) | 26253 (98.1) | 5513 (98.7) |
| cholesterol ratio recorded | 38271 (78.3) | 7897 (81.2) | 24097 (90.1) | 5057 (90.5) |
| HBA1C recorded | 45442 (92.9) | 9184 (94.4) | 24925 (93.1) | 5238 (93.7) |
| BMI mean (SD) | 29.1 (5.2) | 26.4 (4.7) | 29.1 (5.2) | 26.5 (4.8) |
| cholesterol ratio mean (SD) | 4.2 (1.4) | 3.4 (1.2) | 4.2 (1.4) | 3.5 (1.2) |
| systolic blood pressure mean (SD) | 142.6 (20.4) | 128.5 (17.6) | 142.1 (20.7) | 128.4 (17.9) |
| HBA1C mmol/l mean (SD) | 61.9 (20.7) | 70.4 (19.9) | 62.5 (20.9) | 71 (20.3) |

5.2 Incidence rates for CVD events

Table 4 shows the number of incident cases, total and median person years of follow-up & crude and age standardized CVD incidence rates for patients with type 1 and type 2 diabetes in the derivation and validation cohort. In patients with type 2 diabetes in the derivation cohort, there were 10,643 incident CVD events arising from 327,367 person years of observation giving a crude rate of 28.4 per 1000 person years.

Table 4: incidence rates for CVD events in derivation and validation cohort

| | | Derivation cohort | Validation cohort |
|---------------|-------------------------------------|----------------------|----------------------|
| Type 1 | Incident CVD cases | 795 | 465 |
| | Person years | 72,842 | 40,626 |
| | crude incidence rate per 1000 pyrs | 10.9 (10.8 to 11.7) | 11.5 (10.5 to 12.5) |
| | Age standardised rate per 1000 pyrs | 33.9 (28.0 to 39.9) | 39.5 (32.0 to 47.1) |
| | median follow up (years) | 6.4 | 6.0 |
| Type 2 | Incident CVD cases | 10,643 | 5,771 |
| | Person years | 327,367 | 173,775 |
| | crude incidence rate per 1000 pyrs | 32.5 (31.9 to 33.1) | 33.2 (32.4 to 34.1) |
| | Age standardised rate per 1000 pyrs | 28.4 (27.9 to 29.0) | 28.9 (28.1 to 29.6) |
| | median follow up (years) | 5.33 | 5.02 |

5.3 Distribution of CVD risk

In the validation cohort, 83% of patients with type 2 diabetes have a 10 year risk of CVD using QRISK2-2014 of 10% or more.

5.4 Validation statistics: discrimination

Table 5 shows performance statistics using QRISK2 (2014) in the validation cohort.

We tested the scores patients with type 1 and patients with type 2 diabetes. The performance statistics were highest in patients with type 1 diabetes.

Table 5 validation statistics for QRISK2-2014

| | Women mean (95% CI) | Men mean (95% CI) |
|----------------|------------------------|------------------------|
| type 1 | | |
| R ² | 40.8 (33.2 to 48.4) | 48.1 (42.0 to 54.3) |
| D statistic | 1.698 (1.432 to 1.965) | 1.972 (1.729 to 2.215) |
| ROC value | 0.822 (0.788 to 0.856) | 0.841 (0.812 to 0.872) |
| Type 2 | | |
| R ² | 23.2 (21.0 to 25.4) | 20.2 (18.2 to 22.2) |
| D statistic | 1.124 (1.054 to 1.195) | 1.031 (0.967 to 1.095) |
| ROC value | 0.703 (0.691 to 0.715) | 0.696 (0.685 to 0.706) |

There was no significant improvement for a model which included HBA1C and duration of diabetes. We also tested QRISK2-2014 in an separate database called the Clinical Research Practice Data Link (CPRD). The results were similar to those shown in Table 5.

5.5 Validation statistics: calibration

The next two graphs show the observed and mean predicted risks of CVD across the tenths of predicted risk using QRISK2-2014. The results show that QRISK2-2014 is well calibrated in patient with type 1 diabetes and those with type 2 diabetes.

