Effect of competing mortality risks on predictive performance of the QRISK3 cardiovascular risk prediction tool in older people and those with comorbidity: external validation population cohort study

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Summary

Background Primary prevention of cardiovascular disease (CVD) is guided by risk-prediction tools, but these rarely account for the risk of dying from other conditions (ie, competing mortality risk). In England and Wales, the recommended risk-prediction tool is QRISK2, and a new version (QRISK3) has been derived and internally validated. We aimed to externally validate QRISK3 and to assess the effects of competing mortality risk on its predictive performance.

Methods For this retrospective population cohort study, we used data from the Clinical Practice Research Datalink. We included patients aged 25–84 years with no previous history of CVD or statin treatment who were permanently registered with a primary care practice, had up-to-standard data for at least 1 year, and had linkage to Hospital Episode Statistics discharge and Office of National Statistics mortality data. We compared the QRISK3-predicted 10-year CVD risk with the observed 10-year risk in the whole population and in important subgroups of age and multimorbidity. QRISK3 discrimination and calibration were examined with and without accounting for competing risks.

Findings Our study population included 1 484 597 women with 42 451 incident CVD events (4·9 cases per 1000 person-years of follow-up, 95% CI 4·8–4·9), and 1 420 176 men with 53 066 incident CVD events (6·7 cases per 1000 person-years, 6·66–6·78), with median follow-up of 5·0 years (IQR 1·9–9·2). Non-CVD death rose markedly with age (0·4% of women and 0·5% of men aged 25–44 years had a non-CVD death vs 20·1% of women and 19·6% of men aged 75–84 years). QRISK3 discrimination in the whole population was excellent (Harrell’s C-statistic 0·865 in women and 0·834 in men) but was poor in older age groups (<0·65 in all subgroups aged 65 years or older). Ignoring competing risks, QRISK3 calibration in the whole population and in younger people was excellent, but there was significant over-prediction in older people. Accounting for competing risks, QRISK3 systematically over-predicted CVD risk, particularly in older people and in those with high multimorbidity.

Interpretation QRISK3 performed well at the whole population level when ignoring competing mortality risk. The tool performed considerably less well in important subgroups, including older people and people with multimorbidity, and less well again after accounting for competing mortality risk.

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Introduction

Cardiovascular disease (CVD) remains a major cause of morbidity and mortality worldwide despite falling incidences in most high-income countries. Guidelines for the primary prevention of CVD usually recommend the use of risk-prediction tools to target treatment for people above a specified threshold of predicted risk. There has been a progressive reduction in the risk threshold recommended in relation to statin prescription for primary prevention. In England and Wales, the recommended threshold for treatment changed from a 10-year CVD risk of 20% to 10% in 2014, compared with a 7·5% threshold in current US guidelines. These reductions reflect both increasing evidence of statin effectiveness for primary prevention and falling prices, making statins more cost-effective at lower levels of baseline risk. However, age is the most important predictor of CVD risk, and thus most people will exceed current thresholds at some point in early older age (w8 years) irrespective of other risk factors.

Risk-stratified guideline recommendations rely on being able to accurately predict the risk of CVD events. Recommended risk-prediction tools differ between countries, reflecting variations in CVD risk factors and incidence. In England and Wales, the National Institute for Health and Care Excellence recommends the QRISK2 risk-prediction tool, which has been externally validated in UK primary care datasets and found to have...
Research in context

