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SHORT COMMUNICATION

# Level of agreement between frequently used cardiovascular risk calculators in people living with HIV

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**Objectives**

The aim of the study was to describe agreement between the QRISK2, Framingham and Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) cardiovascular disease (CVD) risk calculators in a large UK study of people living with HIV (PLWH).

**Methods**

PLWH enrolled in the Pharmacokinetic and Clinical Observations in People over Fifty (POPPY) study without a prior CVD event were included in this study. QRISK2, Framingham CVD and the full and reduced D:A:D CVD scores were calculated; participants were stratified into 'low' (< 10%), 'intermediate' (10–20%) and 'high' (> 20%) categories for each. Agreement between scores was assessed using weighted kappas and Bland–Altman plots.

**Results**

The 730 included participants were predominantly male (636; 87.1%) and of white ethnicity (645; 88.5%), with a median age of 53 [interquartile range (IQR) 49–59] years. The median calculated 10-year CVD risk was 11.9% (IQR 6.8–18.4%), 8.9% (IQR 4.6–15.0%), 8.5% (IQR 4.8–14.6%) and 6.9% (IQR 4.1–11.1%) when using the Framingham, QRISK2, and full and reduced D:A:D scores, respectively. Agreement between the different scores was generally moderate, with the highest level of agreement being between the Framingham and QRISK2 scores (weighted kappa = 0.65) but with most other kappa coefficients in the 0.50–0.60 range.

**Conclusions**

Estimates of predicted 10-year CVD risk obtained with commonly used CVD risk prediction tools demonstrate, in general, only moderate agreement among PLWH in the UK. While further validation with clinical endpoints is required, our findings suggest that care should be taken when interpreting any score alone.

**Keywords:** agreement, cardiovascular risk prediction, Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) risk score, Framingham, HIV, QRISK2

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*See Appendix for the members of the Pharmacokinetic and Clinical Observations in People over Fifty (POPPY) study group.

## Introduction

As the population of people living with HIV (PLWH) has aged, awareness of the impact of noninfectious causes of morbidity in this group has increased. In particular, cardiovascular disease (CVD) has been reported to occur more frequently, with European guidelines now recommending routine screening for CVD in PLWH [1,2].

The Framingham CVD calculator [3] was the first CVD risk algorithm to be adopted for widespread use in the general population, incorporating information on age, gender, smoking, total and high-density lipoprotein (HDL) cholesterol, systolic blood pressure, treatment for hypertension and type 2 diabetes. In the UK, the National Institute for Health and Care Excellence (NICE) recommends use of the QRISK2 calculator [4] as it is applicable to a wider age range than the Framingham calculator (30–84 years) and as the Framingham calculator may overestimate CVD risk in UK populations [5,6]. QRISK2 additionally incorporates information on ethnicity, body mass index (BMI), a history of angina or myocardial infarction (MI) in a first-degree relative, an individual's own history of rheumatoid arthritis, chronic kidney disease or atrial fibrillation, and the Townsend deprivation index (based on a person's postcode).

While the British HIV Association (BHIVA) recommends use of the QRISK2 calculator for PLWH aged > 40 years, both QRISK2 and Framingham reportedly underestimate risk in PLWH [6,7]. The risk equation estimated in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study is the only current CVD risk calculator derived specifically for PLWH, additionally taking into consideration an individual's CD4 count and history of antiretroviral treatment (ART) use, particularly cumulative exposure to protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) and current use of abacavir [7]. A reduced version of the D:A:D CVD calculator is also available which does not incorporate ART use. While the agreement between different CVD risk scores and clinical outcomes has been assessed in several studies, information within a UK population of PLWH is limited. In particular, QRISK2 has been shown to generate a higher risk score than Framingham in some small UK studies [8,9], although these findings have not been consistently reported [10]. In HIV-negative individuals, agreement between the QRISK2 and Framingham risk calculators was good in individuals at low risk but weakened as risk increased [11].

We describe the level of agreement between the QRISK2, Framingham CVD and D:A:D CVD risk calculators in a large UK study of PLWH.

