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Applicability of Framingham risk equations for studying a low-income Mexican population

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Abstract

Objective. To compare the predicted risk of coronary heart disease (CHD) and incident myocardial infarction (MI) using Framingham score equations with the observed rate of MI in Mexican subjects. **Material and Methods.** Longitudinal study that included 1 667 men and women aged 35 to 64 years without MI at baseline. Incident MI was defined by electrocardiogram or death certificate. The predicted risk of fatal MI, non-fatal MI, and both was calculated using Framingham score equations. Predicted to observed risk ratio of MI was estimated. **Results.** There were 34 incident MI cases and 24 MI deaths (median follow-up 6.2 years). The score equations overestimated the prediction of incident MI and CHD death (ratio 2.27, 95% CI, 1.19-3.34) and incident MI (ratio 2.36, 95% CI, 1.07-3.65) in men. **Conclusions.** The Framingham score overestimated incident MI and CHD death risk in men; however, other studies are needed to confirm our results for recalibrating the score for Mexican subjects.

Key words: myocardial infarction; mortality; prediction; Mexico

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Resumen

Objetivo. Comparar el riesgo predicho y observado de enfermedad coronaria (EC) e infarto al miocardio (IM) usando ecuaciones del puntaje de Framingham en individuos mexicanos. **Material y métodos.** Estudio longitudinal de 1 667 hombres y mujeres de entre 35 a 64 años de edad y sin IM en la medición basal. IM se definió por electrocardiograma o certificado de defunción. Se estimó el riesgo predicho y la razón del riesgo predicho y observado de IM. **Resultados.** Durante el seguimiento (mediana de 6.2 años) hubo 34 casos y 24 defunciones por IM. El puntaje sobreestimó la predicción de IM y muerte por EC (razón 2.27, IC 95% 1.19-3.34) e IM incidente (razón 2.36, IC 95% 1.07-3.65) en hombres. **Conclusiones.** En este estudio, el puntaje de Framingham sobreestimó el riesgo de IM y muerte por IM en hombres; sin embargo, estos resultados necesitan ser confirmados por otros estudios, para la posterior recalibración del puntaje en población mexicana.

Palabras clave: infarto del miocardio; mortalidad; predicción; México

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Incidence and prevalence of coronary heart disease (CHD), particularly myocardial infarction (MI), has increased in most regions of the world over the last decades. This trend is associated with a mounting prevalence of classic cardiovascular risk factors such as diabetes, dyslipidemia, hypertension, obesity, and smoking, among others.¹⁻³ Worldwide, mortality from CHD has also risen, and available population-based studies confirm a high mortality rate in both sexes.^{4,5} In addition, some differences in morbidity and mortality from CHD have been documented by ethnicity and might be accounted for, in part, by different prevalences of the main cardiovascular risk factors.⁶⁻⁹

Currently, CHD prevention has focused on the identification of individuals at high risk by combining individual risk factors and reducing overall absolute cardiovascular risk.¹⁰⁻¹³ Several methods originated in specific populations combine the effect of some cardiovascular risk factors to calculate overall absolute risk. Specifically, the Framingham score equations estimate the risk of developing different cardiovascular outcomes (including fatal and non-fatal CHD) at 5 and 10 years of follow-up.¹⁴⁻¹⁶ The score usually includes age, blood pressure (BP), total cholesterol or LDL-cholesterol, HDL-cholesterol, and diabetes, and estimation is done separately by sex. Perhaps the equation most widely used is that which includes categorical variables to predict total CHD,¹⁵ since its application is easier in the clinical setting.

Previous reports have shown that the Framingham score overestimates cardiovascular risk in several populations,¹⁷⁻²¹ including Puerto Ricans¹⁶ and Spaniards.²² However, the accuracy of the Framingham score in other Hispanic populations such as Mexicans has been scarcely evaluated, in spite of being widely used to define timely therapeutic intervention, especially with cholesterol lowering drugs. In this study, we evaluated the accuracy of some of the Framingham risk equations^{14,15} to predict MI in a low-income Mexican populations, considering fatal and non-fatal MI both together and separately.