Evidence before this study
Guidelines for the primary prevention of cardiovascular disease (CVD) usually recommend risk-stratified treatment. Decisions to start long-term medication to prevent future CVD events are guided by estimation of CVD risk, with treatment offered if patients exceed a particular risk threshold. Recommended risk-prediction tools vary by country, reflecting differences in CVD risk factors and incidence. The recommended risk-prediction tool in the UK is QRISK, but there are two criticisms of recommended tools: first, they often do not predict risk well in older people and people with multimorbidity and second, they do not account for competing mortality risk (the risk of dying from non-CVD causes). We searched PubMed from inception to Jan 8, 2021, for observational studies in English examining competing mortality risks in people with CVD or in the context of incident CVD risk prediction using the search terms (cardiovascular disease [MeSH Major Topic] AND “competing risk” AND (“heart disease risk factors” [MeSH Terms] OR prediction)). We found 12 relevant studies examining over-estimation of CVD rates during follow-up, in the context of incident CVD in the whole population and in high-risk populations, such as people with atrial fibrillation, and in the context of additional CVD-related events in people with multimorbidity.9,10 This is because survival analyses, from another cause, including older people and those who remain in follow-up (eg, if using the Kaplan-Meier estimator). This assumption is incorrect if someone dies of another condition (competing mortality)

CVD risk-prediction models need to be validated in older people and in people with high multimorbidity. Better CVD risk-prediction models are needed to stratify people who are potentially eligible for primary preventive treatments. Clinicians should consider competing mortality risks and non-CVD life expectancy when discussing statin initiation for primary prevention in older people and in people with high multimorbidity.

Methods
Data source and population
For this population cohort study, we externally validated QRISK3 in the UK Clinical Practice Research Datalink (CPRD) Gold, which does not overlap with the derivation dataset, although it is similar in its inclusion of linked primary care, hospital, and mortality data. Included patients were permanently registered with a primary care practice, contributed up-to-standard data for at least 1 year, and had linkage to Hospital Episode Statistics (HES) discharge data and Office of National Statistics (ONS) mortality data; were aged 25–84 years with no previous history of CVD; and had no history of previous statin treatment. Cohort entry was the latest date of Jan 1, 2004, a patient’s 25th birthday, or contribution of up-to-standard data for at least 1 year. Cohort exit was the date of a first CVD event, death, prescription of a statin (since the main use of the prediction model is to make decisions about statin initiation), deregistration from the primary care practice, date of the last data collection from the practice, or the end of the study on March 31, 2016, whichever came first. All outcomes and predictors were recorded during routine clinical care and were therefore recorded blind to the study hypothesis. This study was approved by the CPRD Independent Scientific Advisory Committee (protocol 16_248).
Outcomes
A first CVD event was defined as the earliest recording of any fatal or non-fatal coronary heart disease, ischaemic stroke, or transient ischaemic attack. Fatal CVD events were identified with codes from the International Classification of Diseases, tenth version (ICD-10), recorded in ONS death registration. Non-fatal events were identified either in primary care electronic health records (using Read codes, the standard coding system used in UK clinics) or HES discharge diagnoses (ICD-10 codes). Read and ICD-10 codes defining outcomes were those used in QRISK3 derivation (appendix p 2).4

Prediction model
We implemented the published QRISK3-2017 prediction model (under GNU Lesser General Public Licence, version 3) with some differences: we chose a later cohort entry date (Jan 1, 2004, rather than Jan 1, 1998), we handled missing cholesterol values differently (if no values were available at baseline, QRISK3 derivation allowed cholesterol values from after the index date to be used if they were measured before any event; instead, we only included values recorded before the index date to avoid using future information in prediction), and we evaluated the Townsend deprivation score as the median of the vigintile (equal 20th) of the score for the area within which an individual lived, as individual values were not available. Predictor code sets used in this study and methods of data handling are detailed in the appendix (pp 3–12, 21–165).

Multimorbidity
For each patient at baseline, we additionally calculated a modified Charlson Comorbidity Index (mCCI) based on primary care Read codes (modified such that CVD could not contribute to the score, as all participants were CVD-free at baseline). The mCCI was not used for prediction but was used to stratify the population to examine discrimination and calibration by mCCI score (grouped into 0, 1, 2, and 3 or more).