## Methods

Two groups of PLWH (older PLWH aged ≥ 50 years and younger PLWH aged 18–50 years) were prospectively enrolled in the Pharmacokinetic and Clinical Observations in People over Fifty (POPPY) study, a multicentre observational study to examine the effects of ageing and clinical outcomes of PLWH in the UK and Ireland [12]. Inclusion criteria are: documented HIV infection, self-defined white or black African ethnicity, likely route of infection via sexual exposure, and the ability to comprehend the information leaflet. The younger group of PLWH was frequency matched on gender, ethnicity, sexual orientation and geographical location to the older PLWH. The study also recruited a group of HIV-negative individuals aged ≥ 50 years, who were excluded from present analyses. Individuals were recruited to the study from April 2013 to January 2016 and are seen approximately annually for follow-up visits; only the baseline data were used in the present analyses. The study was approved by the UK National Research Ethics Service (NRES; Fulham, London, UK; reference number 12/LO/1409) and participants provided written informed consent.

Eligible individuals were required to have complete information for the calculation of each risk calculator. Analyses were restricted to individuals aged > 40 years to ensure that the Framingham risk calculator was valid, and individuals who had previously experienced an MI or stroke were excluded. As the POPPY study does not capture information on postcode, QRISK2 scores were calculated assuming that postcode was unavailable. However, as a sensitivity analysis, the score was also calculated using the postcode of the participant's hospital as a surrogate (participants from Mater Misericordiae University Hospital Dublin, Ireland, a non-UK site with no postcode, were excluded from this sensitivity analysis). The published D:A:D score [7] generates an estimate of an individual's five-year risk of CVD; for consistency, 10-year scores were generated using the model previously described [7] but with the absolute 10-year survival risk (0.9697) replacing the published absolute five-year survival risk (0.9853) (M. Law, personal communication).

Participants were stratified into 'low' (< 10%), 'intermediate' (10–20%) and 'high' (> 20%) risk categories for each score. The weighted kappa coefficient was calculated to determine agreement between pairs of risk scores, with moderate agreement defined as a kappa of 0.41–0.60, and substantial agreement as a kappa of 0.61–0.80 [13]. Absolute values of each score were assessed for significance using unpaired *t*-tests and Bland–Altman plots [14].

## Results

Of the 1073 PLWH participating in the POPPY study, 912 were aged > 40 years at recruitment and had not had a prior MI or stroke. Of these, the 730 (80.0%) with complete data for calculation of all scores were included; the majority of those excluded from analyses were missing information on total and/or HDL cholesterol.

Included participants were predominantly male (636; 87.1%) and of white ethnicity (645; 88.5%), with a median age of 53 [interquartile range (IQR) 49–59] years. Current smoking was reported by 178 (24.4%) and 258 (35.3%) were ex-smokers. The median systolic blood pressure was 129 (IQR 118–140) mmHg; 102 (14.0%) reported receiving anti-hypertensive medication. The median total and HDL cholesterol concentrations were 4.9 (IQR 4.2–5.5) and 1.2 (IQR 1.0–1.5) mmol/L, respectively, and the median BMI was 25.6 (IQR 23.4–28.3) kg/m$^2$. Forty-four (6.0%), two (0.3%), eight (1.1%) and one (0.1%) of the participants had diabetes, an estimated glomerular filtration rate (eGFR) of ≤ 30 mL/min/1.73 m$^2$, atrial fibrillation and rheumatoid arthritis, respectively. Of the HIV parameters, the median CD4 count was 630 (IQR 470–807) cells/μL, 693 (94.9%) had ever received NRTIs for a median of 9.4 (IQR 4.8–14.3) years, 431 (59.0%) had ever received PIs for a median of 6.4 (IQR 2.8–11.1) years, and 97 (13.3%) were currently receiving abacavir.