Figure 1 Calibration of QRISK2-2014 in subset of patients with type 1 diabetes

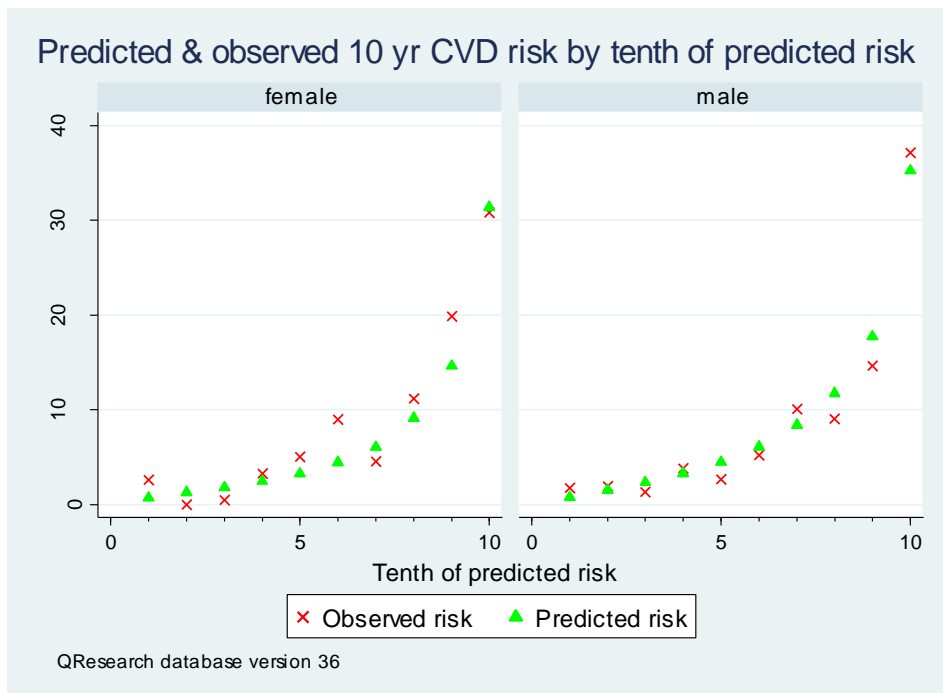
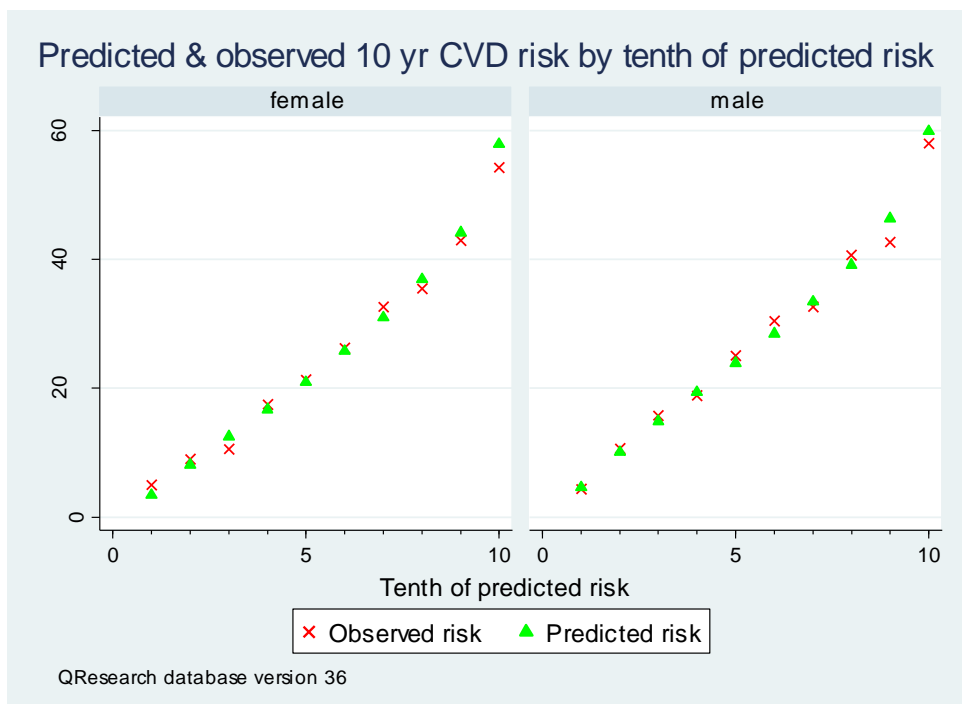