Material and Methods

Study design

The Mexico City Diabetes Study is a prospective, population-based cohort designed to describe the prevalence and incidence of diabetes and cardiovascular risk factors in low-income urban populations in Mexico City. The detailed methodology has been reported elsewhere.²³ Briefly, a population-based sample of 2 282 men and non-pregnant women aged 35 to 64 years from a low-

income sector completed a baseline interview and physical examination in 1989-1990. Two follow-up visits were carried out in 1994-1996 ($n=1\,773$) and in 1998-2000 ($n=1\,764$). A total of 1 667 subjects were included in the present study, after exclusion of 86 subjects with previous MI corroborated by ECG, 492 without ECG at baseline, and 37 without Framingham score information. When comparing included and excluded subjects without MI at baseline, we found no differences with regard to sex, diabetes, serum cholesterol, and HDL-cholesterol; however, we observed significant differences in age (48.1 *vs.* 46.9 years old, respectively), hypertension (23.1 *vs.* 18.2%, respectively), and current smoking (17.8 *vs.* 27.4%, respectively).

Risk factors assessment

At baseline and follow up visits, participants completed risk factor questionnaires through a structured interview and a clinical examination including anthropometry, blood pressure (BP), and blood samples. Subjects were asked about their smoking habits. Systolic (SBP) and diastolic (DBP) blood pressures were measured three times (after resting for at least 5 min) using a random zero sphygmomanometer (Hawksley, London). We used the average of the last two readings to classify BP levels. BP categories were defined according to the Fifth Joint National Committee on Hypertension definition (JNC V) as follows:²⁴ optimal BP (SBP < 120 and DBP < 80 mmHg); normal BP (SBP 120-129 or DBP 80-84 mmHg); high normal BP (SBP 130-139 or DBP 85-89 mmHg); hypertension stage I (SBP 140-159 or DBP 90-99 mmHg), and hypertension stage II-IV (SBP \geq 160 or DBP \geq 100 mmHg). Serum total cholesterol and HDL-cholesterol were determined by cholesterol-esterase and further classified into the following categories: < 200, 200-239, and \geq 280 mg/dL for total cholesterol and < 35, 35-44, and \geq 45 mg/dL for HDL-cholesterol. Blood pressure and cholesterol categorizations were made independently of the use of antihypertensive or lipid lowering drug treatment. Diabetes was diagnosed as fasting glucose \geq 126 mg/dL (7.0 mmol/L), 2-hour glucose \geq 200 mg/dL (11.1 mmol/L) or self-report and treatment with hypoglycemic medication.²⁵ Left ventricular hypertrophy (LVH) was determined by resting standard ECG according to the Minnesota code criteria.²⁶ In addition, metabolic syndrome (MS) was defined following the criteria of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III).²⁷

Laboratory determinations were performed in the research laboratory of the Division of Clinical Epidemiology at the Medicine Department of the University of Texas Health Science Center at San Antonio, USA. The

Institutional Review Boards of both The University of Texas Health Science Center and the Centro de Estudios en Diabetes approved the study protocol. Each participant gave informed consent.

Ascertainment of incident and fatal myocardial infarction

Incident MI comprised cases identified through follow-up visits by resting ECG or by death certificate. A resting standard 12-lead ECG was taken at each examination, with the subject in a supine position. A standard interpretation of ECGs at a reading center (Wake Forest University, EPICARE Center) was made using the Minnesota Code. We included all possible and probable MI based on the following codes: Q-QS pattern with 1.1-1.2.7, Q-QS and T wave pattern with 1.2.8-1.3, and T wave pattern with 5.1-5.3.²⁶ To determine the vital status of the study population, a telephone interview was carried out for the whole sample and death certificates were obtained. Myocardial infarction was considered as cause of death when it was the underlying cause, and classified according to the International Classification of Diseases 10th Rev. (ICD 10^a, codes 410.0-410.9).²⁸ Although we had information about angina by using the Rose questionnaire, we did not include it as an outcome because of poor accuracy to differentiate angina in this population.

