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Title page

Validation of the Framingham General Cardiovascular Risk Score in an Asian Population– a retrospective cohort study

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Abstract

Objective This study aims to examine the validity of the Framingham general cardiovascular disease risk (CVD) risk chart in a primary care setting.

Design This is a 10 year retrospective cohort study.

Setting A primary care clinic in a teaching hospital in Malaysia.

Participants 967 patients' records were randomly selected from patients who were attending the follow up in the clinic.

Main outcome measures Baseline demographic data, history of diabetes and smoking, blood pressure (BP) serum lipids were captured from patient records in 1998. Each patient's Framingham CVD score was computed from these parameters. All atherosclerotic CVD events occurring from 1998-2007 were counted.

Results In 1998, mean age was 57years with 33.8% men, 6.1% smokers, 43.3% diabetics and 59.7% hypertensive. Median BP was 140/80mmHg; total cholesterol 6.0mmol/L (1.3). The median Framingham general CVD risk score for the studied population was 21.5 (IQR 1.2-30.0) while the actual CVD events that occurred was 13.1% (127/967). The median CVD points for men was 30.0 giving a CVD Risk of more than 30% and for women 18.5, CVD risk of 21.5% respectively. The Framingham general CVD risk score discriminates moderately well for Malay race (AUC 0.65, p=0.01), Chinese (AUC 0.60, p=0.03) and Indians as well (AUC 0.65, p=0.001). Our study showed moderate discrimination with AUC of 0.63. There was good calibration with Hosmer-Lemeshow test $\chi 2 = 3.25$, $P = 0.78$

Conclusions Taking into account that this cohort of patients were already on treatment, the Framingham General CVD Risk Prediction Score predicts fairly accurately in men and overestimates somewhat in women. In the absence of local risk prediction charts, the Framingham general CVD risk prediction chart is a reasonable alternative for use in a multi-ethnic group primary care setting.

Strength and Limitation of this study

- The strength of our study is that it is done in the primary care setting where the CVD risk profiles is different from that in secondary care.
- This is the first study that examines the validity and applicability of the Framingham general CVD risk tool for primary care.
- Our sample size is large enough to give us a better picture of CVD risk of a multi-ethnic population in Asia where data about the use and applicability of any CVD risk

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prediction tool is lacking. Our study found that it did fit to be used by all the 3 different ethnic groups with a good calibration.

- However most of our patients were already on treatment that would result in an overestimation of risk in most situations.
- Despite this is a retrospective study in which there will be some missing data to some extent. However, we were able to compare the characteristics of those with missing data and those included in the analysis and found no clinical differences between them.

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Introduction

Guidelines on management of cardiovascular diseases (CVD) recommend assessing overall cardiovascular (CV) risk to determine the necessity of pharmacotherapy [1-9]. To date many CVD risk assessment tools have need devised[10]. The most well studied is the Framingham Coronary Heart Disease (CHD) Risk prediction Chart[11, 12]. This tool has been validated in different populations and found to overestimate risk particularly in women, the older age group, British men and European population and certain ethnicities with lower background risk of CVD like Chinese population[1, 13-17].

Furthermore it has been criticised that the Framingham CHD risk score only predicts risk for fatal and non-fatal coronary events and does not take into account patients already receiving anti-hypertensive therapy, which is the case in many individuals.

Hence the Framingham general CVD risk score tool for primary care was developed in 2008[18]. This newer tool now includes strokes, heart failure and peripheral artery disease and adjusts for patients already on anti-hypertensive therapy. However this risk score chart tool has not been widely validated. Hence our aim was to examine the validity of the Framingham general CVD in a multi-ethnic primary care population.

Materials and Methods

Setting

This is a retrospective cohort study. We computed the Framingham general CVD risk score retrospectively in a randomly selected cohort of patients registered with an urban primary care clinic. This selected sample consisted of adult patients aged 30 years and older who were free of any CV events at baseline and who had complete data needed to compute their overall CV risk. The study was conducted in an outpatient clinic of an academic teaching hospital. Ethics approval for this study was obtained from the Ethics Committee of our institution.

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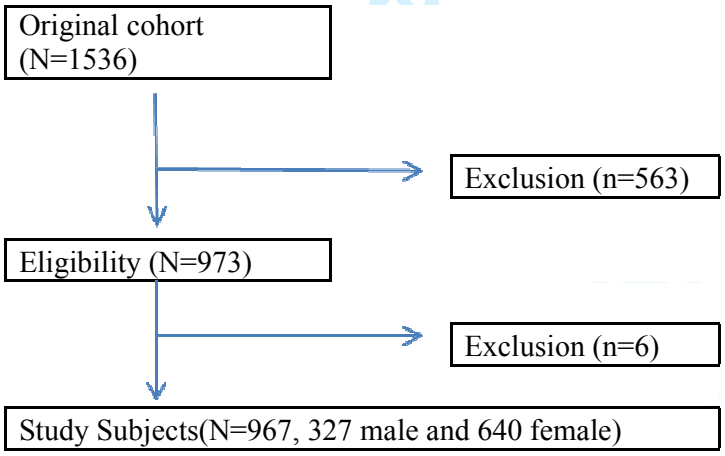
Participants

There were 1536 patients in our original cohort. We excluded 563 patients as they did not have all the variables needed to calculate the FRS. Another 6 patients was excluded as we could not ascertain their CVD status by the end of 2007. Hence a total of 967 patients (62.9%) were eligible for analysis (Figure 1). Out of these, 912 (94.3%) patients completed 10 years follow up and only 55 (5.7%) patients defaulted follow-up. Out of these, 26 (2.7 %) had died with 19 (73%) died of non-CVD causes.

Figure 1: Flowchart of patients included in the analysis



Inclusion criteria

All adult patients 30 years and above, without any CV events and with documented Blood pressure (BP) readings whether on or not on treatment, total cholesterol, HDL-cholesterol, smoking status and presence or absence of diabetes mellitus were eligible for this study. These parameters were needed to compute each individual's general CVD risk level.

Data collection

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This sample was randomly selected using a computer generated number based on the patient's unique registration number with the clinic. All patient records were in paper form.

We extracted the patients' socio-demographic data and clinical information based on the first entry in 1998 from their records manually according to a predetermined proforma (clinical report form). Use of hypoglycaemic and lipid lowering agents were also captured. With the age, SBP (treated or not treated) total-cholesterol, HDL-cholesterol levels, smoking and diabetes status we computed each individual's general CVD risk score.

CVD events namely fatal and non-fatal CHD, fatal and non-fatal strokes, heart failure and peripheral artery disease were also captured from the records. For those who did not complete their subsequent 10 year follow up at our clinic (n=24), we traced and examined the case records from the main hospital to determine their CVD outcome. For those patients who were not complete their follow-up in clinics, we contacted them individually (n=31) to ascertain their CVD status and for any events fatal or non-fatal. Each CVD event was counted as one event in individuals who had more than one event during the 10 years follow up. We further categorised the 10 year CVD risk as low (<10% 10 year risk) medium (10-20% CVD risk) or high >20% CVD risk [19].

