

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.^[1] 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.^[2-5] Studies have shown that more than 50% patients with type 2 diabetes die at an early age mainly due to CHDs.^[6] 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.^[7] Many international guidelines, therefore, continue to recommend estimation of CHD risk among such patients using a validated risk function.^[8-10] Estimation and stratification of CHD risk help clinicians identify patients at high risk and provide them with appropriate personalized medicine to prevent such risk.^[11] Comprehensive diabetes management programs based on risk stratification concepts have been shown to yield better clinical outcomes than those without.^[12,13] 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.^[14,15] 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.^[16] 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.^[17,18] 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).^[19] While some countries have adopted these two risk prediction functions after their appropriate calibration, their performances remain untested for Nepalese population,^[20] which have different genetic

make-up and cardiometabolic risk profiles from the European population.^[21] 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^[22] 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.^[23] 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 the plain 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 \pm standard deviation. Pearson's chi-square test (asymptotic significance (asympt. sig.), two-sided), independent sample test (sig., two-tailed), and Wilcoxon signed-rank test (asympt. 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 ± 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 ($\kappa = 0.39$, 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

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/m ²)	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 (84.3%)	195 (92.4%)	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±0.9	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±8.2	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 (%)	κ-value (95% CI)	
			Low (<10%)	Medium (10-20%)	High (>20%)			
FGM	17.7 ± 12.1	Male	6.8±2.1	14.7±3.5	33.5±11.4	313 (59.7)	0.39 (0.33-0.45) <i>P</i> < 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 [‡]	Male	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

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

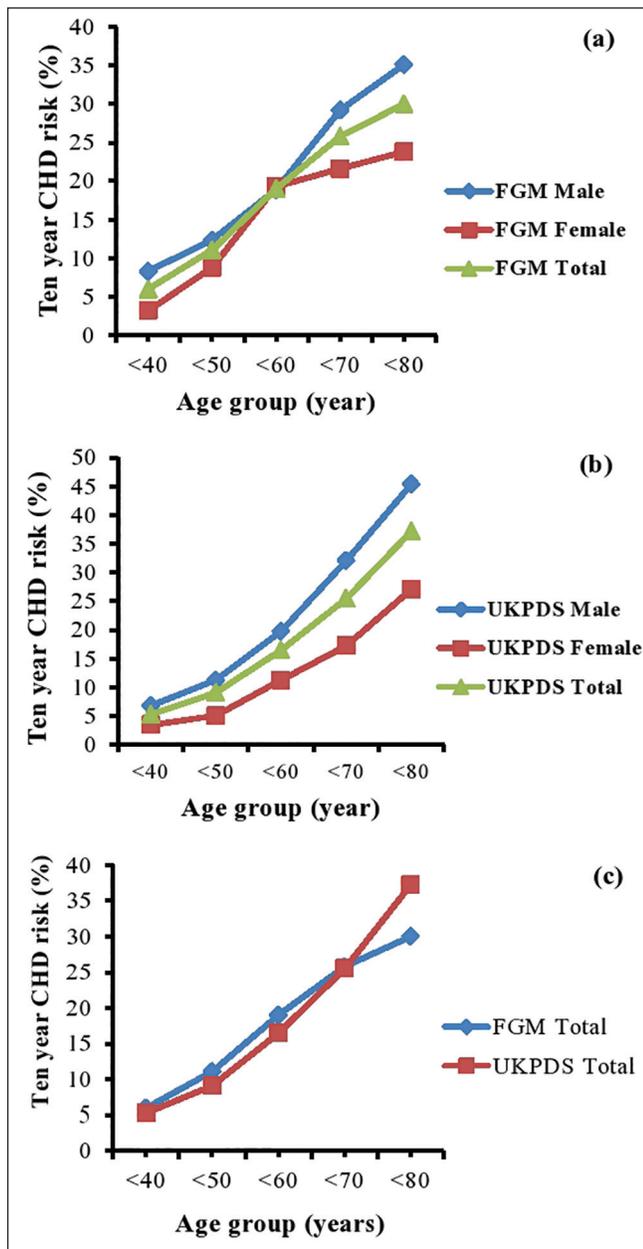


Figure 1: Distribution of 10-year CHD risks according to the age groups of diabetic patients

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

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±16.7
	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 treatment	No	13.2±8.1	18.7±21.5
	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

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

	FGM risk	UKPDS risk	Age	BMI	Waist	WHR	FPG	HbA1c	DurDM
Framingham risk	—	0.48**	0.62**	-0.01	0.18**	0.16**	0.27**	0.27**	0.48**
UKPDS risk	0.48**	—	0.60**	0.00	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 R ²	Constant	B	95% CI	P-values	VIF
Framingham risk	—	0.78	-35.82	—	-42.44, -29.20	<0.001	—
	Age (years)			0.57	0.52, 0.62	<0.001	1.05
	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			—	0.45	-28.22	—
Age (years)	0.88	0.78, 1.10	<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	0.03	1.04			

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 (2) 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

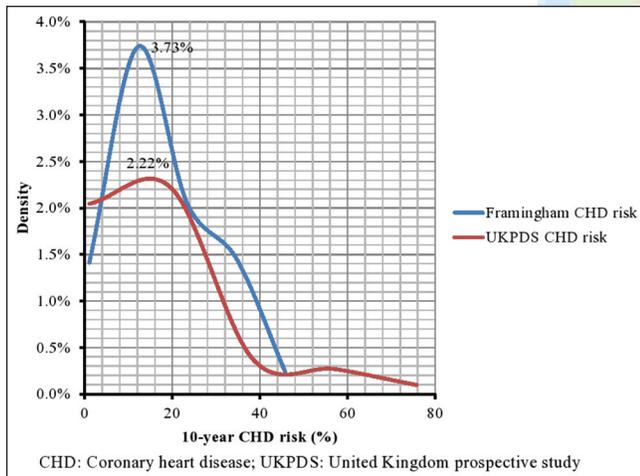


Figure 2: Kernel density distribution of 10-year CHD risks predicted by the Framingham and UKPDS risk prediction functions