Framingham score equations

We used several specific equations to calculate the predicted probability of total CHD, incident MI, and CHD death. We first estimated the predicted risk of total CHD (including angina as possible outcome), applying the β -coefficients of Cox proportional hazards model obtained from the Framingham population by Wilson *et al.*¹⁵ that included age (predefined categories), current smoking, diabetes, blood pressure regardless of hypertensive treatment (predefined BP categories), serum cholesterol (predefined categories), and HDL-cholesterol (predefined categories). In addition, we separately estimated the predicted probability of total CHD, incident MI (only hard outcomes), and CHD death applying the β -coefficients of non-proportional hazards Weibull accelerated failure time model obtained by Anderson *et al.*¹⁴ that included (in their continuous manner, when appropriate) age, sex, SBP or DBP, current smoking, HDL-C, diabetes, and ECG-LVH. For each participant, we obtained a 10-year predicted probability of CHD, incident MI, and CHD death with each of the equations described above. Assuming a constant rate, we estimated the predicted probability at a specific

follow-up time using the equation $p = 1 - [(1-r)^{(1/10)}]^t$, where r is the Framingham 10-year risk and t is the specific follow-up for each subject.

Data analysis

The Framingham score variables were compared between men and women using mean, standard deviation (SD), median, percentiles, and proportions when appropriate. Observed incidence rates and their 95% confidence interval (95% CI) were calculated by the Kaplan-Meier method as the number of people who had fatal or non-fatal MI during follow-up, divided by person-years at risk per 1 000 person-years. Age-adjusted incidence rates were estimated using the direct method taking the 2000 Mexican population as the standard population. On the basis of each of the Framingham score equations, we calculated the predicted number of cases (CHD, incident MI, and CHD death) as the sum of all individual predicted probabilities at specific follow-up time and calculated the predicted rate dividing the predicted number of cases by person-years at risk expressed as rates per 1 000 person-years. We calculated the ratio of predicted rate over the observed rate from each equation for different outcomes (CHD, incident MI, and CHD death) and their 95% CI by predefined age categories. The analyses were conducted using SAS 9.0 (SAS Institute Inc., Cary, NC) and Stata/SE 9.0 (Stata Corporation, Texas).

Results

Description of the study population

Of 1 667 subjects included in this study, 681 (40.9%) were men and 986 (59.1%) were women. Mean age was similar in both men and women. Prevalence of diabetes was 12.0% in men and 13.2% in women. Current smoking in men was more than twice the proportion in women. SBP and DBP were higher in men, while HDL-cholesterol and fasting glucose levels were higher in women (Table I).

During a median follow-up of 6.2 years (range 0.2-9.8 years), 58 subjects developed MI, 34 were detected by ECG (13 men and 21 women) and 24 by death certificate (14 men and 10 women). From cases diagnosed by ECG, 14 were classified as possible and 20 as probable MI. Age-specific incidence rate for MI increased in both sexes with age (Table II). Age-adjusted incidence rate was slightly higher, but not significant, in men (6.5 per 1 000 person-years, 95% CI 4.0-8.9) than in women (5.2 per 1 000 person-years, 95% CI 3.4-7.0), with a 1.3:1 men-to-women ratio. Age-adjusted incidence rates for

Table I
BASELINE CARDIOVASCULAR RISK FACTORS
IN A LOW-INCOME MEXICAN POPULATION BY SEX.
THE MEXICO CITY DIABETES STUDY,
FEBRUARY 1990-NOVEMBER 2000

Cardiovascular risk factors	Men n= 681 mean (SD)	Women n= 986 mean (SD)
Age (years)	46.8 (8.3)	47.0 (8.2)
Current smoking (n, %)	289 (42.4)	184 (18.7)*
SBP (mmHg)	119.1 (15.8)	115.1 (17.4)*
DBP (mmHg)	75.4 (10.4)	71.3 (9.9)*
Hypertension (n, %)	96 (14.10)	108 (11.0)‡
Diabetes (n, %)	82 (12.0)	130 (13.2)
Cholesterol mg/dL	192.9 (41.7)	192.2 (44.3)
HDL-cholesterol mg/dL	30.1 (7.9)	34.6 (9.0)*
Framingham score (%)§	6.0 (3.8-9.5)	3.1* (1.4-6.5)

* $p \leq 0.001$

‡ $p = 0.05$

§ Using the Framingham score equation published by Wilson P, et al¹⁵

SD: standard deviation

SBP: systolic blood pressure

DBP: diastolic blood pressure

HDL: high density lipoprotein

MI in subjects without and subjects with diabetes were 4.4 (95% CI 3.0-5.8) and 10.1 (95% CI 4.7-5.5) per 1 000 person-years, respectively. As for fatal and non-fatal MI, age-adjusted incidence rate was higher in men than in women for the former (3.5 and 1.8 per 1 000 person-years, respectively), and similar in both sexes for the latter (3.1 vs. 3.6 per 1 000 person-years, for men and women, respectively).