Blood Pressure (BP) was measured by our attending doctor using a mercury sphygmomanometer as part of the daily routine practice. Diagnosis of hypertension is made in accordance with standard recommendations [7]. Target control BP was defined as BP < 140/90mmHg for non-diabetics and < 130/80mmHg for patients with diabetes mellitus (DM). Diabetes mellitus was defined as documented by the attending physician or the use of hypoglycaemic agents or both. Smokers were defined if they were still smoking currently. Non-smokers were those who never smoked or currently not smoking regardless of when

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they had stopped smoking. Total cholesterol, LDL and HDL cholesterol were also collected. All blood tests were performed in our teaching hospital's laboratory which is certified by the Royal College of Pathologists of Australasia standards.

Statistical analysis

All statistical analysis was done using the Statistical Package for Social Sciences (SPSS version 21). Continuous data are described as mean and standard deviation if the distribution is normal. When the data is a skewed distribution, median and interquartile range (25-75th percentile) is used. Categorical data are reported as proportions (percentage). Chi-square test or Fisher exact tests were used for the categorical or dichotomous variables.

Discrimination

Discrimination is defined as the ability of the risk prediction model in distinguishing patients who suffered from a CVD event from those do not using an overall c index. C index is analogous to the area under the receiver operating characteristic curve (AUC). Discrimination is defined as good when c index is closer to 1 whereas a value of 0.5 implies that the risk score tool is no better than chance[20].

Calibration

Calibration was used to assess if the observed 10-year CVD events differed significantly from predicted [8]. The calibration of the Framingham general CVD risk score was determined using Hosmer-Lemeshow test [21]. A $\chi 2$ value of greater than 20 or a p value of less than 0.05 indicates poor calibration.

Results

A total of 967 out of 1536 patient records of 1998 (baseline) were entered into our analysis.

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Table 1 shows the demographic data of our cohort. Our study population was made up of three main ethnic groups, namely the Chinese (45.4%), Malays (23.3%) and Indians (30.2%). The mean age was 56.9 (9.9) years. Two third (66.2%) were females. At baseline in 1998, A little over half (59.7%) had hypertension, under half (43.3%) had diabetes and less than 10 percent (6.1%) were current smokers. Out of these, 80.9% (n=339) of these diabetic patients were receiving treatment with either oral hypoglycaemic agents and/or insulin. The mean systolic BP was 140.7±18.6 mmHg and more than half (59.7%) of them was on anti-hypertensive agents. However only 9.8% of the population (n=95) received statin therapy in 1998. We also compared the baseline characteristics for those who were entered into our analysis to the patients who were excluded. Basically there was no significant difference between their baseline characteristics.

Table 1 Comparison of CV risk factors between study population and excluded patients as well as changes in CV risk factors in 1998 and 2007

	Study population (n=973)	**Excluded population (n=563)**	**P-value**	**2007**
Age, year (mean)	56.9±9.9	55.8 ± 10.4	0.06	66.9 ± 9.9
Sex, female (n,%)	640 (66.2)	362 (64.3)	0.45	640 (66.2)
Ethnicity (n,%)			0.16	
Malay	225 (23.3)	155 (27.5)		225 (23.3)
Chinese	438 (45.4)	221 (39.3)		438 (45.4)
Indian	291 (30.2)	180 (32.0)		291 (30.2)
Others	13 (1.2)	7 (1.2)		13 (1.2)
Diabetes mellitus (n,%)	419 (43.3)	260 (46.3)	0.28	556 (57.5)
HbA1C, % (mean)	7.8 ± 1.9	7.9 ± 1.9	0.28	7.5 ± 1.7
DM controlled with HbA1c ≤ 6.5% (n,%)	113(11.6)	64(11.4)	0.89	168 (17.4)
Systolic BP, mmHg (mean)	140.7±18.6	139.0±19.7	0.22	134.9 ± 16.5
Use of anti-hypertensive agents (n,%)	577 (59.7)	308 (54.7)	0.09	791 (81.8)
RAS blocker use (n,%)	71(7.3)	27(4.8)	0.05	465 (48.1)
Total cholesterol, mmol/L (mean)	6.1±1.1	5.8±1.1	0.06	4.9 ± 1.0
HDL cholesterol, mmol/L (mean)	1.2± 0.4	1.4 ±0.2	0.49	1.3± 0.3
LDL cholesterol, mmol/L (mean)				3.0± 0.8
Statin use in 1998 (n,%)	95 (9.8)	32 (5.7)	0.005	608 (62.9)
Smoker (n,%)	59 (6.1)	47 (8.3)	<0.001	59 (6.1)

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Table 1 also demonstrates the change in CVD risk factors between baseline and at the end of 10 years. Despite the number of diabetes patients increased from 43.3% to %, HbA1c control improved from a mean of 7.8% to 7.5%. The mean systolic blood pressure was reduced by 5.8mmHg, from 140.7mmHg to 134.9mmHg. The control rate for blood pressure improved from 41.3% to 55.6%. There was an increase in the use of renin-angiotensin system (RAS) blockers from 7.3% to 48.1%. The number of patients receiving statin increased significantly from 9.8% to 62.9% in 2007. There was also improvement in the lipid profile of patients at the end of 10 years compared to baseline. Mean of total cholesterol was reduced from 6.1 mmol/L to 4.9 mmol/L while the mean HDL increased from 1.2 to 1.3 mmol/L.

Table 2 compares CVD risk factors and events rate in male and female. Generally males were having higher CV risk profiles than females. They are older, more smoker, having poorer control in blood pressure and sugar profiles despite did slighter better in lipids profile. The CHD events were twice more common in male (13.5%) than in female (6.4%). Similarly strokes were higher in male (6.1%) than in female (3.1%). In total, 6 CVD events were fatal in male and only one fatal in female.