The median calculated 10-year CVD risk was 11.9% (IQR 6.8–18.4%) using the Framingham risk score, 8.9% (IQR 4.6–15.0%) using QRISK2, 8.5% (IQR 4.8–14.6%) using the full D:A:D score and 6.9% (IQR 4.1–11.1%) using the reduced D:A:D score (Table 1). The estimated 10-year CVD risk was a mean of 3.0%, 2.7% and 5.7% higher when calculated using the Framingham score than when calculated using the QRISK2 and full and reduced D:A:D scores, respectively. In turn, the estimated 10-year CVD risk was 2.7% higher, on average, when calculated using QRISK2 than when calculated using the reduced D:A:D score, although no significant difference was seen compared with the full D:A:D score. Finally, the estimated 10-year risk was 3.0% higher, on average, when generated using the full D:A:D score than when generated using the reduced D:A:D score.

Overall, the numbers of individuals categorized as being at intermediate or high CVD risk, respectively, were 276 (37.8%) and 157 (21.5%) using the Framingham score, 228 (31.2%) and 99 (13.6%) using QRISK2, 196 (26.9%) and 108 (14.8%) using the full D:A:D score, and 183 (25.1%) and 37 (5.1%) using the reduced D:A:D score. Agreement between scores was generally moderate, with the highest level of agreement being between the Framingham and QRISK2 scores (weighted kappa = 0.65) but with most other kappa coefficients in the 0.50–0.60 range. All figures suggested greater discrepancies between scores as risk increased (Fig. 1). Stratification by age group (Table S1) did not reveal any trend towards improved agreement in older individuals.

After excluding Irish participants without a UK postcode, the median calculated QRISK2 10-year CVD risk in the remaining 693 participants was 10.6% (IQR 5.8–17.3%), with 328 (47.3%), 242 (34.9%) and 123 (17.8%) classified as being at low, intermediate and high CVD risk, respectively. Weighted kappa was 0.70 [95% confidence interval (CI) 0.66–0.74] with Framingham, 0.60 (95% CI 0.55–0.64) with the full D:A:D score, and 0.51

**Table 1** Estimates obtained using different cardiovascular risk equations, and agreement between equations

| | Cardiovascular risk score | | | |
|---|---|---|---|---|
| | Framingham | QRISK2 | D:A:D full | D:A:D reduced |
| 10-year % risk score [median (IQR)] | 11.9 (6.8–18.4) | 8.9 (4.6–15.0) | 8.5 (4.8–14.6) | 6.9 (4.1–11.1) |
| Cardiovascular risk classification [*n* (%)] | | | | |
| Low (< 10%) | 297 (40.7) | 403 (55.2) | 426 (58.4) | 510 (69.9) |
| Intermediate (10–20%) | 276 (37.8) | 228 (31.2) | 196 (26.9) | 183 (25.1) |
| High (> 20%) | 157 (21.5) | 99 (13.6) | 108 (14.8) | 37 (5.1) |
| Agreement between scores (difference calculated as column score minus row score) | | | | |
| Framingham | | | | |
| Difference in predicted 10-year risk (%) [mean (SD)] | - | −3.00 (4.50); $P = 0.0004$ | −2.66 (6.33); $P = 0.0001$ | −5.66 (4.94); $P = 0.0001$ |
| Weighted kappa (95% CI) | | 0.65 (0.61–0.69) | 0.53 (0.49–0.58) | 0.41 (0.37–0.45) |
| QRISK2 | | | | |
| Difference in predicted 10-year risk (%) [mean (SD)] | - | - | 0.34 (6.34); $P = 0.15$ | −2.66 (4.38); $P = 0.0001$ |
| Weighted kappa (95% CI) | | | 0.60 (0.55–0.64) | 0.60 (0.56–0.65) |
| D:A:D full | | | | |
| Difference in predicted 10-year risk (%) [mean (SD)] | - | - | - | −3.00 (5.59); $P = 0.0001$ |
| Weighted kappa (95% CI) | | | | 0.58 (0.53–0.63) |

CI, confidence interval; D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs; IQR, interquartile range; SD, standard deviation.

(95% CI 0.47–0.56) with the reduced D:A:D score, indicating moderate to substantial agreement.