Observed and predicted myocardial infarction

Table II shows a comparison between predicted and observed cases and rates of total CHD by age and sex, based on predefined categories of risk factors as suggested by Wilson *et al.*¹⁵ The Framingham score prediction overestimated the observed number of total CHD cases in both men (50 vs. 27 cases, respectively) and women (48 vs. 31 cases, respectively). Overall ratio of predicted/observed rate was 1.84 (95% CI, 1.15-2.53) for men and 1.55 (95% CI, 1.01-2.08) for women. Both predicted and observed rates of CHD increased with age in men and in women; however, the overestimation tended to be smaller among older participants in both sexes. In addition, the ratio of predicted/observed rate

Table II
COMPARISON OF OBSERVED MYOCARDIAL INFARCTION AND PREDICTED ABSOLUTE CORONARY HEART DISEASE RISK BY SEX AND BY AGE CATEGORIES.

THE MEXICO CITY DIABETES STUDY, FEBRUARY 1990-NOVEMBER 2000

Age (years)	Person-years at risk	No. cases observed	Predicted	Rate* observed (95% CI)	Predicted	Ratio P/O‡ (95% CI)
Men						
35-44	1 936.5	6	14	3.1 (1.4-6.9)	7.3	2.37 (0.48-4.26)
45-54	1 473.4	8	19	5.4 (2.7-10.9)	12.7	2.34 (0.70-3.97)
55-64	888.1	13	17	14.6 (8.5-25.2)	19.0	1.29 (0.61-1.98)
Total	4 298.0	27	50	6.3 (4.3-9.2)	11.6	1.84 (1.15-2.53)
Women						
35-44	2 767.6	6	7	2.2 (1.0-4.8)	2.7	1.25 (0.24-2.25)
45-54	2 180.7	7	20	3.2 (1.5-6.7)	9.0	2.79 (0.72-4.86)
55-64	1 288.3	18	21	14.0 (8.8-22.2)	16.2	1.16 (0.64-1.68)
Total	6 236.6	31	48	5.0 (3.5-7.1)	7.7	1.55 (1.01-2.08)
Both						
35-44	4 704.1	12	21	2.6 (1.4-4.5)	4.6	1.81 (0.79-2.83)
45-54	3 654.1	15	39	4.1 (2.5-6.8)	10.5	2.55 (1.26-3.84)
55-64	2 176.4	31	38	14.2 (10.0-20.3)	17.3	1.22 (0.80-1.63)
Total	10 534.6	58	98	5.5 (4.3-7.1)	9.3	1.68 (1.26-2.11)

* Per 1 000 person-years

‡ Ratio of predicted to observed (P/O) absolute rates

Using the Framingham score equation published by Wilson P, et al¹⁵

was 1.66 (95% CI 1.13-2.20) for subjects with MS and 1.78 (95% CI 1.02-2.53) for subjects without. When the ratio was estimated in subjects with ≥ 3 risk factors of the Framingham score *versus* those with < 3 risk factors, using the moderate risk level for each risk factor as cut point, we found that the overestimation was largely unchanged. Ratios were 1.81 (1.12-2.49) for subjects with ≥ 3 risk factors and 1.59 (1.04-2.13) for those with < 3 . In both stratifications, the overestimation was smaller in older participants. (Data not shown.)

