EVIDENCE BASED PUBLIC HEALTH POLICY AND PRACTICE

Validity of an adaptation of the Framingham cardiovascular risk function: the VERIFICA study

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Background: To assess the reliability and accuracy of the Framingham coronary heart disease (CHD) risk function adapted by the Registre Gironí del Cor (REGICOR) investigators in Spain.
Methods: A 5-year follow-up study was completed in 5732 participants aged 35–74 years. The adaptation consisted of using in the function the average population risk factor prevalence and the cumulative incidence observed in Spain instead of those from Framingham in a Cox proportional hazards model. Reliability and accuracy in estimating the observed cumulative incidence were tested with the area under the curve comparison and goodness-of-fit test, respectively.
Results: The Kaplan–Meier CHD cumulative incidence during the follow-up was 4.0% in men and 1.7% in women. The original Framingham function and the REGICOR adapted estimates were 10.4% and 4.8%, and 3.6% and 2.0%, respectively. The REGICOR-adapted function's estimate did not differ from the observed cumulated incidence (goodness of fit in men, $p=0.078$, in women, $p=0.256$), whereas all the original Framingham function estimates differed significantly ($p<0.001$). Reliabilities of the original Framingham function and of the best Cox model fit with the study data were similar in men (area under the receiver operator characteristic curve 0.68 and 0.69, respectively, $p=0.273$), whereas the best Cox model fitted better in women (0.73 and 0.81, respectively, $p<0.001$).
Conclusion: The Framingham function adapted to local population characteristics accurately and reliably predicted the 5-year CHD risk for patients aged 35–74 years, in contrast with the original function, which consistently overestimated the actual risk.

The acute myocardial infarction (AMI) mortality and incidence rates are unexpectedly low in France and Spain, considering the high consumption of saturated fatty acids and the high prevalence of cardiovascular risk factors, respectively.[1–3] However, coronary heart disease (CHD) will continue to be among the leading causes of death in these countries.[4 5] These facts demand the development of preventive strategies adapted to local cumulative incidence and risk factor prevalence characteristics. Individual risk stratification is essential for such strategies.[6] Unfortunately, calculations based on the Framingham Heart Study risk functions overestimate the actual individual risk in Spanish patients, among others.[7–14]

The Registre Gironí del Cor (REGICOR) investigators adapted the Framingham function to the Spanish population characteristics. The Framingham function was based on a Cox proportional hazards model to compare individual absolute risk with the average population risk of the corresponding sex. The adaptation consisted of estimating the average population risk with the risk factor prevalence and cumulative incidence observed in Spain.[1 3 15] This method to adapt the Framingham function had been proved accurate for several ethnic groups,[8 13] although the REGICOR adaptation had not been validated in Spain.

This study examines the accuracy and reliability of the original Framingham function and its REGICOR adaptation in predicting 5-year CHD cumulative incidence in a Spanish cohort aged 35–74 years recruited between 1995 and 1998. Separate analyses were done for men, women and patients with diabetes.

METHODS

The Validez de la Ecuación de Riesgo Individual de Framingham de Incidentes Coronarios Adaptada (Validity of the Adapted Framingham Individual Risk Equation for Coronary Incidents; VERIFICA) study consisted of a 5-year follow-up of a Spanish cohort aged 35–74 years, recruited between 1995 and 1998, initially free of symptoms of CHD and for whom complete baseline data on risk factors were available. Of the 5736 participants, 4430 were randomly selected from the clinical records of 67 Spanish primary care centres that volunteered to participate in the study. These centres covered the most populated areas of Spain (ie, Andalusia, Aragon, Basque Country, Balearic Islands, Catalonia, Extremadura, Galicia, Madrid and Navarre). A prospective population-representative cohort recruited in 1995 ($n=1306$, response rate 72% at the time of recruitment) was also included in the study[3] (fig 1). The study was approved by the local ethics committee.

Assuming that the observed event rate would be 10% and the minimum difference to be detected from this figure to achieve statistical significance is 6% in the subgroup of highest risk (ie, $\geq$10% at 5 years), the sample size provides a statistical power >95% in men and in patients with diabetes and >80% in women, for a 5% significance level.