## Discussion

Our findings show that estimates of predicted 10-year CVD risk obtained with CVD risk prediction tools commonly used in the UK are, in general, only in moderate agreement among a large UK population of PLWH. In contrast to previous small UK studies, estimates of CVD risk based on the Framingham equation were significantly higher than those based on the QRISK2 equation, which is recommended for use in the UK in this population.

While the QRISK2 algorithm is based on UK health care data and is often preferred for this reason, the D:A:D equations additionally take into consideration other predictors of CVD among PLWH, including exposure to specific antiretroviral drugs and immunosuppression, factors previously demonstrated to be associated with CVD risk [15–17]. Our findings suggest that the full D:A:D risk equation provides similar scores at a population level to those of QRISK2, although with only moderate agreement between these scores. While an optimal analysis would include an assessment of the association between the predicted scores and absolute CVD risk based on clinical endpoints, the average age of POPPY participants and the low expected incidence of CVD in this group mean that such an analysis is unlikely to be feasible, at least in the short term. Thus, while we are unable to comment on the reliability of these scores for identifying those at genuinely high CVD risk, the inclusion of HIV-specific factors in the D:A:D model provides support for its use in this population.

In 2017, an updated version of the QRISK calculator, QRISK3, was released [18]. Contrary to expectations, the presence of HIV/AIDS did not reach statistical significance in the model because of the low number of PLWH registered in the database, and HIV/AIDS was therefore not included in the final model. Although the contribution of HIV itself to CVD risk remains unclear [19], it is likely that incomplete ascertainment of HIV status among individuals attending the primary care practices included in the data set may have reduced the study power to determine an association with HIV infection.

We note that the three risk equations evaluate slightly different composite endpoints. For example, while QRISK2 evaluates an endpoint that includes angina, MI, stroke and transient ischaemic attack, the Framingham CVD risk score additionally incorporates coronary death, coronary insufficiency, peripheral arterial disease and heart failure into the endpoint, whereas the D:A:D scores consider an endpoint comprising MI, stroke, invasive cardiovascular procedures and sudden coronary deaths only. Thus, we would expect some difference in predicted risk between the three equations, with predicted risks for QRISK2 being somewhat lower than those based on Framingham and potentially higher than those based on the D:A:D scores. Thus, our reported differences are consistent with, although somewhat greater than, these expectations.

A proportion of POPPY participants were excluded from our analyses as information was not available on some key factors. This was, however, largely a result of