Table III presents a comparison between predicted and observed cases and rates of total CHD, incident MI, and CHD death by sex using scores for different equations. When the two equations for total CHD were used, the Framingham score overestimated the predicted number of CHD cases compared with the observed MI cases in both men (50 *vs.* 27 and 54 *vs.* 17 cases, respectively) and women (48 *vs.* 31 and 40 *vs.* 26 cases, respectively). The ratio of predicted/observed rate using the first equation was 1.84 (95% CI 1.15-2.53) in men and 1.55 (95% CI 1.01-2.08) in women, whereas the ratio using the second equation was 3.17 (95% CI

1.67-4.68) in men and 1.57 (95% CI 1.67-2.17) in women. The main difference between the two equations is that the first includes most of the categorical variables, whereas the second includes continuous variables, as well as ECG-LHV. Since part of this overestimation can be explained by our not including angina as a potential outcome, we further explored more specific equations that used only "hard" outcomes: non-fatal MI, fatal CHD, or both. Using these equations, we still found overestimation in the whole population, but mainly in men, whereas in women predicted and observed rates were similar. The amount of overestimation was alike when the equations for incident MI and CHD death (ratio 2.27, 95% CI, 1.19-3.34) and incident MI were used (ratio 2.36, 95% CI, 1.07-3.65).

Discussion

Results from this study showed that the Framingham score equations for CHD systematically overestimated the predicted risk of MI (fatal and non-fatal) in a Mexican population. However, we found that the overestima-

Table III
COMPARISON OF OBSERVED FATAL AND NON-FATAL MYOCARDIAL INFARCTION AND PREDICTED ABSOLUTE RISK USING SEVERAL FRAMINGHAM SCORE EQUATIONS. THE MEXICO CITY DIABETES STUDY, FEBRUARY 1990-NOVEMBER 2000

Reference		Outcome		Person-years at risk	No. cases		Rate* Observed (95% CI)	Predicted	Ratio P/O cases† (95% CI)
		Predicted	Observed		O	P			
Men (n= 681)	Wilson P ¹⁵	CHD	Fatal and non-fatal MI	4 298.0	27	50	6.3 (4.3-9.2)	11.6	1.84 (1.15-2.53)
Women (n= 986)				6 236.6	31	48	5.0 (3.5-7.1)	7.7	1.55 (1.01-2.08)
Both (n= 1 667)				10 534.6	58	98	5.5 (4.3-7.1)	9.3	1.68 (1.26-2.11)
Men (n= 670)	Anderson HM ¹⁴	CHD	Fatal and non-fatal MI	4 265.9	17	54	4.0 (2.5-6.4)	12.7	3.17 (1.67-4.68)
Women (n= 979)				6 202.1	26	40	4.2 (2.9-6.2)	6.4	1.57 (1.67-2.17)
Both (n= 1 649)				10 468.0	43	95	5.5 (4.3-7.1)	9.1	2.20 (1.55-2.86)
Men (n= 670)	Anderson HM ¹⁴	Incident MI and CHD death	Fatal and non-fatal MI	4 265.9	17	38	4.0 (2.5-6.4)	8.9	2.27 (1.19-3.34)
Women (n= 979)				6 202.1	26	20	4.2 (2.9-6.2)	3.2	0.76 (0.46-1.05)
Both (n= 1 649)				10 468.0	43	58	5.5 (4.3-7.1)	5.5	1.35 (0.95-1.76)
Men (n= 666)	Anderson HM ¹⁴	Incident MI	Non-fatal MI	4 265.9	13	30	3.1 (1.8-5.3)	7.1	2.36 (1.07-3.65)
Women (n= 974)				6 202.1	21	16	3.4 (2.2-5.2)	2.6	0.74 (0.42-1.07)
Both (n= 1 640)				10 468.0	34	46	3.3 (2.3-4.6)	4.4	1.36 (0.90-1.83)
Men (n= 657)	Anderson HM ¹⁴	CHD death	Fatal MI	42 16.0	4	7	0.9 (0.3-2.5)	1.7	1.85 (0.03-3.67)
Women (n= 958)				61 15.8	5	4	0.8 (0.3-2.0)	0.7	0.70 (0.10-1.31)
Both (n= 1 615)				10 331.8	9	11	0.9 (0.5-1.7)	1.1	1.21 (0.43-2.00)

* Per 1 000 person-years

† Ratio of predicted to observed (P/O) rates

tion was consistent only in men after using equations for specific outcomes such as incident MI and CHD death. Hence, we assumed that most CHD events in this population might be due to MI, at least in men, so overestimation in this group appears to be true.