Missing data
The extent and management of missing data is detailed in the appendix (p 14). As was done in QRISK3 derivation, patients with missing Townsend deprivation scores were excluded from the cohort, those with missing data on ethnicity were assumed to be White, and multiple imputation was used for missing body-mass index, total cholesterol to HDL cholesterol ratio, systolic blood pressure and its variability, and smoking status. Multivariate imputation by chained equations was used to generate five imputed datasets. We combined analyses of these imputed datasets using Rubin’s rules to give summary point estimates with confidence limits that reflected the added uncertainty associated with imputing missing values. As with QRISK3 derivation, morbidities and prescribing used for prediction were assumed to be absent if not recorded (morbidity and prescribing recording in CPRD is generally good).2,10

Statistical analysis
The study size was determined by the data available in CPRD, which was considered sufficient, and no formal power calculation was done.1

We calculated the 10-year risk of having a cardiovascular event for each patient using the published QRISK3 equation without recalibration. The performance of the risk score was assessed by examining discrimination and calibration in the whole population and in subgroups defined by age group (25–44, 45–64, 65–74, and 75–84 years) and by mCCI score. Discrimination is the ability of the risk score to differentiate between patients who had the event of interest during the study and those who did not. We used the truncated version of Harrell’s C-statistic to only include pairs for which the earliest survival time was no later than 10 years after entry. Where considerable censoring occurs, Harrell’s C-statistic might overestimate discrimination. Therefore, we did a sensitivity analysis using a weighted C-statistic accounting for the probability of censoring.16 A C-statistic of 0·5 indicates discrimination that is no better than chance, whereas a C-statistic of 1 indicates perfect discrimination. Two additional measures of discrimination were calculated: Royston’s D-index (based on the prognostic separation in event-free survival between patients with predicted risk scores higher and lower than the median; higher values of Royston’s D-index indicate greater discrimination)17 and a related $R^2$ statistic estimating the explained variation in the context of censored survival data.18 Calibration refers to how closely the predicted and observed probabilities are similar at group level. This was assessed for equally sized groups of participants ranked by predicted risk. Calibration of the risk score predictions was assessed by plotting observed risk of CVD events against predicted risk. Plots were generated separately by sex, for all patients and for prespecified subgroups of age and mCCI, on the basis of summary statistics pooled across the imputed datasets.

The following summary statistics and their SEs were obtained by decile of predicted risk score and for each imputed dataset in turn: non-parametric measures of observed risk or proportions of patients with a CVD event, the Kaplan-Meier estimator (the conventional measure ignoring competing risks) and the Aalen-Johansen estimator (an extension to allow for competing events, non-CVD death in this case), and the mean predicted risk score. All models were fitted in R, version 4.0.0, and STATA, version 11.2.

Role of the funding source
The study funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
Results

Of the patients assessed aged 25–84 with linkage to HES and ONS, 1,650,188 were women, of whom 165,391 (10.0%) were excluded because of data inconsistencies (1,405 [0.1%]), previous CVD (783,032 [4.7%]), statin prescription (83,357 [5.1%]), or missing deprivation score (2797 [0.2%]); and 1,623,394 were men, of whom 203,218 (12.5%) were excluded because of data inconsistencies (1,815 [0.1%]), previous CVD (1,120,733 [6.9%]), statin prescription (86,656 [5.3%]), or missing deprivation score (2,674 [0.2%]). Therefore, 1,484,597 women and 1,420,176 men were included in this study.

Across most baseline characteristics, the study population and the QRISK3 internal validation cohort were similar (table 1) but, in this study, the prevalence of treated hypertension and current smoking was higher and recorded family history of coronary heart disease was lower. Missing data in this study compared with that in the QRISK3 internal validation cohort was less frequent for ethnicity, similar for systolic blood pressure and body-mass index, and more frequent for total cholesterol to HDL cholesterol ratio, systolic blood pressure variability, and smoking status (appendix p 14).