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; ECG, electrocardiogram; HDL, high-density lipoprotein; REGICOR, Registre Gironí del Cor; VERIFICA, Validez de la Ecuación de Riesgo Individual de Framingham de Incidentes Coronarios Adaptada (Validity of the Adapted Framingham Individual Risk Equation for Coronary Incidents)

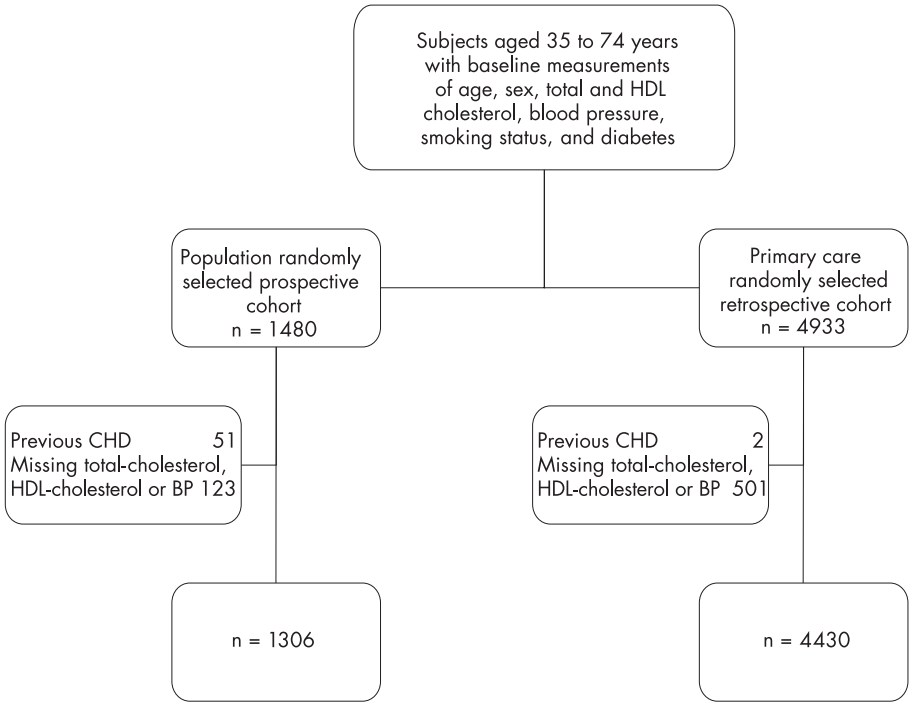

Figure 1 Flowchart of participant inclusion in the combined cohorts. BP, blood pressure; CHD, coronary heart disease; HDL, high-density lipoprotein.

All established major cardiovascular risk factors were measured by standard methods.[3 16] Participants were considered to be diabetic if they had been diagnosed with diabetes and were following a diabetic diet or taking drugs such as oral agents or insulin. Participants with a history of hypertension, under treatment for hypertension, or with systolic blood pressure $\geqslant$140 mm Hg or diastolic blood pressure $\geqslant$90 mm Hg were considered hypertensive. Those who reported smoking $>$1 cigarette/day in the preceding year were considered smokers. All necessary baseline lipid and blood pressure measurements were collected to estimate the risk of each participant. In the primary care centres, the last recorded value was used unless more than one value existed in clinical records for the year before the date of recruitment; in that case, the average systolic and diastolic blood pressure and the average total and high-density lipoprotein (HDL) cholesterol from these visits were recorded.

In the population cohort, a 5-year follow-up with a personal contact was organised to obtain an electrocardiogram (ECG) and administer a structured questionnaire to determine whether coronary events had occurred in the interim. All hospital and general practitioners' clinical records for all hospitalised or deceased participants were examined to ascertain the discharge diagnosis or cause of death. In fatal cases, relatives were interviewed when deemed necessary to clarify the cause of death.

In the retrospective primary-care cohort, medical records and re-examination as necessary were used to identify patients who experienced coronary events during the follow-up period.

A patient was censored at the time of the first eligible event or at the time the final contact was established; in four cases this was $<$1 year after inclusion.

