Estimation of 10-Year Risk of Coronary Heart Disease in Nepalese Patients with Type 2 Diabetes: Framingham Versus United Kingdom Prospective Diabetes Study

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Abstract

Background: Predicting future coronary heart disease (CHD) risk with the help of a validated risk prediction function helps clinicians identify diabetic patients at high risk and provide them with appropriate preventive medicine. Aim: The aim of this study is to estimate and compare 10-year CHD risks of Nepalese diabetic patients using two most common risk prediction functions: The Framingham risk equation and United Kingdom Prospective Diabetes Study (UKPDS) risk engine that are yet to be validated for Nepalese population. Patients and Methods: We conducted a hospital-based, cross-sectional study on 524 patients with type 2 diabetes. Baseline and biochemical variables of individual patients were recorded and CHD risks were estimated by the Framingham and UKPDS risk prediction functions. Estimated risks were categorized as low, medium, and high. The estimated CHD risks were compared using kappa statistics, Pearson’s bivariate correlation, Bland-Altman plots, and multiple regression analysis. Results: The mean 10-year CHD risks estimated by the Framingham and UKPDS risk functions were 17.7 ± 12.1 and 16.8 ± 15 (bias: 0.88, P > 0.05), respectively, and were always higher in males and older age groups (P < 0.001). The two risk functions showed moderate convergent validity in predicting CHD risks, but differed in stratifying them and explaining the patients’ risk profile. The Framingham equation predicted higher risk for patients usually below 70 years and showed better association with their current risk profile than the UKPDS risk engine. Conclusions: Based on the predicted risk, Nepalese diabetic patients, particularly those associated with increased numbers of risk factors, bear higher risk of future CHDs. Since this study is a cross-sectional one and uses externally validated risk functions, Nepalese clinicians should use them with caution, and preferably in combination with other guidelines, while making important medical decisions in preventive therapy of CHD.

Keywords: Convergent validity, coronary heart disease, framingham risk equation, Nepal, risk prediction, type 2 diabetes, UKPDS risk engine

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Introduction

Type 2 diabetes mellitus, once considered a disease of the affluent world, is reaching an endemic scale in Nepal leading to an increased burden on the national healthcare system. Patients with type 2 diabetes bear up to sixfold higher risk of future coronary heart diseases (CHDs), equivalent to nondiabetic patients with preexisting heart disease. Studies have shown that more than 50% patients with type 2 diabetes die at an early age mainly due to CHDs. For this reason, they are treated as patients of CHDs. However, this may not always be effective because the actual CHD risk varies greatly among them. Many international guidelines, therefore, continue to recommend estimation of CHD risk among such patients using a validated risk function. Estimation and stratification of CHD risk help clinicians identify patients at high risk and provide them with appropriate personalized medicine to prevent such risk. Comprehensive diabetes management programs based on risk stratification concepts have been shown to yield better clinical outcomes than those without. Therefore, estimation and stratification of CHD risk provide a good basis for efficient management of diabetes mellitus.

A validated or recalibrated CHD risk prediction function utilizes a point scoring system that allows several risk factors to be considered together, calculates the accurate CHD risk of a large number of people, and favorably influences the decisions of the clinicians. The two most widely adopted popular risk prediction functions are the Framingham risk equation and United Kingdom Prospective Diabetes Study (UKPDS) risk engine. The Framingham risk equation was originally developed from a prospective study based on the general North American white population between 30 and 74 years with less than 10% diabetic population. This equation takes into account the cumulative effects of age, sex, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), blood pressure (BP), smoking, and diabetes mellitus for prediction of the incidence risk of CHD. Modified versions of this risk equation developed for some European populations resulted in overestimation of the CVD risk in such populations. One such modified version of the Framingham risk equation, the UKPDS risk engine, was developed for a large cohort of newly diagnosed European patients with type 2 diabetes. It is more diabetes-specific than the Framingham risk equation as it includes variables such as the duration of diabetes and levels of glycated hemoglobin (HbA1c). While some countries have adopted these two risk prediction functions after their appropriate calibration, their performances remain untested for Nepalese population, which have different genetic make-up and cardiometabolic risk profiles from the European population. It is, therefore, necessary to assess their predictive performance before they could also be adopted for the Nepalese population. While their complete assessment of predictive potential requires a population-based longitudinal study, we conducted only a hospital-based, cross-sectional study to use them for the estimation of CHD risk among Nepalese patients with type 2 diabetes.