### Table 1: Baseline data in external validation cohort and in original QRISK3 internal validation cohort

| Characteristic                                | Women External validation cohort (n=1,484,597) | Women Original QRISK3 internal validation cohort (n=1,360,457) | Men External validation cohort (n=1,420,176) | Men Original QRISK3 internal validation cohort (n=1,110,841) |
|-----------------------------------------------|-----------------------------------------------|---------------------------------------------------------------|---------------------------------------------|---------------------------------------------------------------|
| Age, years                                    | 46.0 (15.3)                                   | 42.3 (15.3)                                                  | 44.8 (12.9)                                 | 42.6 (12.8)                                                  |
| Body-mass index                               | 25.9 (5.7)                                    | 25.4 (5.7)                                                  | 26.6 (4.7)                                  | 25.9 (4.2)                                                   |
| Total cholesterol to HDL cholesterol ratio    | 3.7 (1.1)                                     | 3.6 (1.2)                                                   | 4.4 (1.3)                                   | 4.4 (1.3)                                                   |
| Systolic blood pressure, mm Hg                | 125.4 (18.0)                                  | 123.1 (18.1)                                                | 131.1 (16.2)                                | 128.8 (16.2)                                                |
| Systolic blood pressure variability           | 10.0 (5.7)                                    | 9.3 (6.1)                                                   | 10.3 (5.2)                                  | 9.3 (6.8)                                                   |
| Ethnicity                                     |                                               |                                                              |                                             |                                                               |
| White or not recorded                         | 1,363,146 (91.8%)                             | 1,218,391 (89.6%)                                           | 1,336,221 (94.1%)                           | 1,171,281 (89.4%)                                           |
| Indian                                        | 22,488 (1.5%)                                 | 23,464 (1.7%)                                              | 15,322 (1.1%)                               | 26,479 (2.0%)                                               |
| Pakistani                                     | 9,550 (0.6%)                                  | 10,919 (0.8%)                                              | 6,647 (0.5%)                                | 14,787 (1.1%)                                               |
| Bangladeshi                                   | 2,934 (0.2%)                                  | 8,738 (0.6%)                                               | 2,145 (0.2%)                                | 11,914 (0.9%)                                               |
| Other Asian                                   | 13,697 (0.9%)                                 | 17,078 (1.3%)                                              | 9,973 (0.7%)                                | 15,566 (1.2%)                                               |
| Black Caribbean                               | 9,055 (0.6%)                                  | 13,142 (1.0%)                                              | 6,687 (0.5%)                                | 10,642 (0.8%)                                               |
| Black African                                 | 18,804 (1.3%)                                 | 27,678 (2.0%)                                              | 12,822 (0.9%)                               | 25,251 (1.9%)                                               |
| Chinese                                       | 6,739 (0.5%)                                  | 8,992 (0.7%)                                               | 3,503 (0.2%)                                | 6,098 (0.5%)                                                |
| Other                                         | 38,074 (2.6%)                                 | 32,373 (2.4%)                                              | 26,829 (1.9%)                               | 28,423 (2.2%)                                               |
| Smoking status (% of non-missing)             |                                               |                                                              |                                             |                                                               |
| Non-smoker                                    | 70,774 (59.8%)                                | 70,671 (51.9%)                                              | 478,671 (49.0%)                             | 512,252 (39.1%)                                             |
| Former smoker                                 | 217,404 (18.4%)                               | 194,545 (14.3%)                                             | 216,883 (22.2%)                             | 196,459 (15.0%)                                             |
| Light smoker                                  | 85,277 (7.2%)                                 | 154,565 (11.4%)                                             | 75,260 (7.7%)                               | 177,693 (13.6%)                                             |
| Moderate smoker                               | 111,690 (9.4%)                                | 74,933 (5.5%)                                              | 112,411 (11.5%)                             | 84,914 (6.5%)                                               |
| Heavy smoker                                  | 62,236 (5.3%)                                 | 38,218 (2.8%)                                              | 91,457 (9.6%)                               | 64,107 (9.4%)                                               |
| Family history of CHD*                        | 97,624 (6.6%)                                 | 164,023 (12.1%)                                             | 75,237 (5.3%)                               | 121,039 (9.4%)                                              |
| Type 1 diabetes                               | 3752 (0.3%)                                   | 3351 (0.2%)                                                | 4843 (0.3%)                                 | 3932 (0.3%)                                                 |
| Type 2 diabetes                               | 17,022 (1.3%)                                 | 15,872 (1.2%)                                              | 21,077 (1.5%)                               | 19,218 (1.5%)                                               |
| Treated hypertension                          | 115,944 (7.8%)                                | 77,694 (5.7%)                                              | 82,768 (5.8%)                               | 56,920 (4.3%)                                               |
| Rheumatoid arthritis                          | 12,702 (0.9%)                                 | 15,129 (1.1%)                                              | 4,724 (0.3%)                                | 7,055 (0.5%)                                                |
| Atrial fibrillation                           | 8199 (0.6%)                                   | 5229 (0.4%)                                                | 10,620 (0.7%)                               | 6,874 (0.5%)                                                |
| Chronic kidney disease (stage 3, 4, or 5)     | 69,185 (0.5%)                                 | 69,498 (0.5%)                                              | 5,659 (0.4%)                                | 4,322 (0.3%)                                                |
| Migraine                                      | 117,672 (7.9%)                                | 89,504 (6.6%)                                              | 41,471 (3.2%)                               | 36,141 (2.8%)                                               |
| Corticosteroid use                            | 206,714 (14.4%)                               | 311,775 (23.2%)                                             | 11,824 (0.8%)                               | 18,634 (1.4%)                                               |
| HIV or AIDS                                   | 289 (0.1%)                                    | 1595 (0.1%)                                                | 445 (<0.1%)                                 | 2945 (<0.2%)                                                |
| Systemic lupus erythematosus                  | 1725 (0.1%)                                   | 3349 (0.1%)                                                | 165 (<0.1%)                                 | 134 (<0.1%)                                                 |
| Atypical antipsychotic use                    | 8469 (0.6%)                                   | 6268 (0.5%)                                                | 8336 (0.6%)                                 | 6597 (0.5%)                                                 |
| Severe mental illness                         | 110,793 (7.5%)                                | 94,724 (7.0%)                                              | 57,264 (4.0%)                               | 57,830 (4.4%)                                               |
| Erectile dysfunction diagnosis or treatment   | NA                                            | NA                                                          | 39,264 (2.8%)                               | 31,136 (2.4%)                                               |