Table 2: Comparison of CV risk factors and events according gender

	Male (N=327)	Female (N=640)	P-value
Age , year (mean)	57.7(10.1)	56.5 (9.7)	0.07
Hypertension	217(37.6)	360(62.4)	0.002
Systolic BP, mmHg (mean)	142.3(17.6)	139.9(19.1)	0.07
Diastolic BP, mmHg (mean)	87.6(10.4)	83.3(9.5)	<0.001
Blood pressure control rate (N,%)	22(25.0))	66(75.0)	<0.001
Total cholesterol, mmol/L (mean)	5.8(1.1)	6.2(1.1)	<0.001
HDL cholesterol, mmol/L (mean)	1.1(0.4)	1.3(0.3)	<0.001
Triglyceride, mmol/L,(mean)	1.9(1.0)	1.6(0.9)	<0.001
LDL cholesterol, mmol/L (mean)	3.4±0.9	3.8±1.1	0.04
LDL cholesterol <2.6%, mmol/L (N,%)	29 (46.8)	33(53.2))	0.03

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Smoking (N,%)	51(86.4)	8(13.6)	<0.001
Diabetes	143(34.1)	276(65.9)	0.89
HbA1C %(mean)	7.5(1.6)	7.9(1.9)	0.03
HbA1C % ≤6.5% (N,%)	40(36.0)	71(64.0)	0.59
Body mass index kg/m2 (mean)	26.6(4.3)	26.7(4.9)	0.73

Events N (%)	Male (N=327) n (%)	Female (N=640) n (%)	
Coronary heart disease N=85 (8.8%)	44(13.5)	41(6.4)	<0.001
Fatal Myocardial infarction	2(0.6)	1(0.2)	0.23
Non-fatal Myocardial infarction	3(0.9)	4(0.6)	0.61
New angina	39(11.9)	36(5.6)	0.001
Heart failure N=7 (0.7%)	1(0.3)	6(0.9)	0.27
Cerebral vascular event N=41 (4.2%)	20(6.1)	20(3.1)	0.03
Fatal stroke	4(1.2)	0(0.0)	0.005
Non-fatal stroke	17(5.2)	20(3.1)	0.11
Peripheral vascular disease N=0 (0%)	0(0.0)	0(0.0)	-

Table 3 shows the risk categories of Framingham general CVD risk score and the CVD events that occurred. The median Framingham general CVD risk score for the study population was 21.1% (IQR 1.2-30.0%). The actual number of CVD events that occurred in the 10 years was 127 (13.1%) while the predicted was 204(21.1%). In male, their median pooled cohort risk score was 30.0% while the events that occur was 62 (19%). In female, their median pooled cohort risk score 18.5% while the event that occur was 65 (10.2%). The number of events occurring in the low risk group in both men and women were consistent with the number predicted. In the medium risk group the risk score tool over-predicted risk in men and women but more so in men. In the high risk group of men, the prediction of CVD events is consistent with the actual events that occurred. However in females with high risk, the tool score over predicted the CVD risk.

Table 3: Comparison of risk categories of Framingham general CVD risk score and CVD events in a 10-year interval (1998-2007)

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Framingham general CVD risk score in 1998,%	Total, N	Observed CVD event (n, %)	Predicted CVD Events (n, %)	
All adults				
Median score: 21.1%	**967**	**127(13.1)**	**204 (21.1)**	**<0.001**
<10%	148	9 (6.1)	9 (6.3)	
10-20%	292	25 (8.6)	40 (13.7)	
>20%	527	93(17.6)	158 (30.0)	
Male				
Median score: 30.0%	**327**	**62(19.0)**	**98 (30.0)**	**0.003**
<10%	12	1(8.3)	1(6.3)	
10-20%	56	2 (3.6)	9 (15.4)	
>20%	259	59(22.8)	74 (28.7)	
Female				
Median score: 18.5%	**640**	**65(10.2)**	**118 (18.5)**	**0.098**
<10%	136	8 (5.9)	9 (6.3)	
10-20%	236	23 (9.7)	34 (14.4)	
>20%	268	34(12.7)	72 (27.0)	

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Table 4 shows the risk categories of Framingham general CVD risk score and medications used in a 10-year interval (1998-2007). Overall the use of medications for CVDs was highest in the high risk group in both men and women at baseline. Nearly three quarters of men and women in the high risk group were already receiving anti-hypertensive at baseline. Medication use increased across all risk categories in both men and women over the 10 years, the greatest increase in use being the use of anti-hypertensive in the female with medium risk (increment of 34%) and use of ant lipid agents among female with high risk groups (increment of 70%).

Table 4 Comparison of risk categories of Framingham general CVD risk score and medications used in a 10-year interval (1998-2007)

Sex	Framingham: CVD Risk Category in 1998	Anti-HPT agents (n, %)		Anti-lipid agents (n, %)		Hypoglycaemic agents (n, %)	
		1998	2007	1998	2007	1998	2007
Male (N=327)	Low risk score <10	4 (33)	8(80)	1(8.3)	4(40)	6(50)	5(50)
	Medium risk score 10- 20	29(52)	43(78)	5(9)	27(49)	19(34)	23(43)
	High risk Score > 20	184(71)	224(94)	19(7)	145(60)	143(55)	168(70)
Female (N=640)	Low risk score <10	45(33)	85(66)	17(13)	78(60)	59(44)	57(44)
	Medium risk score 10- 20	120(51)	193(85)	29(12)	158(69)	112(48)	135(59)

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	High risk Score > 20	195(73)	238(96)	24(9)	196(79)	160(60)	187(75)

The AUC for Framingham general CVD risk score was 0.63 showing moderate discrimination as shown in Figure 2. The calibration for Framingham general CVD risk score was good as the Hosmer-Lemeshow test result was $\chi 2 = 3.25$, $P = 0.78$.

Figure 2: ROC and AUC for Framingham general CVD risk score

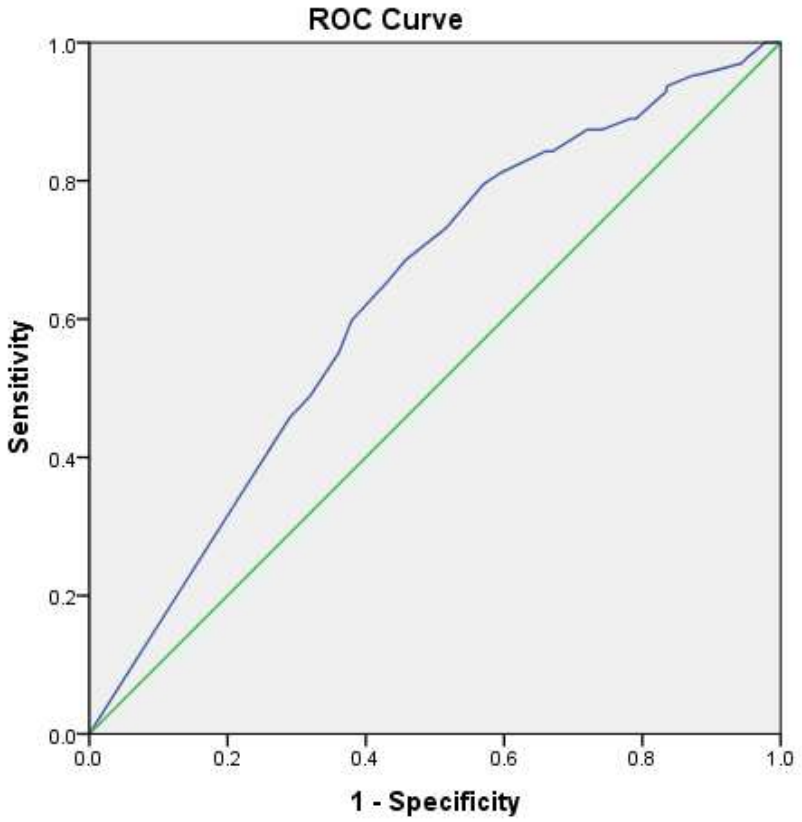

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Table 5 shows the comparison between Framingham general CVD risk score and CVD events according to ethnicity. The Framingham general CVD risk score discriminates moderately well for Malay race (AUC 0.65, p=0.01), Chinese (AUC 0.60, p=0.03) and Indians as well (AUC 0.65, p=0.001). Male (AUC0.63, p=0.002) seems to have better discrimination index from female (AUC 0.58, p=0.04).