Eligible outcomes during follow-up

The CHD events considered include: (1) non-fatal AMI, determined when hospital clinical records indicated a characteristic ECG, enzyme or troponin increase (not explained by other conditions), with suggestive symptoms, and the patient survived at least 28 days after symptom onset; (2) fatal AMI, when all AMI criteria were met and the patient died within 28 days of symptom onset, a diagnostic necropsy existed or sudden death occurred with suggestive symptoms that could not be explained by other diseases (when a patient with a non-fatal AMI died $>$28 days after onset of symptoms, two events were recorded); (3) angina pectoris, when at least a positive ischaemia test or coronary angiography was reported or characteristic ECG changes occurred during chest pain; (4) unrecognised AMI in the population cohort, when the follow-up ECG showed Q waves or ischaemia signs that were absent in the initial ECG examination and were confirmed by echocardiography and cardiac scintigraphy showing signs of a myocardial scar. All ECG were blindly interpreted and compared with the baseline ECGs by the same senior cardiologist.

Risk functions

All estimates were for 5-year risk. The risk functions used in this study include the Framingham function[17] and the REGICOR adaptation to the risk factor prevalence and event characteristics of the population in Spain.[15]

Statistical analysis

Clinical records from a random sample of 15% of all participants selected in the primary care setting were re-examined by trained external personnel for quality control purposes. κ and intra-class correlation coefficient agreement statistics were used to determine the accuracy of data collected by local investigators.

The cohort was divided into four groups of probability according to the original Framingham function, using 5-year risk cut-points at 5%, 7.5% and 10%; this represented a good approximation to the 10%, 15% and 20% risk cut-points used in clinical practice for 10-year risk.

Table 1 Baseline characteristics and events by sex in the Spanish cohort of the Validez de la Ecuación de Riesgo Individual de Framingham de Incidentes Coronarios Adaptada (or Validity of the Adapted Framingham Individual Risk Equation for Coronary Incidents) study

	All n = 5732, n (%)	Women n = 3285, n (%)	Men n = 2447, n (%)
Age (years)*	56.3 (10.5)	56.8 (10.4)	55.7 (10.6)
Diagnosed diabetes	941 (16.4)	481 (14.6)	460 (18.8)
SB (mm Hg)*	135.1 (18.4)	135.2 (18.8)	135.0 (17.8)
DBP (mm Hg)*	81.4 (10.6)	80.9 (10.8)	81.9 (10.3)
Blood pressure (categories; mm Hg)			
Optimal SBP<120 and DBP<80	754 (13.2)	467 (14.2)	287 (11.7%)
Normal SBP 120–129 or DBP 80–84	999 (17.4)	550 (16.7)	449 (18.3)
Normal–high SBP 130–139 or DBP 85–89	1273 (22.2)	678 (20.6)	595 (24.3)
Grade I SBP 140–159 or DBP 90–99	1925 (33.6)	1139 (34.7)	786 (32.1)
Grades II–III SBP≥160 or DBP≥100	781 (13.6)	451 (13.7)	330 (13.5)
Previous diagnosis of hypertension	2568 (44.8)	1549 (47.2)	1019 (41.7)
Pharmacological treatment of hypertension	1771 (30.9)	1107 (33.8)	664 (27.3)
Total cholesterol (mg/dl)*	231.8 (41.5)	234.1 (42.1)	228.8 (40.5)
Total cholesterol (mg/dl; categories)			
<160	215 (3.8)	107 (3.3)	108 (4.4)
160–199	1052 (18.4)	573 (17.4)	479 (19.6)
200–239	2060 (35.9)	1152 (35.1)	908 (37.1)
240–279	1727 (30.1%)	1013 (30.8%)	714 (29.2%)
≥280	678 (11.8)	440 (13.4)	238 (9.7)
HDL cholesterol (mg/dl)*	53.7 (14.7)	57.6 (14.2)	48.5 (13.6)
HDL cholesterol (mg/dl; categories)			
<35	368 (6.4)	94 (2.9)	274 (11.2)
35–44	1249 (21.8)	450 (13.7)	799 (32.7)
45–49	896 (15.6)	505 (15.4)	391 (16)
50–59	1466 (25.6)	913 (27.8)	553 (22.6)
≥60	1753 (30.6)	1323 (40.3)	430 (17.6)
Pharmacological treatment of cholesterol	661 (11.5)	398 (12.1)	263 (10.6)
Active smoker	1418 (24.7)	347 (10.6)	1071 (43.8)
History			
Cerebrovascular disease	98 (1.7)	44 (1.3)	54 (2.2)
Congestive heart failure	67 (1.2)	39 (1.2)	28 (1.1)
Peripheral artery disease	63 (1.1)	18 (0.5)	45 (1.8)
Valve disease	89 (1.6)	45 (1.4)	44 (1.8)
Original Framingham function 5-year risk*	7.2 (6.3)	4.8 (3.7)	10.4 (7.6)
Adjusted REGICOR function 5-year risk*	2.7 (2.3)	2.0 (1.6)	3.6 (2.8)
Kaplan–Meier observed 5-year event rate (%)	3.2	1.7	4.0
Numbers of eligible outcomes			
Fatal myocardial infarction	16	9	7
Non-fatal myocardial infarction (with symptoms)	44	9	35
Unrecognised myocardial infarction†	3	2	1
Angina	117	48	69
Any of the above	180	68	112