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,

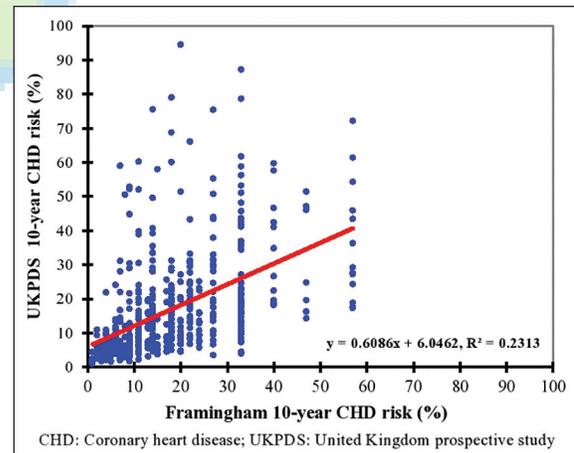


Figure 3: Scatter plot between 10-year CHD risks predicted by the Framingham and UKPDS risk functions

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.^[32,33] 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.^[34-36] However, presence of multiple risk factors does not necessarily imply that all of our patients are already at

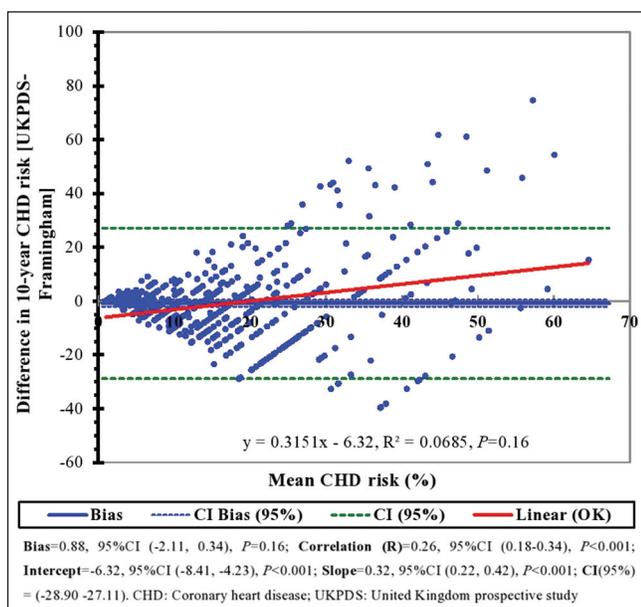


Figure 4: Bland–Altman plot showing the difference in mean 10-year CHD risks predicted by the Framingham and UKPDS risk functions

high risk group, but suggests that they may very soon progress towards high risk group if those risk factors are not controlled on time.

The overall CHD risks predicted by two risk functions did not differ significantly, but showed a gender-wise variation; with males showing 1.2 and 1.8 times higher risk according to the Framingham and UKPDS risk functions, respectively. As might be expected, the CHD risks predicted both by these risk functions were the highest among older patients of either sex associated with multiple risk factors. Studies on other populations have also shown similar results.^[34,35] Although the two predicted CHD risks showed enough overlapping, they did not show strong convergent validity. We found only a moderate correlation between the two, and found differences in classifying our patients into low, medium, and high risk groups. The mean CHD risk predicted by the UKPDS risk engine was lower in about 35% of diabetic patients, particularly in females, who were associated with multiple risk factors classified under medium or high risk groups according to the Framingham risk equation. These diabetic patients, who were below 70 years, met the criteria for preventive therapy using aspirin and statins. On the other hand, the UKPDS estimated risk was higher for those male patients who were above 70 years of age, dysglycemic, and chronic diabetic. The Framingham estimated CHD risk better accounted for the synergetic effects of major classical risk factors prevalent in the study patients, particularly of increased age, sex, HTN, decreased serum HDL, and increased LDL cholesterol. In contrast to our expectations, the UKPDS risk accounted only a few

risk factors such as age, sex, and LDL-cholesterol. For example, it did not take into account the effect of HbA1c level, an important parameter on which the risk engine was based. We expect that this lack of association with HbA1c might be due to the small sample size of diabetic patients in our study who had poor glycemic control (>6.5%). The CHD risk estimated by a properly validated risk prediction function is expected to show association with the majority of the risk factors such as age, sex, obesity, HTN, dyslipidemia, poor glycemic control, and duration of diabetes. This is because keeping many of these risk factors under control has been shown to lower the CHD risk significantly.^[17,37]

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.^[38,39] 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.^[40]

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

were from different socioeconomic strata and ethnic groups, and hailed from different areas of mid-western Nepal, and are therefore expected to be a good representation of the diabetic population in the country. Our study has for the first time predicted the 10-year CHD risk of a subset of Nepalese diabetic population using two most common risk prediction functions and attempted to make basic comparison of their predicted risks. It has established that these risk functions show moderate agreement in predicting CHD risk in diabetic patients. Our study also informs Nepalese clinicians that they should use these risk functions only as the references, along with other established guidelines, while making important decision regarding the prevention and treatment of patients with higher risk of CHD event. Moreover, it also provides the baseline data for future validation of these and other risk prediction functions in Nepal. The major limitation of our study is that we could not calibrate these risk functions against the Nepalese population and enroll study patients that could better represent the general population of Nepal.

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.

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