Patients and Methods

Study design and patients

We carried out a hospital-based, cross-sectional study from July 2012 to June 2013 at Manipal Teaching Hospital (MTH), Pokhara, Nepal. A total of 524 type 2 diabetic patients aged 32-74 years from different outpatient departments of MTH were enrolled for this study. The study protocol was approved by the institutional ethical committee and informed consent was obtained from all the patients.

Patients were diagnosed to have type 2 diabetes when they fulfilled the World Health Organization (WHO) diagnostic criteria for diabetes mellitus and were 30 years or older at the time of diagnosis, had not undergone insulin therapy for a year after the diagnosis, and had no history of diabetic ketoacidosis. Patients with acute or chronic complications, atrial fibrillation, previous history of CHDs, and antilipemic treatment were excluded from this study. Demographic, clinical, and biochemical data of the patients were collected from personal interviews using a preformed set of questionnaires, anthropometric measurements, and biochemical analyses of their blood samples. The primary variables recorded included their age, sex, waist circumference (WC), waist–hip ratio (WHR), body mass index (BMI), BP (systolic (SBP) and diastolic (DBP)), fasting plasma glucose (FPG), HbA1c, duration and treatment status of diabetes and hypertension (HTN), smoking habit, triglycerides (TG), total cholesterol (TC), HDL-C, and LDL-C. Patients, who were taking oral hypoglycemic drugs with or without insulin, were considered to be under diabetes treatment.

Measurement of anthropometric and physiological variables

Height, weight, and waist and hip circumferences of the study patients were measured using standard protocols and the BMI and WHR values were calculated. BMI and WC status were classified according to recent WHO guidelines for South Asian population. Patients were said to have general obesity when their BMI was ≥25 kg/m² and central obesity when their WC was ≥90 cm (for men) and ≥80 cm (for women). SBP and DBP were measured...
in triplicates using digital sphygmomanometer (TaiDoc Technology Corporation, Taiwan) and categorized according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[24]

**Laboratory measurement of biochemical variables**

A total of 5 ml fasting venous blood was drawn from each study patient and divided into fluoride-oxalate vials, ethylenediaminetetraacetic acid (EDTA) vacutainers, and plain test tubes. FPG was measured in blood collected in fluoride-oxalate vials by glucose oxidase/peroxidase method. HbA1c was measured in the EDTA mixed blood by ion-exchange resin method. Serum lipids (TG, TC, and HDL-C) were directly measured in theplain blood and the value of LDL-C was calculated using the Friedwald formula.[25] All these parameters were analyzed using a semiautomated chemistry analyzer (Humalyzer-3500) and ready-to-use reagent kits according to the manufacturer’s instructions (Human Diagnostics, Germany). Serum lipid reference level was based on the Third Report of the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) guideline,[26] with hypercholesterolemia being defined as TC >200 mg/dl, high LDL-C >100 mg/dl, hypertriglyceridemia TG >150 mg/dl, and low HDL-C <40 mg/dl. Dyslipidemia was defined as the presence of one or more abnormal serum lipid concentrations, while metabolic syndrome was defined according to the Harmonized criteria.[27]

**Estimation of the 10-year CHD risk**

The Framingham risk equation and UKPDS risk engine were used for the estimation of 10-year CHD risk for each study patient. The Framingham risk was estimated by the sex-specific LDL-C based prediction equation,[14] while the UKPDS risk was estimated by offline risk engine version 2.[28] For the UKPDS risk estimation, study patients were treated as Asian Indians. Estimated CHD risks were then categorized as low (<10%), medium (10-20%), and high (>20%).

**Statistical analysis**

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 17.0 for Windows (SPSS, IL, Chicago, USA), XLSTAT, and NumXL. Data for categorical variables were expressed in number and percentage (N, %) or 95% confidence interval (CI). Numerical data for continuous variables were expressed as mean ± standard deviation. Pearson’s chi-square test (asymptotic significance (asymp. sig.), two-sided), independent sample test (sig., two-tailed), and Wilcoxon signed-rank test (asymp. sig., two-tailed) were used to test the statistical significance of the differences between the proportions and mean values of two or more groups of variables.