DBP, diastolic blood pressure; HDL, high-density lipoprotein; REGICOR, Registre Gironí del Cor; SBP, systolic blood pressure.
*Mean (SD).
†New Q waves observed in follow-up ECG, obtained only in the population cohort.

The Framingham function adaptation consists essentially in replacing the Framingham cumulative incidence and risk factor prevalence by those of the country in which it is intended to be applied (ie, Spain in our case). This method has been extensively described elsewhere.[7 8 15]

Accuracy and reliability of the classification provided by the original and REGICOR-adapted Framingham functions were assessed separately by sex as follows:

1. The coefficients estimated by the Cox model that best fitted the cohort data (best Cox) were compared with those of the original Framingham function by a z score test.[8 18] For statistical power reasons, the model was fitted with total-cholesterol and HDL-cholesterol as continuous variables.
2. A calibration test, by sex, assessed the accuracy of the original Framingham and REGICOR-adapted functions by comparing their estimated risk equations with the observed event rate in the four risk groups established by the original Framingham function. The D'Agostino-Nam version of the Hosmer and Lemeshow goodness-of-fit test was used to calculate a χ^2 value.[8 18] χ^2 values <6 were considered to indicate a substantial fit for four groups, regardless of the p value.[18]
3. The discrimination capacities of the original and adapted Framingham functions were analysed by comparing the area under the curve obtained by the receiver operator characteristics of the original function and that obtained by the best Cox model fit of CHD event fitted to the cohort data. It is important to note that the adaptation procedure does not affect discrimination.

Kaplan–Meier survival estimates were used to calculate 5-year observed cumulative incidence. The analyses were done

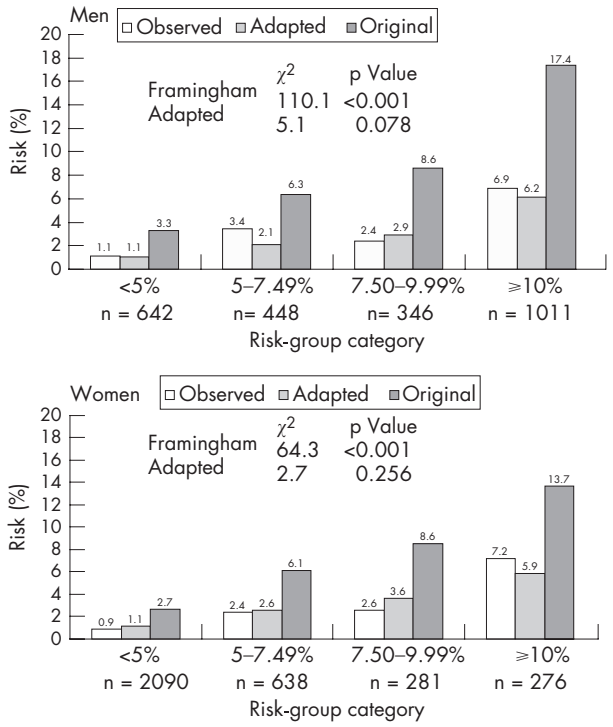

Figure 2 Distribution of participants, by sex, in four groups of coronary heart disease risk according to the 5-year Framingham function, showing the observed event rate and the rate expected by the REGICOR-adapted and original Framingham functions, together with the goodness-of-fit χ^2 statistics and significance levels.

with S-Plus 2000 (Insightful Corporation, Seattle, Washington, USA) and SAS V.8.2.