Data are mean (SD) or n (%). CHD=coronary heart disease. NA=not applicable. *In a first-degree relative younger than 60 years.
42,451 incident cases of CVD were observed in women during 8,594,620 years of follow-up (4·9 cases per 1000 person-years, 95% CI 4·89–4·99), compared with 51,066 incident cases in men during 7,896,704 years of follow-up (6·7 cases per 1000 person-years, 6·66–6·78). CVD incidence rose progressively with age (appendix p 15) and was moderately lower than that observed in QRISK3 derivation.

Median follow-up in the whole cohort was 5·0 years (IQR 1·9–9·2), with older participants and people with higher multimorbidity. Censoring due to non-CVD death was more common in younger, than in older, participants and the group with highest multimorbidity (mCCI ≥3).

Overall discrimination was excellent and similar to that of QRISK3 internal validation for women, Harrell’s C-statistic 0·865 for external validation vs 0·880 for internal validation, D 2·43 vs 2·49, R² 58% vs 59·6%; for men, Harrell’s C-statistic 0·834 vs 0·858, D 2·10 vs 2·26, R² 51·3% vs 55·0%; table 3). However, discrimination varied markedly within the age group and mCCI categories, with discrimination being best in the youngest group (25–44 years) and the group with lowest multimorbidity (mCCI 0) and worst in the oldest group (75–84 years) and the group with highest multimorbidity (mCCI ≥3). Sensitivity analysis using a censoring-adjusted C-statistic found a somewhat lower discrimination than in the main analysis, but did not alter the overall interpretation (appendix p 16).