The agreement between the Framingham and UKPDS risk prediction functions for classifying patients into different risk groups was determined by the kappa statistics. The level of agreement was categorized as poor, $\kappa \leq 0.20$; fair, $\kappa = 0.21-0.40$; moderate, $\kappa = 0.41-0.60$; substantial, $\kappa = 0.61-0.80$; and very good, $\kappa > 0.80$.[32] Bland–Altman analysis was performed using XLSTAT to compare the convergent validity of these two risk functions. The equation for lines and correlation coefficients were obtained by linear regression. Pearson’s bivariate correlation and stepwise linear multiple regression analyses were performed to assess the extent of association between the predicted risks and CHD risk factors present in the study patients. The Pearson’s correlation coefficients ($r$) values of ±1 was interpreted as perfect correlation, $r$-values between ±0.7 and ±0.9 as strong correlations, $r$-values in the range of ±0.4 to ±0.6 as moderate correlations, $r$-values between ±0.1 and ±0.3 as weak correlations, and $r$-value of 0 as no correlation. Kernel density estimation determined using the NumXL was used to plot the frequency distribution of the 10-year predicted CHD risk scores. The tests were considered statistically significant when $P < 0.05$.

**Results**

**General and biochemical characteristics of the study patients**

A total of 523 patients were enrolled, out of which 313 (59.7%) were males and 211 (40.3%) were females; and 175 (33.4%) patients were obese, 391 (74.6%) dyslipidemic, 192 (35.7%) hypertensive, and 146 (27.9%) were current smokers. BMI, WC, TG, TC, LDL-C, and DBP were significantly higher ($P < 0.05$) in males, while the number of metabolic syndrome components was significantly higher in females ($P < 0.05$). The frequency of obesity, hypertriglyceridemia, HTN, current smoking habit, nonvegetarian diet, and metabolic syndrome were significantly higher in males ($P < 0.05$) [Table 1].

The 10-year CHD risks estimated by the Framingham and the UKPDS risk functions, their stratification into low, medium, and high risk groups and statistical agreement are shown in Table 2. The mean CHD risks estimated by the two risk prediction functions did not differ significantly (bias = 0.88, $P = 0.16$) and were always higher in males ($P < 0.001$). Both of the risk prediction functions showed fair agreement ($k = 0.39$, 95% CI (0.33-0.45), $P < 0.001$) in classifying the patients into low, medium, and high risk groups. There were 166 (31.7%) patients at low, 167 (31.9%) at medium, and 191 (36.4%) at high risk according to the Framingham risk equation; while
224 (42.7%) patients were at low, 148 (28.2%) at medium, and 152 (29%) at high risk according to the UKPDS risk engine. They also identified more males than females ($P < 0.05$) at medium and high risk. Patients associated with obesity, poor glycemic control, longer duration of diabetes, dyslipidemia, HTN, and current smoking habit had higher CHD risk than those without [Table 3]. However, the CHD risk estimated for such patients by the UKPDS risk engine was significantly lower than the one estimated by the Framingham risk equation. Both the predicted 10-year CHD risks increased gradually with the age of the patients, although the overall increase was always higher in males [Figure 1]. Except for the age groups 40-44, and 70-74 years, both the predicted CHD risks showed substantial overlap with each other.

The Framingham-estimated CHD risk showed significant correlation with many risk factors prevalent in the study patients than the UKPDS-estimated risk. Surprisingly, neither of the estimated CHD risks showed significant