RESULTS

Table 1 presents the risk factors, 5-year risk estimates and baseline characteristics of the 5732 participants, with complete follow-up by sex.

Quality control

The κ statistics comparing the categorical data collected by the study investigators and those extracted from clinical records by trained independent investigators were >0.75 for risk factors and demographic data, and >0.84 for type of event during follow-up. Intraclass correlation coefficients (age, total and HDL cholesterol, systolic and diastolic blood pressure) were >0.90 in all instances, indicating good to excellent agreement.

Follow-up

The observed number of patients with at least one CHD event was 180 (table 1); 41% of 5-year overall CHD and 69.8% of fatal CHD events occurred after age 65 years. In addition, 24 fatal non-CHD cardiovascular events and 107 non-cardiovascular deaths were observed during follow-up. Only four patients were lost to follow-up.

The original Framingham function overestimated the observed event rate in women and men by a factor of 2.8 and 2.6, respectively. The REGICOR-adapted function improved substantially the goodness of fit for both sexes: the distribution of observed events did not differ from that predicted by the adapted function (fig 2).

We fitted a proportional hazards Cox model with the cohort data to estimate the β coefficients for each risk factor level. None of the coefficients significantly differed from the original Framingham function in men and only that of smoking differed in women (table 2).

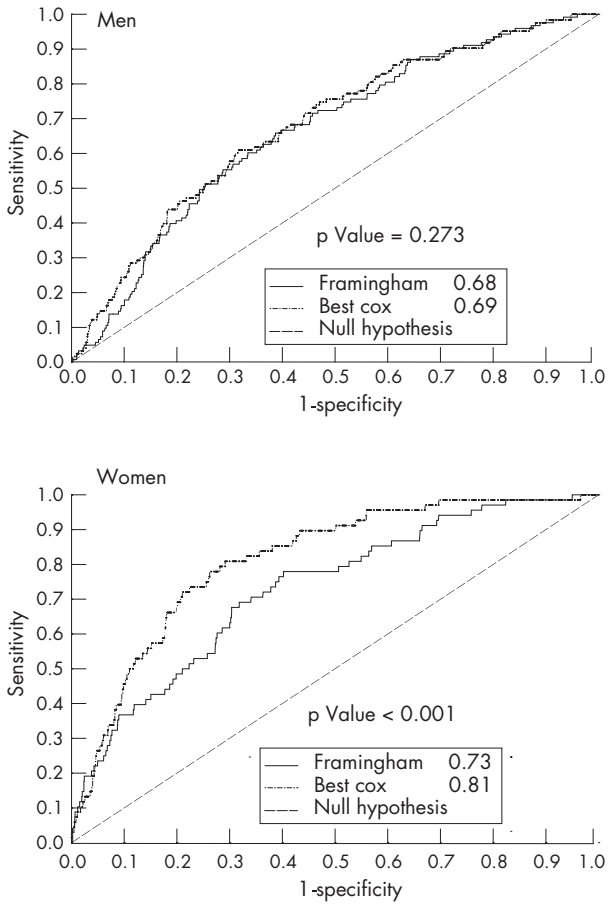

Figure 3 Area under the receiver operating curves for the predicted risk according to the original function and the best Cox model fit with the study cohort, by sex.

The area under the receiver operator characteristic curve obtained with the best-fitting Cox function was similar to that of the original Framingham function in men, indicating a similar discrimination capacity. By contrast, the best Cox model fit provided a higher area under the curve than the original function in women, suggesting that the coefficients estimated with local data significantly improved the identification of women who developed an event during follow-up (fig 3).

In men and women with diabetes (n = 941), the Kaplan–Meier observed overall 5-year CHD event rate was 4.9%. The original Framingham function significantly overestimated the event rate by a factor >2.6; the prediction of the REGICOR-adapted function did not differ from the observed rate (fig 4).