Ignoring competing mortality risks, calibration was excellent for women overall, and also excellent for
women aged 25–44 years (figure 1; appendix pp 17–18). However, QRISK3 over-predicted CVD risk in older age groups. When stratifying by mCCI, we found evidence of some over-prediction in the group with lowest multimorbidity (mCCI 0) and poor calibration and under-prediction in patients with highest multimorbidity (mCCI ≥3).

When competing mortality risks were accounted for (figure 1), we observed over-prediction of risk at higher levels of predicted CVD risk in all women. The same pattern of increasing over-prediction with increasing age was observed, but in greater magnitude, and calibration was poor in older age groups. Although we observed some under-prediction of risk in patients with mCCI scores of 3 or higher for those at lower predicted CVD risk, the overall pattern was over-prediction of CVD risk, which increased with multimorbidity, and poor calibration in the groups with highest multimorbidity (mCCI 2 and ≥3).

Ignoring competing mortality risks, calibration was excellent for all men, although with somewhat greater over-prediction at higher levels of predicted CVD risk in all women. The same pattern of increasing over-prediction with increasing age was observed, but in greater magnitude, and calibration was poor in older age groups. Although we observed some under-prediction of risk in patients with mCCI scores of 3 or higher for those at lower predicted CVD risk, the overall pattern was over-prediction of CVD risk, which increased with multimorbidity, and poor calibration in the groups with highest multimorbidity (mCCI 2 and ≥3).

When competing mortality risks were accounted for (figure 2), we observed over-prediction of risk at higher levels of predicted CVD risk in all men. Calibration was excellent for men aged 25–44 years, but QRISK3 progressively over-predicted CVD risk with increasing age. We observed evidence of some over-prediction in the group with lowest multimorbidity (mCCI 0) and poor calibration and under-prediction in the group with highest multimorbidity (mCCI ≥3).

When competing mortality risks were accounted for (figure 2), we observed over-prediction of risk at higher levels of predicted CVD risk in all men. Calibration was poor, with large over-prediction in older age groups. Although we observed some under-prediction of risk in patients with mCCI scores of 3 or higher for those at lower predicted CVD risk, the overall pattern was over-prediction of CVD risk, which increased with multimorbidity, and poor calibration in the groups with highest multimorbidity (mCCI 2 and ≥3).

### Discussion

This external validation study found that, at the whole population level, QRISK3 had excellent discrimination overall (the ability of the model to distinguish people at higher or lower risk. However, as is expected when examining discrimination in subsets of the modelled population, discrimination was moderate at best in older people and in people with high levels of multimorbidity. Calibration (the extent to which predicted and observed event rates are similar) was excellent in the whole population when ignoring competing mortality risks, but we found evidence of systematic over-prediction of CVD risk after competing risks were accounted for. Calibration was considerably worse in older people and in those with higher levels of multimorbidity, for whom QRISK3 systematically over-predicted risk, particularly after competing mortality risks were accounted for.

At the whole population level, QRISK3 does appropriately sort the whole population into groups with varying levels of cardiovascular risk (with some small over-prediction), but the model performs relatively poorly in older people and people with high multimorbidity, partly because of high competing mortality risk.

The strengths of our study include methodological conduct consistent with recommendations, comprehensive detailing of all code sets to facilitate replication, and explicit assessment of prediction in subgroups and competing mortality risks.