### Table 1: Baseline characteristics of study patients

| Test parameters | Total | Male | Female | $P$-value* |
|-----------------|-------|------|--------|------------|
| Total numbers   | 524   | 313 (59.7%) | 211 (40.3%) |             |
| Age (years)     | 52.8±10.5 | 52.4±10.0 | 53.4±11.0 | 0.29        |
| Age at diagnosis of diabetes (years) | 47.7±8.9 | 47.2±8.7 | 48.3±9.2 | 0.17        |
| Body mass index (kg/m²) | 24.2±2.4 | 24.5±2.2 | 23.9±2.6 | <0.01       |
| General obesity | 175 (33.4%) | 122 (39.0%) | 53 (25.1%) | <0.001      |
| Waist circumference (cm) | 93.2±7.5 | 95.1±6.6 | 90.4±7.8 | <0.001      |
| Central obesity | 265 (49.3%) | 195 (42.4%) | 459 (87.6%) | <0.01       |
| Fasting blood glucose (mg/dl) | 138.0±45.6 | 138.0±48.0 | 139.0±42.0 | 0.80        |
| HbA1c (%)       | 6.4±1.0 | 6.4±1.0 | 6.4±1.0 | 0.88        |
| Abnormal glycemic control (>65 mM/M) | 29 (5.6%) | 17 (5.5%) | 12 (5.7%) | 0.83        |
| Patients under diabetes treatment | 512 (97.7%) | 307 (98.1%) | 205 (97.2%) | 0.49        |
| Total duration of DM (years) | 5.1±3.8 | 5.1±3.9 | 5.0±3.8 | 0.89        |
| Triglycerides (mg/dl) | 207.0±151.0 | 221.0±159.0 | 187.0±137.0 | 0.81        |
| Hypertriglyceridemia | 345 (65.8%) | 217 (69.3%) | 128 (60.7%) | 0.04        |
| Total cholesterol (mg/dl) | 203.0±49.2 | 207.0±48.0 | 198.0±51.0 | <0.01       |
| Hypercholesterolemia | 238 (45.4) | 154 (49.2) | 84 (39.8) | 0.03        |
| LDL-C (mg/dl) | 123.0±47 | 125.0±50.0 | 122.0±43.0 | <0.01       |
| High LDL-C | 382 (72.9%) | 235 (75.1%) | 147 (69.7%) | 0.17        |
| HDL-C (mg/dl) | 38.6±8.2 | 38.6±8.0 | 38.6±8.5 | 0.99        |
| Low HDL-C | 240 (45.8%) | 145 (46.3%) | 95 (45.0%) | 0.77        |
| Dyslipidemia | 391 (74.6%) | 241 (77.0%) | 150 (71.1%) | 0.13        |
| Systolic blood pressure (mmHg) | 126.0±12.7 | 127.0±12.0 | 125.0±14.0 | 0.15        |
| Diastolic blood pressure (mmHg) | 82.2±8.8 | 83.0±7.5 | 81.0±9.0 | <0.01       |
| Hypertension | 192 (36.7%) | 121 (38.7%) | 71 (33.7%) | <0.01       |
| Duration of hypertension (years) | 4.4±4.6 | 4.7±4.8 | 4.0±4.4 | 0.31        |
| Current smokers | 146 (27.9%) | 119 (38.0%) | 27 (12.8%) | <0.001      |
| Metabolic syndrome | 459 (87.6%) | 254 (81.2%) | 205 (97.2%) | <0.001      |

Data are mean ± SD or N (%). *Groups were compared using Student’s t-test for continuous variables and chi-square tests for categorical variables. All P-values reported are two-tailed. HbA1c = Glycated hemoglobin A1c, DM = Diabetes mellitus, LDL-C = Low-density lipoprotein cholesterol, HDL-C = High-density lipoprotein cholesterol, SD = Standard deviation

### Table 2: Ten-year mean CHD risk among diabetic patients estimated by the Framingham and UKPDS risk functions

| CHD risk calculators | Mean CHD risk (%) | Sex | 10 year CHD risk (%) | Total N (%) | $\kappa$-value (95% CI) |
|----------------------|-------------------|-----|----------------------|-------------|------------------------|
|                      |                   | Male | Low (<10%) | Medium (10-20%) | High (>20%) |                  |
| FGM                  | 17.7 ± 12.1       |      | 6.8±2.1   | 14.7±3.5       | 33.5±11.4 | 313 (59.7) 0.39 (0.33-0.45) P < 0.001 |
|                      |                   | Female | 5.4±2.7   | 13.9±2.1       | 26.7±5.7* | 211 (41.3) |
|                      |                   | Total  | 6.1±2.5   | 14.5±3.2       | 30.6±9.9  | 524 (100)   |
| UKPDS                | 16.8 ± 15.4†      |      | 6.9±2.4   | 15.6±6.9       | 35.3±16.2 | 313 (59.7) |
|                      |                   | Female | 5.3±2.4   | 14.5±4.5       | 31.3±18.7** | 211 (41.3) |
|                      |                   | Total  | 6.0±2.5   | 15.2±6.2       | 34.4±16.8 | 524 (100)   |

*Data are mean ± SD, N (%) or 95% CI. Group means were compared using Student’s t-test. The concordance of the Framingham and UKPDS risk functions for estimating 10-year CHD risk was determined using kappa statistics. $P = 0.16$, *$P = 0.007$, **$P < 0.001$ (two-tailed). CHD = Coronary heart disease, FGM = Framingham, UKPDS = United Kingdom prospective diabetes study, SD = Standard deviation, CI = Confidence interval