DISCUSSION

The study findings show that the accuracy of the CHD risk estimated by the REGICOR-adapted function is better than that of the original Framingham function in Spanish men, women and patients with diabetes. The REGICOR adaptation has proved to reliably provide accurate CHD risk estimates for ages 35–74 years in Spain. The adaptation method is a valid instrument for CHD risk assessment in countries with cardiovascular risk factor and event rate characteristics different from those of the Framingham population.

An overestimation of risk by the Framingham function has been shown to exist not only in the Spanish population[7] but

Table 2 Estimates of the coefficients for each variable included in the Framingham original function and in the best Cox model adjusted for treatments for hypertension and lipid lowering, by sex

	Men					Women				
	Framingham original		REGICOR Best Cox		z score	Framingham original		REGICOR Best Cox		z-score
	Coef	SE	Coef	SE	p Value	Coef	SE	Coef	SE	p Value
Age	0.049	0.005	00 43	0.012	0.631	0.338	0.074	0.291	0.222	0.84
Age >2 years	—	—	—	—	—	−0.003	0.001	−0.002	0.002	0.56
Total cholesterol (1 mg)	0.007	0.001	0.002	0.003	0.067	0.005	0.002	−0.001	0.004	0.119
HDL cholesterol (1 mg)	−0.027	0.005	−0.02	0.009	0.485	−0.027	0.005	−0.048	0.012	0.093
Blood pressure classification										
Optimal SBP<120 and DBP<80 mm Hg	−0.009	0.194	−0.589	0.522	0.298	−0.52	0.256	−0.014	0.704	0.499
Normal SBP 120–129 or DBP 80–84 mm Hg	—	—	—	—	—	—	—	—	—	—
Normal-high SBP 130–139 or DBP 85–89 mm Hg	0.275	0.171	−0.147	0.358	0.288	−0.047	0.231	−0.043	0.495	0.992
HT Grade I SBP 140–159 or DBP 90–99 mm Hg	0.524	0.159	0.339	0.321	0.604	0.269	0.205	−0.046	0.444	0.52
HT Grades II-III SBP≥160 or DBP≥100 mm Hg	0.631	0.173	0.126	0.408	0.254	0.485	0.218	0.162	0.499	0.553
Diagnosed diabetes	0.417	0.177	0.017	0.259	0.201	0.617	0.212	0.798	0.3	0.622
Current smoker	0.53	0.104	0.564	0.215	0.886	0.235	0.142	1.382	0.44	0.017

Coef, coefficient in the proportional hazards regression model; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HT, hypertension; REGICOR, Registre Gironí del Cor; SBP, systolic blood pressure.

also in northern and western European countries.[9–12] For example, an overestimation of about 60% was observed in the UK[14]; however, this is far from the >260% overestimation observed in Spain.[7] The greater magnitude of the overestimation in Spain may be related to the fact that the relative risk of CHD for higher values of total cholesterol and blood pressure as compared with lowest values is similar in all countries, but the absolute risk strongly depends on the country where data are gathered.[19 20] If we are to adequately predict CHD risk in areas where the AMI incidence rate is, comparatively, very low, we need to urgently adapt the Framingham function to the population characteristics of those countries, to prevent overtreatment, particularly with lipid-lowering drugs, stemming from risk overestimation.

The accuracy of risk estimates is a key to determine the best primary prevention strategies, and has important practical implications. For example, even in regions of high CHD incidence, the low cost effectiveness of statin use in primary prevention makes it difficult for public health services to assume this expense.[21–23] Primary prevention in Spain, a country of low CHD incidence (eg, half to one-third the incidence in UK),[1] is even less cost effective. The effectiveness and safety of long-term primary prevention with statins remains uncertain, at least in patients with low-to-moderate coronary risk.[24 25]

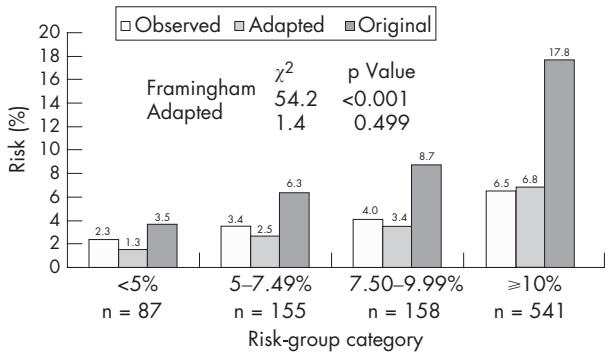

Figure 4 Distribution of patients with diabetes in four groups of coronary heart disease risk according to the 5-year Framingham function, showing the observed event rate and the rate expected by the REGICOR-adapted and original Framingham functions.