The limitations of this study largely reflect problems common to all studies using routine primary care data, including the original QRISK3 derivation. The prevalence of missing data for key predictors was high. As was done in the original QRISK3 derivation, we used multiple imputation for missing data but, in this context, the assumption that data are missing at random is a strong one because risk factors are plausibly more likely to be measured in people at higher risk (as observed in other studies). However, this limitation of routine data compared with research

### Table 3: Discrimination and model fit

| Age group, years | Harrell's C (95% CI) | Royston's D (95% CI) | R² (95% CI) |
|------------------|----------------------|----------------------|-------------|
| All patients     | 0.865 (0.861–0.868)  | 2.43 (2.41–2.45)     | 58.5% (58.1–58.8) |
| 25–44            | 0.758 (0.747–0.769)  | 1.69 (1.63–1.76)     | 40.7% (38.8–42.5) |
| 45–64            | 0.707 (0.702–0.713)  | 1.25 (1.22–1.28)     | 27.2% (26.1–28.3) |
| 65–74            | 0.641 (0.635–0.647)  | 0.82 (0.77–0.86)     | 13.7% (12.4–15.1) |
| 75–84            | 0.611 (0.605–0.616)  | 0.61 (0.56–0.66)     | 8.1% (6.9–9.3 )  |
| 0                | 0.863 (0.859–0.867)  | 2.40 (2.38–2.43)     | 57.9% (57.4–58.4) |
| 1                | 0.846 (0.840–0.852)  | 2.20 (2.17–2.24)     | 53.6% (52.8–54.4) |
| 2                | 0.789 (0.788–0.799)  | 1.73 (1.67–1.78)     | 41.6% (39.9–43.2) |
| ≥3               | 0.744 (0.728–0.760)  | 1.40 (1.32–1.48)     | 31.8% (29.2–33.4) |

mCCI=modified Charlson Comorbidity Index.
cohort with fewer missing data is balanced by routine data cohorts being more representative. All recent QRISK models have also used Jan 1, 1998, as the index date (the earliest that patients can enter the study). Therefore, much observed follow-up in model derivation is historical, and there is a trade-off between using an index date in the distant past (when CVD incidence was higher than it presently is) or a more recent index date (in which case more patients are excluded because of previous statin use). Our choice of a more recent index date might partly explain why QRISK3 was observed to over-predict risk in our validation. Deriving clinical prediction tools on increasingly historical data is probably biased, but using more recent data with greater rates of previous statin initiation might also be biased. There is clearly no optimal resolution to this dilemma. Finally, loss to follow-up before a CVD event was common, which is

Figure 1: Calibration in women without accounting for competing risks (left) and accounting for competing risks (right)
CVD=cardiovascular disease. mCCI=modified Charlson Comorbidity Index. *Observed risk was based on the Kaplan-Meier estimator, which does not account for competing mortality risk. †Observed risk was based on the Aalen-Johansen estimator, which accounts for competing mortality risk.
relevant to model assumptions about censored patients. We specifically examined the effect of censoring due to non-CVD death, but it is also an assumption that those who deregistered from practices had the same CVD risk as those who did not. This seems likely to be the case for younger people, but less so for older people, for whom change of address will be more commonly driven by change in health status (eg, moving to sheltered housing or a care home).

External validations of previous QRISK tools have also found excellent discrimination and calibration at the whole population level when competing mortality risks were ignored (ie, answering the question of what the risk of CVD is, assuming this person does not die of anything else in the following 10 years). Our findings are comparable at the whole population level (ignoring competing risks) but even so, calibration was poor in patients aged 75–84 years and only moderate in those

Figure 2: Calibration in men without accounting for competing risks (left) and accounting for competing risks (right)
CVD=cardiovascular disease. mCCI=modified Charlson Comorbidity Index. *Observed risk was based on the Kaplan-Meier estimator, which does not account for competing mortality risk. †Observed risk was based on the Aalen-Johansen estimator, which accounts for competing mortality risk.
aged 65–74 years and in those with the highest levels of multimorbidity (mCCI ≥3).