The Framingham score equations for CHD risk assessment were developed in a predominantly middle-class non-Hispanic white population^{14,15} and have not been extensively validated for other ethnic groups. These score equations have been widely reported to overestimate the risk of predicted CHD in European,^{17-19,21} Japanese,²⁹ Chinese,²⁰ and Native American populations,¹⁶ but there is less information about Hispanic populations.¹⁶ An evaluation of the Framingham equations in Puerto Rican¹⁶ and Spaniard²² populations found that they significantly overestimated the risk of CHD, although these results are not necessarily applicable to other Hispanic groups. Clearly, CHD risk overestimation depends on the study population and ranges from 20% to 50%.^{17-21,30} As in our analysis, in many others the overestimation effect has been more remarkable in men than in women,^{20,21} partly because of the unfavorable baseline cardiovascular risk profile in the former. Among explanations for overestimation of CHD predicted risk are the differences in the prevalence of the score variables, the possible differential interaction between variables or with unmeasured covariates, and the low incidence of CHD morbidity and mortality among these target populations compared with the Framingham population.^{22,30}

A few studies have reported an underestimation of CHD using the Framingham score, including one on an aboriginal population from Australia,³¹ and some others from a number of minority population groups from Europe as well as from Asia and Africa.³² Furthermore, there is evidence of an important underestimation in populations with high levels of socioeconomic deprivation and high mortality rates for cardiovascular diseases.³³ Particularly, these populations have reported low mortality from CHD, which is also related to other cardiovascular risk factors not included in the score. In addition, there is evidence that the Framingham score underestimated the CHD risk in subjects with diabetes,^{34,35} which may be related to the absence of glycemic control and diabetes duration among the score variables.

Risk calculators have been generated from the Framingham Heart Study to predict CVD risk in asymptomatic patients, but the accuracy of these risk predictors is somewhat limited in applicability among certain populations, and some well-known risk factors are not incorporated.³⁶ These are known limitations of the Framingham risk score, although the Framingham

Heart Study is an ongoing project and forthcoming risk prediction models will incorporate additional risk factors.

In order to evaluate selection bias due to exclusion criteria, we compared included *versus* excluded subjects and we observed that the former were older, had a higher percentage of hypertension, and smoked less than the latter. As two of the three characteristics were worse in the included subjects, we assumed that if a selection bias were present, it could contribute slightly to overestimation of the MI prediction. Because of the similar response rate during follow-up examinations, lost to follow-up related to the lack of information on MI (incidence or mortality) ascertainment was null.

A limitation to our study is our not including angina as an outcome. Rose questionnaire does not differentiate adequately the diagnosis in this population or in other non-Caucasian populations,³⁷ and its inclusion would have led to a misclassification of the main outcome of our analysis. It could be argued that the exclusion of angina as an outcome might explain at least part of the overestimation using the general equation. However, the use of ECG to identify incident MI even in the absence of any symptom, rather than using strict clinical and enzymatic criteria, as does the original Framingham study to establish the predictive equation, increases our number of observed outcomes and probably helps identify some of the angina cases.

Another limitation to our study was the small number of observed cases, which did not let us make a strong conclusion about the amount of overestimation of the risk for the score variables. In addition, we were unable to generate a specific equation for the study population; moreover, we need evidence from larger studies to assess the recalibration procedure of the Framingham score in the Mexican population. Although the Framingham score equations have been shown to accurately predict CHD with the use of a recalibration,^{16,29,30} it would be useful to have risk profiles specifically developed for the Mexican population.

Several guidelines¹⁰⁻¹³ that have been employed to identify populations at high-risk of developing CHD and of dying are consequently based on scores such as those of the Framingham study. The final aim of all these instruments is to establish preventive measures that accord with the risk level of the subjects, including initiation of antihypertensive or antihyperlipidemic medication. The clinical implications of these decisions depend on the sensitivity and specificity of the scores in specific groups, so we should use appropriate guidelines in each case to avoid errors in risk estimation.

In conclusion, regardless of the Framingham score equation used, the prediction of CHD and MI (fatal

and non-fatal) in this population appears to be overestimated, particularly in men; we therefore need more information to support this evidence and to generate a specific equation aimed at the Mexican population.

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