Characteristics and limitations of the study

Hypertension and lipid-lowering drugs may be independent factors that modulate the coefficient estimates for risk factors. In our study, none of these treatments was independently associated with event occurrence in either sex (data not shown). However, the best Cox model fit was adjusted for both.

The fact that the coefficient for smoking was significantly higher for women in the best Cox model fit than for those in the original function suggests that smoking may be more relevant to CHD development for women in Spain, where the incidence rate for smoking is much lower than that in Framingham. It should be noted, of course, that the prevalence of smoking in younger women in Spain was much lower than in Framingham 30 years ago, but has been increasing in recent years. However, the cumulative incidence observed in the last 15 years in Spain still corresponds to the effects of low exposure to smoking 30 years ago. Therefore, applying the Framingham β for smoking in Spain may still lead to an overestimation of the effect, given the lag in women's exposure to smoking.

We used the population-based sample to test whether any difference existed in the results as compared with the overall cohort. Beyond the sample size restrictions, no substantial differences were found (results not shown) in this subgroup analysis.

The diabetic subgroup showed a higher 5-year event rate (5.3%) and higher risk (2.5%) than the rest of the general population in our study. The latest publications have found the event risk in CHD patients without diabetes to be 1.9 times higher than that in CHD-free patients with diabetes.[26] A controversy exists as to whether the increased cardiovascular risk of patients with diabetes should lead to secondary prevention intervention in these patients.[27–29] These findings support the principle of applying caution in this context: patients with diabetes should be more carefully followed and may need more intensive regimens of treatment with drugs, but it is difficult to accept that they must be assigned the same level of risk as patients offered secondary prevention. We could not

What is already known

- Individual risk stratification is essential for primary preventive strategies to be properly set up.
- The risk calculations based on the Framingham Heart Study risk functions overestimate the actual individual risk in many countries.
- Adapting the cardiovascular risk functions to local risk and risk factor prevalence characteristics has been recommended to obtain accurate local estimates.

What this study adds

- The accuracy of the coronary heart disease (CHD) risk estimated by the Registre Gironí del Cor (REGICOR)-adapted function is better than that of the original Framingham function in Spanish men, women and patients with diabetes.
- To date, the REGICOR adaptation is the only one that has proved to reliably provide accurate CHD risk estimates for people aged 35–74 years in Spain.

Policy implications

- Given the fact that the REGICOR adaptation of the Framingham cardiovascular risk function is the only study to have shown accuracy and reliability in a Spanish population aged 35–74 years, it should be adopted as the standard for this population. Other cardiovascular risk functions should be validated in the target population before they can be safely used in this country.
- Accurate cardiovascular risk estimates will contribute to more precise determination of the subset of population in which best primary prevention activities should be more intensively pursued and, in consequence, to improved cost effectiveness of treatment with drugs, particularly with lipid-lowering drugs.

undertake appropriate subgroup analysis of patients with diabetes by sex due to limited statistical power.

The fatal and symptomatic non-fatal AMI annual incidence rate observed in our study is higher than that observed in Spain in the population aged 35–74 years (122 and 81 per 100 000 women, and 420 and 314 per 100 000 men, respectively), which is consistent with the predominantly primary care origin of the studied cohort.[30]

In summary, the original Framingham function applied to the Spanish population significantly overestimated the 5-year observed CHD rate. However, the adapted function reliably and accurately predicted the observed 5-year CHD cumulative incidence. Adaptation of the Framingham function is a valid alternative to the creation of new functions derived from local cohorts.

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A full roster of the VERIFICA Investigators is provided in the appendix and at www.regicor.org/verifica_inv.

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APPENDIX

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