We observed greater over-prediction at the whole population level once competing mortality risk was accounted for. Calibration was notably poorer once competing risk was accounted for, particularly in older patients and those with higher multimorbidity. These findings are consistent with other studies examining the effect of competing risks on estimated CVD risk in people without CVD,25,26,27,28 with established CVD,27 and in other contexts, including stroke risk in people with atrial fibrillation.39,40 QRISK2 has also been shown to systematically over-predict CVD risk in a contemporary population of people with type 2 diabetes, with increasingly poor discrimination with increasing age, highlighting that good performance at the whole population level does not necessarily mean good performance in important subgroups.29,30

At the population level, QRISK3 does segment the population into groups in which the observed risk of CVD is very similar to the predicted risk (supporting its use to guide risk-stratified treatment decisions). However, this overall assessment of prediction performance was largely driven by good performance in younger people with fewer coexisting long-term conditions. For older people and people with more long-term conditions, prediction was poor to fair, particularly when competing risks were accounted for. Still, even the lower degree of over-prediction observed in younger and less multimorbid groups can also sometimes change treatment recommendations. Similar issues probably apply to other CVD risk-prediction models that do not account for competing risk. We believe that predicting CVD events without accounting for risk of death from other causes is misleading, particularly in people at high risk of non-CVD death. Therefore, clinicians should carefully consider life expectancy related to other conditions when discussing long-term cardiovascular primary preventive treatment.

Further research would be beneficial in several areas. CVD causes a large proportion of deaths in many high-income countries, which will reduce the effect of competing risks. Additional studies are needed to examine the effect of competing risk when predicting less fatal conditions, for which the effect on predictive performance is likely to be greater. It is also uncertain whether a better approach to CVD prediction would be to create separate models for important subgroups of age and multimorbidity (as is already done for sex), not least because the relationship between classic CVD risk factors and CVD might weaken with age. Further research is needed to evaluate the relative merits of omnibus versus subgroup models, and to better quantify the uncertainty at the individual level of risk-prediction tools that perform well at a population level.29,30 A weakness of existing UK primary care datasets in deriving risk-prediction rules is the large loss to follow-up when there is a long time horizon for risk prediction. This study has examined the effect of competing risk, but loss to follow-up due to practice deregistration is likely to create over-prediction in at least some population subsets. External validation in large geographical populations with lower loss to follow-up (such as the SAIL Databank in Wales) would be valuable, as would larger-scale data federation to derive and validate new risk-prediction tools for comparison with QRISK3 and other prediction models.31 New risk prediction tools could also usefully include statin treatment at baseline in prediction, in the way that QRISK3 includes antihypertensive treatment in prediction.4 Finally, the value of risk-factor treatment in older people with multimorbidity and co-prescribing who are routinely excluded from trials could be usefully clarified with targeted randomised controlled trials.32

In conclusion, QRISK3 performs well at the whole population level but systematically over-predicts CVD risk in older people and people with high multimorbidity. Clinicians should consider broader effects on life expectancy when discussing statin initiation for primary prevention in older people and people with high multimorbidity, in whom CVD risk is likely to be over-predicted. Better calibrated prediction models are needed in these groups.

Contributors
The study was conceived of and designed by BG, KP, DRM, PTD, and AJT who obtained the funding. All authors contributed to study design and interpretation. SL, BG, DRM, and PTD led data management and SL led the analysis, supported by BG, DRM, and PTD. SL and BG drafted the paper, which all authors reviewed and edited. SL, BG, and DRM verified the underlying data. The corresponding author had full access to all the data and the final responsibility to submit for publication.

Declaration of interests
PTD reports a grant from AbbVie, outside the submitted work, and is a member of the NHS Scottish Medicines Consortium. J-HY is currently employed by ICON PLC Clinical Research. DRM reports grants from the Chief Scientist Office, Health Data Research UK, and National Institute for Health Research, outside the submitted work. All other authors declare no competing interests.

Data sharing
The data controller is the CPRD and, under the data licence granted, we are not allowed to share data. Researchers can apply to CPRD directly for access to the raw data.

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