Table 5: Comparison Framingham general CVD risk score and CVD events according to ethnicity and gender

	Framingham general CVD risk score (%)	**CVD event**		**AUC (95%CI)**	**p-value**
		Observed N (%)	Predicted N (%)		
Overall(N=967)	21.1	127(13.1)	204(21.1)	0. 63 (0.58,0.68)	<0.001
Malay(N=225)	18.5	26(11.6)	42(18.5)	0. 65 (0.53,0.77)	0.014
Chinese(N=438)	23.2	45(10.3)	102(23.2)	0. 60 (0.52,0.68)	0.027
Indian(N=291)	21.5	54(18.6)	63(21.5)	0. 65 (0.57,0.73)	0.001
Male (N=327)	30.0	62(19.0)	98(30.0)	0.63 (0.56,0.70)	0.002
Female (N=640)	18.5	65(10.2)	118(18.5)	0.58 (0.51,0.65)	0.04

Discussion

Our study showed that the Framingham general CVD risk score tool has moderate discrimination and good calibration in an Asian population. These findings are not surprising as the cohort are patients from a clinic and not subjects in the community. Further their overall profile for CVD risk factors is already high before CVD events have occurred, with the majority of them having underlying diabetes and/or hypertension. Therefore a clustering of patients with higher risk and fewer patients with lower risk will explain why our finding of

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only moderate discrimination. Perhaps this risk prediction model may give a better discrimination in a general population of subjects with a wider range of CV risk.Similarly the overall CVD risk as predicted by the Framingham general CVD risk score tool of our cohort of primary care patients was high in male and medium in female. This is again not a surprising finding as the male in our cohort generall had a higher CVD risk profiles (poorer blood pressure and HbA1C control). Thus they also suffered more CVD events and having hiher mortality rates. It indicates we still have a lot of more to do with these high risks groups.

In-spite of the Framingham risk score seemingly over-predicting CVD risk to some extent, we feel that it is appropriate for use in our cohort. This is because the prediction is accurate for both men and women with low risk and for men with high risk. In fact one could argue that the tool under-estimates risk as the majority of high risk patients were already receiving one or another medication against cardiovascular disease, and hence their risk is expected to be reduced.

Our study found in general that this new risk tool overestimated risk in women. This is consistent with findings in the other studies which used other risk tools [1, 13-17]. While this appears like an overestimation, this may not be the case. It could be because of the increase in use of antihypertensive agents which would have lowered their risk. For example the greatest increase in the use of anti- hypertensive agents sometime in the 10-year period of follow-up was seen. Similarly while use of antihypertensive increased across all risk categories, the greatest increase was seen in the both men and women with medium risk. Furthermore, at the end of 10 years, the achieved mean BP was lower and the control rate of BP higher in the medium risk group compared to the high risk group. The greater use of medication and better

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control of BP could have led to a greater reduction in CV events, and hence leading to what appears to be like an overestimation of risk.

Our present study has several strengths and some limitations. The strength of our study is that it is done in the primary care setting where the CVD risk profiles is different from that in secondary care. To the best of our knowledge, this is the first study that examines the validity and applicability of the Framingham general CVD risk tool for primary care. Secondly, our sample size is large enough to give us a better picture of CVD risk of a multi-ethnic population in Asia where data about the use and applicability of any CVD risk prediction tool is lacking. Our study found that it did fit to be used by all the 3 different ethnic groups with a good calibration although it seems to be apparent overestimate their risk but don't forget that it could be due to the treatment effect. Use of such a tool is of particular importance in the light of limited resources and the rapidly increasing CVD burden in the region.

A limitation of our study is use of CV risk prediction tools are meant to be used to estimate overall CV risk in order on treatment. Most of our patients were already on treatment that would result in an overestimation of risk in most situations. However based on current clinical practice, it would be unethical to do such a study. Despite this is a retrospective study in which there will be some missing data to some extent. However, we were able to compare the characteristics of those with missing data and those included in the analysis and found no clinical differences between them, suggesting there was no substantial bias.

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Conclusions

The Framingham general CVD risk prediction tool is valid for use in primary care population. In the absence of local risk prediction tools, the Framingham CVD risk tool can be used as a surrogate to stratify risk and hence determine the indication for pharmacotherapy. Furthermore this Framingham general CVD risk prediction tool which is meant for use in primary care is fit to be used in a multi-ethnic population in Asia.

Contributions statement

YCC and SYWG contributed to the conceptualizing the paper, data entry and writing of the manuscript while SMC, KC and HML contributed in data analysis and writing of the manuscript. YCC is the corresponding author. All the authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Data sharing

The data is deposited under the website of https://mynotebook.labarchives.com/, an open access repository under name of manuscript and the DOI link is **10.6070/H48W3B96**.

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Title page

Validation of the Framingham General Cardiovascular Risk Score in a multi-ethnic Asian Population– a retrospective cohort study

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Abstract

Objective This study aims to examine the validity of the Framingham general cardiovascular disease risk (CVD) risk chart in a primary care setting.

Design This is a 10 year retrospective cohort study.

Setting A primary care clinic in a teaching hospital in Malaysia.

Participants 967 patients' records were randomly selected from patients who were attending follow up in the clinic.

Main outcome measures Baseline demographic data, history of diabetes and smoking, blood pressure (BP) and serum lipids were captured from patient records in 1998. Each patient's Framingham CVD score was computed from these parameters. All atherosclerotic CVD events occurring between 1998 - 2007 were counted.