†Data are mean ± SD, N (%) or 95% CI. Group means were compared using Student’s t-test. The concordance of the Framingham and UKPDS risk functions for estimating 10-year CHD risk was determined using kappa statistics. $P = 0.16$, *$P = 0.007$, **$P < 0.001$ (two-tailed). CHD = Coronary heart disease, FGM = Framingham, UKPDS = United Kingdom prospective diabetes study, SD = Standard deviation, CI = Confidence interval
correlation with the BMI of the patients [Table 4]. Age, sex, LDL-C, HDL-C, and DBP were found to be the strong predictors of the Framingham risk; while only age, sex, and LDL-C were identified as the strong predictors of the UKPDS risk [Table 5].

The Kernel density distribution plot of the predicted CHD risks is shown in Figure 2. The highest Kernel densities for the Framingham and UKPDS risk were at 3.7 and 2.2, respectively. Despite a substantial overlap, the density of the UKPDS risk distribution was more concentrated towards the higher side of the risk spectrum than that of the Framingham risk. These two risks showed nonlinear association with each other [Figure 3]. The difference showed a positive bias (0.88, 95% CI −2.11, 0.34) between the two risk prediction functions with majority of the difference falling within the range of −28.9 to 27.1. The distributions of the difference were all heteroscedastic, with a cone-shaped distribution suggesting a bigger variability among patients with higher CHD risk [Figure 4].

**Discussion**

A validated CHD risk prediction function helps clinicians identify individuals in a high risk group and devise the most appropriate and cost-effective personalized therapeutic approach. Accurate prediction of future CHD risk among type 2 diabetes patients as well as the general population is not yet possible in Nepal due to lack of validated or calibrated risk prediction functions.[20] There are examples where the CHD risk prediction functions developed elsewhere have been imported and utilized for the local population after proper calibration and adjustment.[30,31] Normally, a large, population-based prospective study is required to validate such external risk prediction functions before they could be imported and fully utilized for the local population. However, in the absence of such study which is usually costlier and time consuming, we simply conducted a hospital-based, cross-sectional study to snapshot their risk prediction potential and comparative performance in the forms that

**Table 3: Framingham- and UKPDS-estimated 10-year CHD risk based on the presence of various risk factors**

| Risk factors for CHD | Ten-year mean CHD risk |
|----------------------|-----------------------|
|                      | Framingham            | UKPDS                 |
| **BMI**              |                       |                       |
| Normal               | 17.5±11.8             | 15.5±13.8***          |
| At risk              | 16.4±12.0             | 17.1±14.7**           |
| Obese I and II       | 18.7±11.4             | 17.1±14.7**           |
| HbA1c %              |                       |                       |
| Normal (≤6.5%)       | 15.2±10.8             | 15.8±15.3             |
| Increased (>6.5%)    | 20.9±12.9             | 18.0±15.4***          |
| DM                   |                       |                       |
| No                   | 13.2±8.1              | 18.7±21.5             |
| treatment            |                       |                       |
| Yes                  | 17.8±12.2             | 16.8±15.2***          |
| Dyslipidemia         |                       |                       |
| No                   | 11.4±7.6              | 15.5±15.0*            |
| Yes                  | 19.8±12.6             | 17.3±15.5***          |
| Blood pressure       |                       |                       |
| Normal               | 10.7±7.7              | 12.9±13.8             |
| Prehypertension      | 15.7±9.0              | 16.9±15.2             |
| Hypertension I and II| 24.6±13.8             | 19.5±16.0***          |
| Current smoking      |                       |                       |
| No                   | 16.5±11.3             | 16.0±15.6**           |
| Yes                  | 19.3±13.8             | 17.9±15.0***          |
| Metabolic syndrome   |                       |                       |
| No                   | 10.9±6.6              | 17.1±15.6***          |
| Yes                  | 18.7±12.4             | 16.8±15.3***          |

Data are mean ± SD. Group means (Framingham vs UKPDS) were compared using the Wilcoxon signed-rank test. *P = 0.029, **P < 0.010, ***P < 0.001 (two-tailed). CHD = Coronary heart disease, BMI = Body mass index, HbA1c = Glycated hemoglobin adult type 1c, DM = Diabetes mellitus, UKPDS = United kingdom prospective diabetes study, SD = Standard deviation.
are not yet validated for Nepalese diabetic population. We hope that this study provides the baseline data and opens the avenue for future validation or development of the risk prediction functions in Nepal.