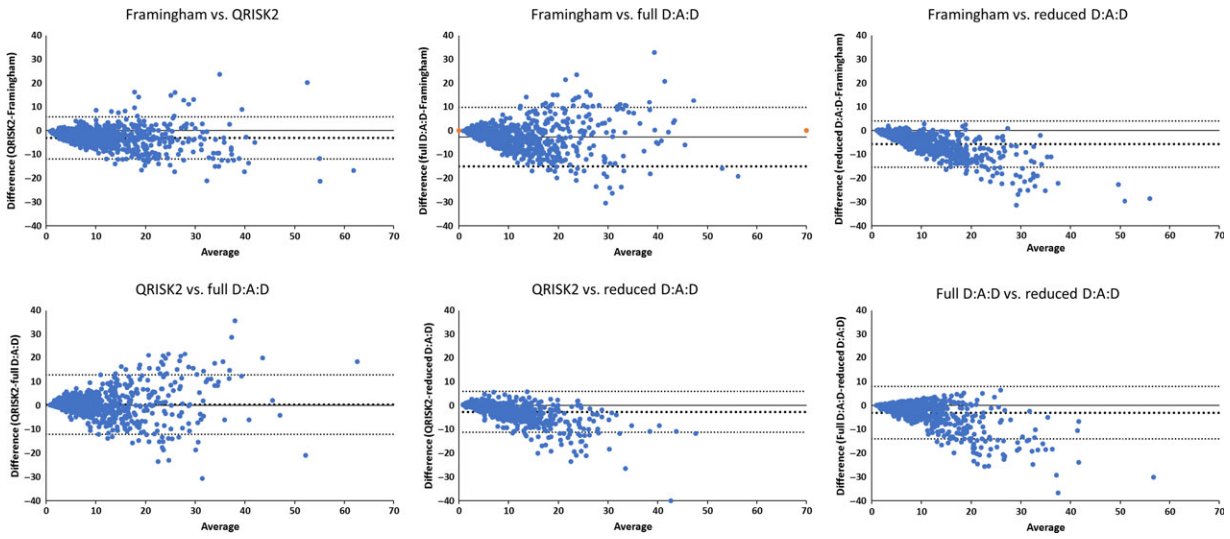


**Fig. 1** Bland–Altman plots showing levels of agreement between the four cardiovascular disease risk scores. D:A:D, Data Collection on Adverse Events of Anti-HIV Drugs.

cholesterol levels being unavailable from one participating clinic, and thus is unlikely to have introduced substantial bias. Although our primary analyses used the version of QRISK2 that did not require individual postcodes, similar findings were obtained when we utilized the hospital postcode as a surrogate measure. POPPY participants are of white or black African ethnicity, and the majority of participants are men, reflecting the epidemiology of HIV in this age group in the UK. While we performed some stratified analyses by age group, our sample is too small to reliably stratify by either gender or ethnicity, and we cannot, therefore, comment on predicted CVD risk in specific gender/ethnicity subgroups. Furthermore, the published D:A:D risk score was extrapolated to give a 10-year rather than five-year risk prediction, which may introduce errors, particularly as cumulative exposures to some ART drugs in the POPPY study may exceed those in the D:A:D data set used to generate the scores.

In summary, around 15% of PLWH aged > 40 years in our UK study had a high predicted 10-year risk of CVD based on either the QRISK2 or full D:A:D scores, supporting the monitoring of CVD risk and provision of CVD risk reduction strategies as part of routine care. While a similar proportion of individuals were predicted to have a high CVD risk, agreement between the two equations was only moderate and thus care should be taken when interpreting either score alone.

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*Conflicts of interest:* CAS has received funding from Gilead Sciences, ViiV Healthcare and Janssen-Cilag for membership of data safety and monitoring boards, advisory boards and speaker panels and for the preparation of educational materials. FP has received research grants from Gilead Sciences and ViiV Healthcare, and funding from Gilead Sciences, ViiV Healthcare, Merck Sharp and Dohme and Janssen-Cilag for membership of advisory boards and speaker panels and/or for the preparation of educational materials. MB has received speaking fees from Gilead Sciences, Merck Sharp and Dohme and Janssen-Cilag, advisory fees from ViiV Healthcare, Gilead Sciences and Merck Sharp and Dohme, honoraria from Gilead Sciences for membership of a speaker bureau and a travel grant from Gilead Sciences, and has been the principal investigator in clinical trials sponsored by Gilead Sciences, ViiV Healthcare, Mylan, Janssen-Cilag and Bristol-Myers Squibb. JA has received grants, personal fees and nonfinancial support from Gilead Sciences, Merck Sharp and Dohme, Janssen-Cilag and Bristol-Myers Squibb, and nonfinancial support from ViiV Healthcare. PWM has received funding for membership of advisory boards and speaker panels, and preparation of educational materials, and/or research grants to his institution from Gilead Sciences, ViiV Healthcare, Bristol-Myers Squibb, Merck Sharp and Dohme, Abbvie and Janssen-Cilag. AW has received honoraria or research grants from ViiV Healthcare, Gilead Sciences, Bristol-Myers Squibb, Merck Sharp and Dohme and Janssen-Cilag. EB, MS, IW, JV, MJ and DB have nothing to declare.

## Appendix

*POPPY Management Team:* Daphne Babalis, Marta Boffito, Amalia Ndoutoumou, Paddy Mallon, Frank Post, Caroline Sabin, Memory Sachikonye and Alan Winston.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** Weighted kappa statistics stratified by age group