Results In 1998, mean age was 57years with 33.8% men, 6.1% smokers, 43.3% diabetics and 59.7% hypertensive. Median BP was 140/80mmHg; total cholesterol 6.0mmol/L (1.3). The predicted median Framingham general CVD risk score for the study population was 21.5% (IQR 1.2-30.0) while the actual CVD events that occurred in the 10 years was 13.1% (127/967). The median CVD points for men was 30.0 giving a CVD risk of more than 30% and for women 18.5, a CVD risk of 21.5%. Our study found that the Framingham general CVD risk score to have moderate discrimination with an AUC of 0.63. It also discriminates well for Malay (AUC 0.65, p=0.01), Chinese (AUC 0.60, p=0.03) and Indians (AUC 0.65, p=0.001). There was good calibration with Hosmer-Lemeshow test $\chi 2 = 3.25$, $P = 0.78$

Conclusions Taking into account that this cohort of patients were already on treatment, the Framingham General CVD Risk Prediction Score predicts fairly accurately for men and overestimates somewhat for women. In the absence of local risk prediction charts, the Framingham general CVD risk prediction chart is a reasonable alternative for use in a multi-ethnic group in a primary care setting.

Strength and Limitation of this study

- The strength of our study is that it is done in a primary care setting where the CVD risk profiles is different from that in secondary care.

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- Another strength is that it examines the validity and applicability of the Framingham general CVD risk tool in a multi-ethnic primary care population.
- Our sample size is large enough to give us a better picture of CVD risk of a multi-ethnic population in Asia where data about the use and applicability of any CVD risk prediction tool has not extensively validated particularly to include non-fatal events.
- Our study found the Framingham General CVD risk score to have a good calibration and hence can be used by all the 3 different ethnic groups.
- However most of our patients were already on treatment and resulted in a seemingly overestimation of cardiovascular risk.
- As this is a retrospective study there will be missing data to some extent. However, we were able to compare the characteristics of those with missing data to those included in the analysis and found no clinical differences between them.

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Introduction

Guidelines on management of cardiovascular diseases (CVD) recommend assessing overall cardiovascular (CV) risk to determine the necessity of pharmacotherapy [1-9]. To date many CVD risk assessment tools have need devised [10]. The most well studied is the Framingham Coronary Heart Disease (CHD) risk prediction Chart [11, 12]. This tool has been validated in different populations and was found to overestimate risk particularly in women, the older age group, British men and European population and certain ethnicities with lower background risk of CVD like the Chinese population [1, 13-17].

Furthermore it has been criticised that the Framingham CHD risk score only predicts risk for fatal and non-fatal coronary events and does not take into account strokes as well as patients already receiving anti-hypertensive therapy, which is the case in many individuals.

Hence the Framingham general CVD risk score tool for primary care was developed in 2008[18]. This newer tool now includes strokes, heart failure and peripheral artery disease and adjusts for patients already on anti-hypertensive therapy. However this risk score chart tool has not been widely validated particularly in the communities with different races. Malaysia is a multi-ethnic country with a population of 30 million. The major ethnic group is the Malay (50.3%) followed by Chinese (21.7%), Indians (6.5%) and others (21.5%) [19].

Hence our aim was to examine the validity of the Framingham general CVD in a multi-ethnic primary care population.

Materials and Methods

Setting

This is a retrospective cohort study. We computed the Framingham general CVD risk score retrospectively in a randomly selected cohort of patients registered with an urban primary care

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clinic. This selected sample consisted of adult patients aged 30 years and older who were free of any cardiovascular events at baseline and who had complete data needed to compute their overall cardiovascular risk. The study was conducted in an outpatient clinic of an academic teaching hospital. Ethics approval for this study was obtained from the Ethics Committee of our institution.

Participants

There were 1536 patients in our original cohort. We excluded 563 patients as they did not have all the variables needed to calculate the FRS. Another 6 patients was excluded as we could not ascertain their CVD status by the end of 2007. Hence a total of 967 patients (62.9%) were eligible for analysis (Figure 1). Out of these, 912 (94.3%) patients completed 10 years follow up and only 55 (5.7%) patients defaulted follow-up. Out of these, 26 (2.7 %) had died with 19 (73%) deaths of non-CVD causes.

Inclusion criteria

All adult patients 30 years and older , without any cardiovascular events and with documented blood pressure (BP) readings whether on or not on treatment, total cholesterol, HDL-cholesterol, smoking status and presence or absence of diabetes mellitus were eligible for this study. These parameters were needed to compute each individual's general CVD risk level.

Design

This sample was randomly selected using a computer generated number based on the patient's unique registration number with the clinic. All patient records were in paper form.

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Data collection

We extracted the patients' socio-demographic data and clinical information based on the first entry in 1998 from their records manually according to a predetermined proforma (clinical report form). Use of hypoglycaemic and lipid lowering agents were also captured. Using age, SBP (treated or not treated) total-cholesterol, HDL-cholesterol levels, smoking and diabetes status we computed each individual's general CVD risk score.

CVD events namely fatal and non-fatal CHD, fatal and non-fatal strokes, heart failure and peripheral artery disease were also captured from the records. For those who did not complete their subsequent 10 year follow up at our clinic (n=24), we traced and examined the case records from the main hospital to determine their CVD outcome. For those patients who did not complete their follow-up in our clinic, we contacted them individually (n=31) to ascertain their CVD status and for any events fatal or non-fatal. Each CVD event was counted as one event in individuals who had more than one event during the 10 years follow up. We further categorised the 10 year CVD risk as low (<10% 10 year CVD risk) medium (10-20% CVD risk) or high >20% CVD risk [20].

Blood Pressure (BP) was measured by our attending doctor using a mercury sphygmomanometer as part of the daily routine clinical practice. Diagnosis of hypertension was made in accordance with standard recommendations [7]. Target control BP is defined as BP < 140/90mmHg for non-diabetics and < 130/80mmHg for patients with diabetes mellitus (DM). Diabetes mellitus is defined as documented by the attending physician or the use of hypoglycaemic agents or both. Smokers were defined if they were still smoking currently. Non-smokers were those who never smoked or currently not smoking regardless of when they had stopped smoking. Total

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cholesterol, LDL and HDL cholesterol were also collected. All blood tests were performed in our teaching hospital's laboratory which is certified by the Royal College of Pathologists of Australasia standards.

Statistical analysis

All statistical analysis was done using the Statistical Package for Social Sciences (SPSS version 21). Continuous data are described as mean and standard deviation if the distribution is normal. When the data is a skewed distribution, median and interquartile range (25-75th percentile) is used. Categorical data are reported as proportions (percentage). Chi-square test or Fisher exact tests were used for the categorical or dichotomous variables.

Discrimination

Discrimination is defined as the ability of the risk prediction model in distinguishing patients who suffered from a CVD event from those who do not using an overall c index. C index is analogous to the area under the receiver operating characteristic curve (AUC). Discrimination is defined as good when c index is closer to 1 whereas a value of 0.5 implies that the risk score tool is no better than chance [21]. A value of 0.75 is considered as good discrimination. Values between 0.51-0.74 is considered moderate and ≤0.5 as poor [22].