Like any other diabetic patients, our patients were also associated with many established CHD risk factors such as smoking, obesity, poor glycemic control, dyslipidemia, and HTN. The prevalence of many of these risk factors was significantly higher in males, an observation also supported by studies conducted among other subsets of the Nepalese population. Presence of many of these risk factors including insulin resistance and obesity has been shown to be strongly associated with future CHD events in diabetic peoples of all ethnic origin. However, presence of multiple risk factors does not necessarily imply that all of our patients are already at

### Table 4: Pearson bivariate correlation between the 10-year CHD risks and independent variables

| Variables | FGM risk | UKPDS risk | Age | BMI | Waist | WHR | FPG | HbA1c | DurDM |
|-----------|----------|------------|-----|-----|-------|-----|-----|-------|-------|
| Framingham risk | 0.48** | 0.48** | 0.62** | -0.01 | 0.18** | 0.16** | 0.27** | 0.27** | 0.48** |
| UKPDS risk | 0.48** | 0.69** | 0.06 | 0.06 | 0.11* | 0.07 | 0.34** |
| TG | TC | LDL-C | HDL-C | SBP | DBP | DurHTN | HTNtrt | Smoking |
| Framingham risk | 0.12** | 0.57** | 0.62** | -0.56** | 0.46** | 0.41** | 0.44** | 0.37** | 0.14** |
| UKPDS risk | 0.00 | 0.16** | 0.18** | -0.14** | 0.16** | 0.14** | 0.25** | 0.15** | 0.16** |

*Correlation (r) significant at the level of P = 0.41, **correlation (r) significant at the level of P < 0.010 (two-tailed). CHD = Coronary heart disease, FGM = Framingham, UKPDS = United Kingdom prospective diabetes study, BMI = Body mass index, WHR = Waist-to-hip ratio, FPG = Fasting plasma glucose, HbA1c = Glycated hemoglobin adult type 1c, DurDM = Duration of diabetes mellitus, TG = Triglycerides, TC = Total cholesterol, LDL-C = Low-density lipoprotein cholesterol, HDL-C = High-density lipoprotein cholesterol, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, DurHTN = Duration of hypertension, HTNtrt = Treatment for hypertension

### Table 5: Stepwise linear multiple regression analysis with the predicted 10-year CHD risks as dependent variables

| Dependent variables | Independent variables | Adjusted R² | Constant | 95% CI | P-values | VIF |
|---------------------|-----------------------|-------------|----------|--------|----------|-----|
| Framingham risk | Age (years) | 0.78 | -35.82 | -42.44, -29.20 | <0.001 | - |
| | Sex (male/female) | -3.24 | -4.23, -2.23 | <0.001 | 1.02 |
| | HDL-C (mg/dl) | -0.38 | -0.45, -0.31 | <0.001 | 1.38 |
| | LDL-C (mg/dl) | 0.09 | 0.08, 0.10 | <0.001 | 1.40 |
| | DBP (mmHg) | 0.35 | 0.29, 0.41 | <0.001 | 1.06 |
| UKPDS risk | Age (years) | 0.45 | -28.22 | -33.55, -22.89 | <0.001 | 1.04 |
| | Sex (male/female) | -9.48 | -12.32, -5.80 | <0.001 | 1.00 |
| | LDL-C (mg/dl) | 0.02 | 0.00, 0.04 | <0.001 | 1.03 |

Dependent variables: The Framingham and UKPDS estimated 10-year CHD risks; independent variables included in the model equations (i) for Framingham risk: Age, sex (female = 0, male = 1), HDL-C, LDL-C, and DBP; and (ii) for UKPDS risk: Age, sex (female = 0, male = 1), LDL-C. CHD = Coronary heart disease, VIF = Variance inflation factor, HDL-C = High-density lipoprotein cholesterol, LDL-C = Low-density lipoprotein cholesterol, DBP = Diastolic blood pressure, UKPDS = United Kingdom prospective diabetes study

**Figure 2:** Kernel density distribution of 10-year CHD risks predicted by the Framingham and UKPDS risk prediction functions