Figure 2 Calibration of QRISK2-2014 in subset of patients with type 2 diabetes



6 Conclusion

We have reviewed the published evidence used as the basis for recommending UKPDS for cardiovascular risk assessment in patients with diabetes. There is no consistent evidence to support the superiority of UKPDS compared with Framingham and no information at all on the performance of the approach of summing the results of separate CHD and stroke models as recommended in this draft guidance. The validation of QRISK2-2014 in the subset of patients with either type 1 or type 2 diabetes is similar to that reported for UKPDS in comparable populations.

Whilst the guideline states an advantage of UKPDS is the inclusion of HBA1C, this is only in the CHD model as it was not significant in the stroke model which is also recommended. The definition of duration of diabetes in UKPDS is unclear since the model was derived on a cohort of newly diagnosed diabetics. On the other hand, there are additional variables in QRISK2 which are not present in UKPDS which are known to affect CVD risk and improve performance of the tool at a population level while improving face validity for individuals. This includes deprivation, body mass index, a much more granular definition of ethnicity and smoking status, inclusion of chronic renal disease and rheumatoid arthritis.

While differences in the accuracy of risk scores are relevant, perhaps the most important issue is to ensure that appropriate risk assessment occurs and that the process is as easy as possible for practitioners. There are some clear practical advantages of using QRISK2 in patients with diabetes – QRISK2 is integrated into all four GP system suppliers and is accepted practice. QRISK2 is also updated annually and so can be recalibrated to changing incidence of CVD events over time. It can also take advantage of improvements of data quality and evolving requirements of NICE and other guidelines. From a clinician's perspective, it makes it easier to have one tool such as QRISK2, which will work for all patients. This is particularly important when there are requirements, for example, to calculate CVD risk in patients who have both diabetes and rheumatoid arthritis. Should clinicians use a tool which includes both variables such as QRISK2 or use one such as UKPDS which ignores the increased risk associated with rheumatoid arthritis? Similarly, CVD risk assessment is required on patients up to the age of 84 years which is possible with QRISK2 but not with UKPDS since UKPDS was derived from patients under the age of 66 years.

A recommendation to stop using QRISK2 in people with diabetes and move to one derived from an unrepresentative hospital population, that is unfamiliar to GPs, cumbersome to use and with a limited range of variables important for individuals, is likely to disrupt the ambition for CVD risk assessment to be a routine part of clinical care.

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7.1 Acknowledgements

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7.2 Contributorship

JHC initiated the study, undertook the literature review, data extraction, data manipulation and primary data analysis and write the first draft of the paper. CC contributed to the design, analysis, interpretation and drafting of the paper. PB contributed to the development of core ideas, the analysis plan, the interpretation of the results and the drafting of the paper.

7.3 Funding

None.

7.4 Competing Interests

JHC is professor of clinical epidemiology at the University of Nottingham and co-director of QResearch[®] – a not-for-profit organisation which is a joint partnership between the University of Nottingham and EMIS (leading commercial supplier of IT for 60% of general practices in the UK). JHC is also director of ClinRisk Ltd which produces open and closed source software to ensure the reliable and updatable implementation of clinical risk algorithms within clinical computer systems to help improve patient care. CC is associate professor of Medical Statistics at the University of Nottingham and a consultant statistician for ClinRisk Ltd. PB has received no financial support for undertaking this work. This work and any views expressed within it are solely those of the co-authors and not of any affiliated bodies or organisations. There are no other relationships or activities that could appear to have influenced the submitted work.