Calibration

Calibration was used to assess if the observed 10-year CVD events differed significantly from predicted [8]. The calibration of the Framingham general CVD risk score was determined using Hosmer-Lemeshow test [23]. A $\chi 2$ value of greater than 20 or a p value of less than 0.05 indicates poor calibration.

Results

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A total of 967 out of 1536 patient records of 1998 (baseline) were entered into our analysis.

Table 1 shows the demographic data of our cohort. Our study population was made up of three main ethnic groups, namely the Chinese (45.4%), Malays (23.3%) and Indians (30.2%). The mean age was 56.9 (9.9) years. Two third (66.2%) were females. At baseline in 1998, over half (59.7%) had hypertension, under half (43.3%) had diabetes and less than 10 percent (6.1%) were current smokers, 80.9% (n=339) of the diabetic patients were receiving treatment with either oral hypoglycaemic agents and/or insulin. The mean systolic BP was 140.7±18.6 mmHg and more than half (59.7%) of them was on anti-hypertensive agents. However only 9.8% of the population (n=95) received statin therapy in 1998. We also compared the baseline characteristics for those who were entered into our analysis to the patients who were excluded. Basically there was no significant differences between their baseline characteristics except for the smoking status and statin use.

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Table 1 Comparison of CV risk factors between study population and excluded patients as well as changes in CV risk factors in 1998 and 2007

	Study population (n=973)	Excluded population (n=563)	P-value	2007
Age, year (mean)	56.9±9.9	55.8 ± 10.4	0.06	66.9 ± 9.9
Sex, female (n, %)	640 (66.2)	362 (64.3)	0.45	640 (66.2)
Ethnicity (n, %)			0.16	
Malay	225 (23.3)	155 (27.5)		225 (23.3)
Chinese	438 (45.4)	221 (39.3)		438 (45.4)
Indian	291 (30.2)	180 (32.0)		291 (30.2)
Others	13 (1.2)	7 (1.2)		13 (1.2)
Diabetes mellitus (n, %)	419 (43.3)	260 (46.3)	0.28	556 (57.5)
HbA1C, % (mean)	7.8 ± 1.9	7.9 ± 1.9	0.28	7.5 ± 1.7
DM controlled with HbA1c ≤ 6.5% (n, %)	113(11.6)	64(11.4)	0.89	168 (17.4)
Systolic BP, mmHg (mean)	140.7±18.6	139.0±19.7	0.22	134.9 ± 16.5
Use of anti-hypertensive agents (n, %)	577 (59.7)	308 (54.7)	0.09	791 (81.8)
RAS blocker use (n, %)	71(7.3)	27(4.8)	0.05	465 (48.1)
Total cholesterol, mmol/L (mean)	6.1±1.1	5.8±1.1	0.06	4.9 ± 1.0
HDL cholesterol, mmol/L (mean)	1.2± 0.4	1.4 ±0.2	0.49	1.3± 0.3
LDL cholesterol, mmol/L (mean)				3.0± 0.8
Statin use in 1998 (n, %)	95 (9.8)	32 (5.7)	0.005	608 (62.9)
Smoker (n, %)	59 (6.1)	47 (8.3)	<0.001	59 (6.1)

Table 1 also demonstrates the change in CVD risk factors between baseline and at the end of 10 years. In spite of the increase in the prevalence of diabetes from 43.3% to 46.3%, HbA1c control actually improved from a mean of 7.8% to 7.5%. The mean systolic blood pressure was reduced by 5.8mmHg, from 140.7mmHg to 134.9mmHg. The control rate for blood pressure improved from 41.3% to 55.6%. There was an increase in the use of renin-angiotensin system (RAS) blockers from 7.3% to 48.1%. The number of patients receiving statin increased significantly from 9.8% to 62.9% in 2007. There was also improvement in the lipid profile of patients at the

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end of 10 years compared to baseline. Mean total cholesterol was reduced from 6.1 mmol/L to 4.9 mmol/L while the mean HDL increased from 1.2 mmol/L to 1.3 mmol/L.

Table 2 compares CVD risk factors at baseline and events rate at the end of 10 years in males and females. Generally males had higher CV risk profiles than females. They were older, more smokers and had poorer control of blood pressure and lipid profiles but they had slighter better glucose profile. The CHD events were twice more common in males (13.5%) than in females (6.4%). Similarly strokes were higher in males (6.1%) than in females (3.1%). In total, 6 CVD events were fatal in males and only one fatal in female.

Table 2: Comparison CV risk factors in 1998 and events at the end of 10 years according to gender

	Male (N=327)	Female (N=640)	P-value
Age , year (mean)	57.7(10.1)	56.5 (9.7)	0.07
Hypertension	217(66.4)	360(56.3)	0.002
Systolic BP, mmHg (mean)	142.3(17.6)	139.9(19.1)	0.07
Diastolic BP, mmHg (mean)	87.6(10.4)	83.3(9.5)	<0.001
Blood pressure control rate (N, %)	22(25.0))	66(75.0)	<0.001
Total cholesterol, mmol/L (mean)	5.8(1.1)	6.2(1.1)	<0.001
HDL cholesterol, mmol/L (mean)	1.1(0.4)	1.3(0.3)	<0.001
Triglyceride, mmol/L,(mean)	1.9(1.0)	1.6(0.9)	<0.001
LDL cholesterol, mmol/L (mean)	3.4±0.9	3.8±1.1	0.04
LDL cholesterol <2.6%, mmol/L (N, %)	29 (46.8)	33(53.2))	0.03
Smoking (N, %)	51(15.6)	8(1.3)	<0.001
Diabetes	143(43.7)	276(43.1)	0.89
HbA1C %(mean)	7.5(1.6)	7.9(1.9)	0.03
HbA1C % ≤6.5% (N, %)	40(12.2)	71(11.1)	0.59
Body mass index kg/m2 (mean)	26.6(4.3)	26.7(4.9)	0.73
Events N (%)	Male (N=327) n (%)	Female (N=640) n (%)	
Coronary heart disease N=85 (8.8%)	44(13.5)	41(6.4)	<0.001
Fatal Myocardial infarction	2(0.6)	1(0.2)	0.23

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Non-fatal Myocardial infarction	3(0.9)	4(0.6)	0.61
New angina	39(11.9)	36(5.6)	0.001
Heart failure N=7 (0.7%)	1(0.3)	6(0.9)	0.27
Cerebral vascular event N=41 (4.2%)	20(6.1)	20(3.1)	0.03
Fatal stroke	4(1.2)	0(0.0)	0.005
Non-fatal stroke	17(5.2)	20(3.1)	0.11
Peripheral vascular disease N=0 (0%)	0(0.0)	0(0.0)	-

Table 3 shows the risk categories of Framingham general CVD risk score and the CVD events that occurred. The median Framingham general CVD risk score for the study population was 21.1% (IQR 1.2-30.0%) with a 95% confidence interval (CI) of 19.9% to 21.1%. The actual number of CVD events that occurred in the 10 years was 127 (13.1%) while the predicted was 204 (21.1%). In males, their median risk score was 30.0% (95% CI 24.9%, 26.4%) while the events that occur was 62 (19%). In females, their median risk score was 18.5% (95% CI 24.9%, 26.4%) while the event that occur was 65 (10.2%).