**Figure 3:** Scatter plot between 10-year CHD risks predicted by the Framingham and UKPDS risk functions

CHD: Coronary heart disease; UKPDS: United Kingdom prospective study
Figure 4: Bland–Altman plot showing the difference in mean 10-year CHD risks predicted by the Framingham and UKPDS risk functions

Risk prediction functions are statistical models that predict the CHD risk reflecting the cumulative effect of the established risk factors present in the subjects under study. Hence, it is expected that higher the number of established risk factors present, the higher will be the predicted risk, although it may not happen in the reality. We had expected the UKPDS risk engine to predict higher risk for our diabetic patients than the Framingham risk equation as the former is believed to be more diabetic specific than the later one. However, the UKPDS risk engine actually estimated lower than expected risk for our diabetic patients who were associated with multiple risk factors and below 70 years. The Framingham risk equation, on the other hand, predicted higher risk for this group of patients and showed better association with their existing risk profile. However, this risk equation estimated lower than expected for patients who were older, centrally obese, and not under diabetes treatment. These observations suggest that neither of these risk prediction functions may reliably be used to predict the CHD risk of wider spectrum of Nepalese diabetic patients until they are validated locally. Studies conducted on other similar populations have also raised questions about their reliability in predicting accurate CHD risk.[17,18] Some studies have even suggested that these risk prediction functions may now be outdated for longstanding diabetic patients due to improvement in diabetic medications and clinical care since the time of their inception, and therefore their refinement for better reflection of the current risk profile, diagnostics, and medications may be essential.[19,20] Moreover, since these risk prediction functions were developed for the western white Caucasian population, it is also possible that they do not accurately reflect the CHD risk of South Asians who have different genetic makeup and risk profile. In light of this, the British Cardiac Society has clearly warned against the generalization of risk prediction functions for South Asians in the absence of validated models.[21]

The strength of our study is based on the enrollment of clearly defined and uncomplicated type 2 diabetic patients with no previous history of CHDs. The patients...
Conclusion

In conclusion, the Framingham and the UKPDS risk prediction functions that are yet to be validated for the Nepalese diabetic population showed moderate convergence in predicting 10-year CHD risk, despite their differences in classifying diabetic patients into different risk groups. The Framingham risk equation predicted higher CHD risk and showed better association with the current risk profile than the UKPDS risk engine. However, both the risk functions could not fully account for the complete risk profile of the study patients and, therefore, their performances for the Nepalese diabetic population remains questionable until they are locally validated or calibrated. The availability of a population-specific validated or calibrated risk function would greatly assist Nepalese clinicians in mitigating the CHD-related morbidity and mortality in diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

References

1. Bhandari GP, Angdembe MR, Dhimal M, Neupane S, Bhusal C. State of non-communicable diseases in Nepal. BMC Public Health 2014;14:23.
2. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229-34.
3. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Type 2 diabetes as a “coronary heart disease equivalent”: An 18-year prospective population-based study in Finnish subjects. Diabetes Care 2005;28:2901-7.
4. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434-44.
5. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
6. Grundy SM. Diabetes and coronary heart disease: What does it mean? Diabetes Care 2006;29:457-60.
7. Chinnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJ. Cardiovascular risk assessment scores for people with diabetes: A systematic review. Diabetologia 2009;52:2001-14.
8. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2008;32:S1-201.
9. American Diabetes Association: Standards of medical care in diabetes-2013. Diabetes Care 2013;36:S1-66.
10. Cooper A, O’Flynn N, Guideline Development Group. Risk assessment and lipid modification for primary and secondary prevention of cardiovascular disease: Summary of NICE guidance. BMJ 2008;336:1246-8.
11. Eddy DM, Adler J, Patterson B, Lucas D, Smith KA, Morris M. Individualized guidelines: The potential for increasing quality and reducing costs. Ann Intern Med 2011;154:627-34.
12. Clark CM Jr, Snyder JW, Meek RL, Stutz LM, Parkin CG. A systematic approach to risk stratification and intervention within a managed care environment improves diabetes outcomes and patient satisfaction. Diabetes Care 2001;24:1079-86.
13. KoGT, So WY, Tong PC, LeCoguec F, Kerr D, Lyubomirsky G, et al. From design to implementation — The Joint Asia Diabetes Evaluation (JADE) program: A descriptive report of an electronic web-based diabetes management program. BMC Med Inform Decis Mak 2010;10:26.
14. Wilson PW, D’Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-47.
15. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow up of the prospective cardiovascular Münster (PROCAM) study. Circulation 2002;105:310-5.
16. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: A statement for healthcare professionals from the American Heart Association.
and the American College of Cardiology. Circulation 1999;100:1481-92.

17. Coleman RL, Stevens RJ, Retnakaran R, Holman RR. Framingham, SCORE and DECODE risk equations do not provide reliable cardiovascular risk estimates in type 2 diabetes. Diabetes Care 2007;30:1292-3.

18. Kengne AP, Patel A, Colaguzzi S, Heller S, Hamet P, Marre M, ADVANCE Collaborative Group. The Framingham and UK Prospective Diabetes Study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: The Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) Study. Diabetologia 2010;53:821-31.

19. Stevens RJ, Kohari V, Adler AI, Stratton IM, United Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: A model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671-9.

20. Hussain SM, Oldenburg B, Wang Y, Zongnag S, Tonkin AM. Assessment of cardiovascular disease risk in South Asian populations. Int J Vasc Med 2013;2013:786801.

21. Joshi P, Islam S, Pais P, Reddy S, Dorairaj P, Kazmi K, et al. Risk factors for early myocardial infarction in South Asians compared with individuals in other countries. JAMA 2007;297:286-94.

22. WHO Consultation. Definition, diagnosis and classification of diabetes mellitus and its complications: Report of a WHO Consultation Part 1: Diagnosis and classification of diabetes mellitus. WHO/NCD/NCS/99.2. Geneva: World Health Organization; 1999. [Publication no. WHO/NCD/NCS/99.2].

23. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.

24. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. National heart, lung, and blood institute; national high blood pressure education program coordinating committee. Hypertension 2003;42:1206-52.

25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.

26. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive summary of the third report of the national cholesterol education program (NCEP). J Am Med Assoc 2001;285:2486-97.

27. Alberti KG, Eckel RH, Grundy SM, Zimet PD, Cleeman JL, Donato KA, et al., International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.

28. The University of Oxford, Diabetes trial unit, The Oxford centre for diabetes, endocrinology and metabolism, UKPDS risk engine. (Accessed July 2, 2014, at http://www.dtu.ox.ac.uk/riskengine/download.php).

29. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.

30. Marrugat J, Subirana I, Comín E, Cabezas C, Vila J, Losuau R, et al., VERIFICA Investigators. Validity of an adaptation of the Framingham cardiovascular risk function: The VERIFICA study. J Epidemiol Community Health 2007;61:40-7.

31. Jiao FF, Novari H, Cung C, McGee SM. Comparison of four cardiovascular risk prediction functions among Chinese patients with diabetes mellitus in the primary care setting. J Diabetes Investig 2011;5:300-1.

32. Sharma SK, Ghimire A, Radhakrishnan J, Thapa L, Shrestha NR, Paudel N, et al. Prevalence of hypertension, obesity, diabetes, and metabolic syndrome in Nepal. Int J Hypertens 2011;2011:821971.

33. Turner RC, Mills H, Neil HA, Stratton IM, Manley SE, Matthews DR, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ 1998;316:823-8.

34. Mozaffarian D, Wilson PW, Kannel WB. Beyond established and novel risk factors: Lifestyle risk factors for cardiovascular disease. Circulation 2008;117:3031-8.

35. Laakso M, Kuusisto J. Insulin resistance and hyperglycemia in cardiovascular disease development. Nat Rev Endocrinol 2014;10:293-302.

36. Lloyd-Jones DM. Cardiovascular risk prediction: Basic concepts, current status, and future directions. Circulation 2010;121:1768-77.

37. Hennaez R, Choque L, Giménez M, Costa A, Márquez JI, CongeI. Coronary risk assessment in subjects with type 2 diabetes mellitus. General population-based scores or specific scores? Rev Esp Cardiol 2004;57:577-80.

38. Lu SE, Beckles GL, Crosson JC, Bilik D, Karter AJ, Gerzoff RB, et al. Evaluation of risk equations for prediction of short-term coronary heart disease events in patients with long-standing type 2 diabetes: The Translating Research into Action for Diabetes (TRIAD) study. BMC Endocr Disord 2012;12:12.

39. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society: Joint British recommendations on prevention of coronary heart disease in clinical practice. British Cardiac Society, British Hyperlipidaemia Association, British Hypertension Society, endorsed by the British Diabetic Association. Heart 1998;80:51-29.