The number of events occurring in the low risk group in both men and women were consistent with the number predicted. In the medium risk group, the risk score tool over-predicted risk in men and women but more so in men. In the high risk group of men, the prediction of CVD events is consistent with the actual events that occurred. However in females with high risk, the risk score tool over predicted the CVD risk.

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Table 3: Comparison of risk categories of Framingham general CVD risk score and CVD events in a 10-year interval (1998-2007)

Framingham general CVD risk score in 1998,%	Total, N	Predicted CVD Events (n, %)	Observed CVD event (n, %)	
All adults				
Median score: 21.1%	**967**	**204 (21.1)**	**127(13.1)**	**<0.001**
<10%	148	9 (6.3)	9 (6.1)	
10-20%	292	40 (13.7)	25 (8.6)	
>20%	527	158 (30.0)	93(17.6)	
Male				
Median score: 30.0%	**327**	**98 (30.0)**	**62(19.0)**	**0.003**
<10%	12	1(6.3)	1(8.3)	
10-20%	56	9 (15.4)	2 (3.6)	
>20%	259	74 (28.7)	59(22.8)	
Female				
Median score: 18.5%	**640**	**118 (18.5)**	**65(10.2)**	**0.098**
<10%	136	9 (6.3)	8 (5.9)	
10-20%	236	34 (14.4)	23 (9.7)	
>20%	268	72 (27.0)	34(12.7)	

Table 4 shows the risk categories of Framingham general CVD risk score and medications used in a 10-year interval (1998-2007). Overall the use of medications for CVDs was highest in the high risk group in both men and women at baseline. Nearly three quarters of men and women in the high risk group were already receiving anti-hypertensive at baseline. Medication use increased across all risk categories in both men and women over the 10 years, the greatest increase in use being the use of anti-hypertensive in the female with medium risk (increment of 34%) and use of ant lipid agents among female with high risk groups (increment of 70%).

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Table 4 Comparison of risk categories of Framingham general CVD risk score and medications used in a 10-year interval (1998-2007)

Sex	Framingham: CVD Risk Category in 1998 (%)	Anti-HPT agents (N, %)		Anti-lipid agents (N, %)		Hypoglycaemic agents (N, %)	
		1998	2007	1998	2007	1998	2007
Male (N=327)	Low risk score <10	4 (33)	8(80)	1(8)	4(40)	6(50)	5(50)
	Medium risk score 10- 20	29(52)	43(78)	5(9)	27(49)	19(34)	23(43)
	High risk Score > 20	184(71)	224(94)	19(7)	145(60)	143(55)	168(70)
Female (N=640)	Low risk score <10	45(33)	85(66)	17(13)	78(60)	59(44)	57(44)
	Medium risk score 10- 20	120(51)	193(85)	29(12)	158(69)	112(48)	135(59)
	High risk Score > 20	195(73)	238(96)	24(9)	196(79)	160(60)	187(75)

The AUC for Framingham general CVD risk score was 0.63 showing moderate discrimination as shown in Figure 2. The calibration for Framingham general CVD risk score was good as the Hosmer-Lemeshow test result was $\chi 2 = 3.25$, $P = 0.78$.

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Table 5 shows the comparison between Framingham general CVD risk score and CVD events according to ethnicity. The Framingham general CVD risk score discriminates moderately well for Malay race (AUC 0.65, p=0.01), Chinese (AUC 0.60, p=0.03) and Indians as well (AUC 0.65, p=0.001). Males (AUC0.63, p=0.002) seem to have better discrimination index than female (AUC 0.58, p=0.04).

Table 5: Comparison Framingham general CVD risk score and CVD events according to ethnicity and gender

	Framingham general CVD risk score (%)	**CVD event**		**AUC (95%CI)**	**p-value**
		Observed N (%)	Predicted N (%)		
Overall(N=967)	21.1	127(13.1)	204(21.1)	0. 63 (0.58,0.68)	<0.001
Malay(N=225)	18.5	26(11.6)	42(18.5)	0. 65 (0.53,0.77)	0.014
Chinese(N=438)	23.2	45(10.3)	102(23.2)	0. 60 (0.52,0.68)	0.027
Indian(N=291)	21.5	54(18.6)	63(21.5)	0. 65 (0.57,0.73)	0.001
Male (N=327)	30.0	62(19.0)	98(30.0)	0.63 (0.56,0.70)	0.002
Female (N=640)	18.5	65(10.2)	118(18.5)	0.58 (0.51,0.65)	0.04

Discussion

Our study shows the Framingham general cardiovascular risk score tool to have moderate discrimination and good calibration in an Asian population. These findings are not surprising as our study cohort are actually patients from a clinic and not subjects in the community, Hence not unexpectedly the overall CVD risk profile of our cohort is already high before CVD events have occurred, with the majority of them having underlying diabetes and/or hypertension.

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Therefore a clustering of patients with higher risk and fewer patients with lower risk explain our finding of only moderate discrimination. Perhaps this risk prediction model may give a better discrimination in a general population of subjects with a wider range of CV risk. Similarly the overall CVD risk as predicted by the Framingham general CVD risk score tool of our cohort of primary care patients was high in males and medium in females. This is again not a surprising finding as the males in our cohort generally had a higher CVD risk profiles (poorer blood pressure and LDL<2.6%). Conseqeuently they also had more CVD events and higher mortality rates. Thus the Framingham CVD risk tool helps to identify appropriately patients at high risk where more needs to be done to reduce their risk . A recent study validated the Framingham cardiovascular risk score in Tehran , a Middle Eastern population and found it to work very well too [24].

In-spite of the Framingham risk score seemingly over-predicting CVD risk to some extent, we feel that it is appropriate for use in our cohort. This is because the prediction is accurate for both men and women with low risk and for men with high risk in that the predicted and the observed risk score belong to the same category of risk i.e when the predicted risk is high, the observed risk is also high. In fact one could argue that the tool under-estimates risk as the majority of high risk patients were already receiving one or another medication for the cardiovascular disease, and hence their risk is expected to be reduced.

Our study found in general that this new risk tool overestimated risk in women. This is consistent with findings in the other studies which used other risk tools [1, 13-17]. While this appears like an overestimation, this may not be the case. It could be because of the increase in use of

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antihypertensive agents which would have lowered their risk. For example the greatest increase in the use of anti- hypertensive agents sometime in the 10-year period of follow-up was seen [25]. Similarly while use of antihypertensive increased across all risk categories, the greatest increase was seen in the both men and women with medium risk. Furthermore, at the end of 10 years, the achieved mean BP was lower and the control rate of BP higher in the medium risk group compared to the high risk group. The greater use of medication and better control of BP could have led to a greater reduction in CV events, and hence leading to what appears to be like an overestimation of risk.

Our present study has several strengths and some limitations. The strength of our study is that it is done in the primary care setting where the CVD risk profiles is different from that in secondary care. Another strength of this study is that it examines the validity and applicability of the Framingham general CVD risk tool in a multi-ethnic primary care population. Secondly, our sample size is large enough to give us a better picture of CVD risk of a multi-ethnic population in Asia where data about the use and applicability of any CVD risk prediction tool is lacking. Our study found that it did have a good fit and good calibration to be used by all the 3 different ethnic groups Although it seems to be apparently overestimating risk it must be remembered that this could be due to treatment effect thus giving a seemingly overestimation of risk. Use of such a tool is of particular importance in the light of limited resources and the rapidly increasing CVD burden in the region to help identify those most at risk who needs to be treated in order to reduce their risk.

A limitation of our study is that the use of CV risk prediction tools are meant to be used to estimate overall CV risk in order to decide on treatment. Most of our patients were already on treatment and that would result in an overestimation of risk in most situations. However based on

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current clinical practice, it would be unethical to do a study where patients at risk are not treated in order to derive a risk tool without treatment being on board. As this is a retrospective study there will be missing data to some extent. However, we were able to compare the characteristics of those with missing data (and hence excluded from the analysis) to those included in the analysis and found no major clinical differences between them, suggesting there was no substantial bias.

Conclusions

The Framingham general CVD risk prediction tool is valid for use in primary care population. In the absence of local risk prediction tools, the Framingham CVD risk tool can be used as a surrogate to stratify risk and hence determine the indication for pharmacotherapy. Furthermore this Framingham general CVD risk prediction tool which is meant for use in primary care provides a good fit for use in a multi-ethnic population in Asia.

Figure legends

Figure 1: Flowchart of patients included in the analysis
Figure 2: ROC and AUC for Framingham general CVD risk score

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Contributions statement

YCC and SYWG contributed to the conceptualizing the paper, data entry and writing of the manuscript while SMC, KC and HML contributed in data analysis and writing of the manuscript. YCC is the corresponding author. All the authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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Data sharing

The data is deposited under the website of https://mynotebook.labarchives.com/, an open access repository under name of manuscript and the DOI link is **10.6070/H48W3B96**.

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Figure 1: Flowchart of patients included in the analysis

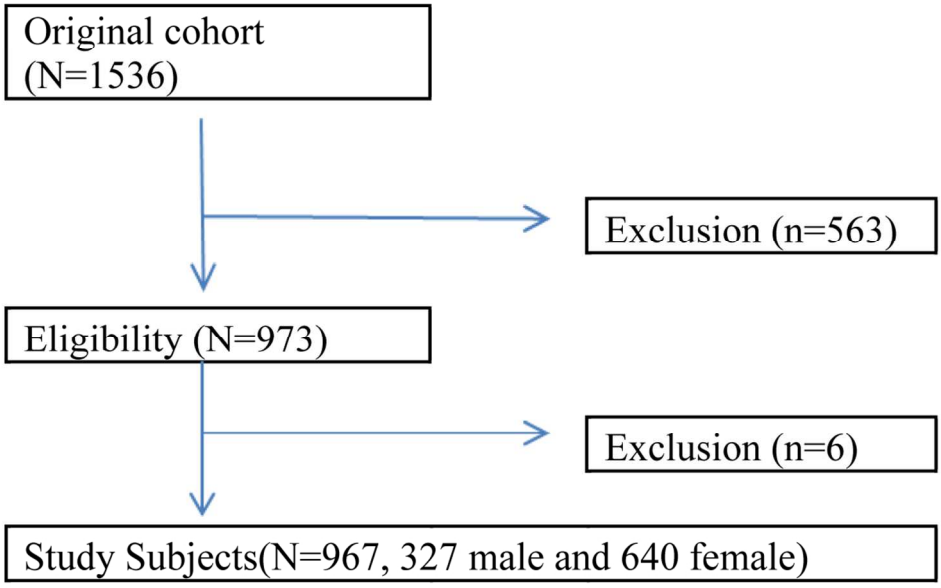

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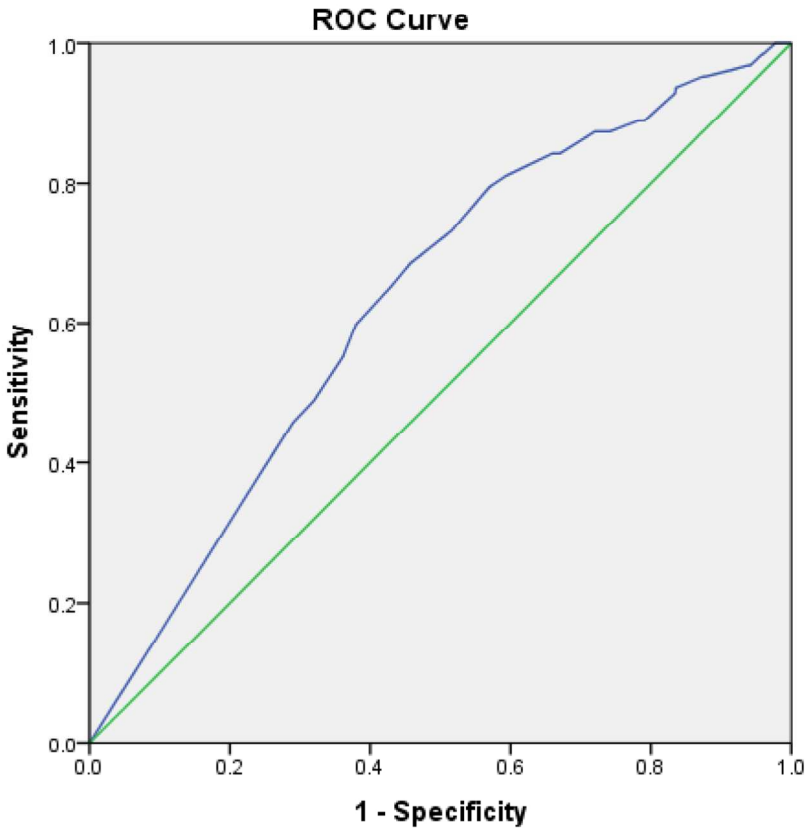
Figure 2: ROC and AUC for Framingham general CVD risk score



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