The Framingham prediction rule is not valid in a European population of treated hypertensive patients

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Background **Stratification of population groups according to cardiovascular risk level is recommended for primary prevention.**

Objective **To assess whether the Framingham models could accurately predict the absolute risk of coronary heart disease (CHD) and stroke in a large cohort of middle-aged European patients with hypertension, and rank individual patients according to actual risk.**

Design **A prospective cohort study comparing the actual risk with that predicted by either the Framingham equations or models derived from the INSIGHT study.**

Patients and setting **From the INSIGHT prospective trial, conducted in eight countries of Western Europe and Israel, we selected 4407 European patients younger than 75 years without previous cardiovascular events.**

Interventions **None.**

Main outcome measures **Major cardiovascular events.**

Results **In this population (45% men, mean age 64.1 years), 124 (2.8%) patients had CHD and 96 (2.2%) had strokes after a median follow-up of 3.7 years. Overestimation of absolute CHD risk by the Framingham equation was observed in all countries (from 2% in the UK to 7% in France), whereas predicted risk of stroke was close to the actual risk. However, patients in the highest risk quintile within each country had a threefold greater risk of a cardiovascular event than those in the lowest quintile.**

Conclusions **The Framingham models should not be used to predict absolute CHD risk in the European population as a whole. However, these models may be used within each country, provided that cut-off points defining high-risk patients have been determined within each country.**
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Introduction

Coronary heart disease (CHD) and stroke were the two leading causes of death worldwide in 1990, and projections show that this will still be the case in 2020 [1–3]. Prediction of risk of cardiovascular disease (CVD), including CHD and stroke, could therefore be of primary importance for public health policies. Prediction models are increasingly used to determine the absolute risk of CHD and stroke in primary prevention settings, to identify high-risk patients who would benefit from intervention on one or several risk factors and to motivate patients to adhere to risk-reduction treatments. Although several models using logistic regression, Cox proportional hazards regression and accelerated failure time analysis have been developed using data from the Framingham Heart Study [4–6], these data were obtained in an untreated, high-risk, middle-aged American population recruited during the 1950s. Consequently, these models may no longer be appropriate for the assessment of risk in European populations because these populations are at lower risk for CVD, and many patients are already treated with antihypertensive or cholesterol-decreasing drugs, or both. Despite these changes in treatment, Framingham-based methods remain the most widely used to predict the absolute risk of CHD [7]. Although several

other models based on data from European cohorts have been proposed [8–11], these models have not been validated in a representative sample of the diverse populations in Europe. Haq *et al.* [12] showed that the Framingham risk function was reasonably accurate. However, these results were obtained in a population at high cardiovascular risk.

To ensure that primary prevention guidelines can be used in medical practice, validation of prediction rules according to appropriate methodological criteria is crucial for both CHD and stroke [13]. Our goal was to evaluate the extent to which Framingham models predicted risk of CVD, CHD and stroke events, and ranked patients according to individual risk in a large cohort of middle-aged hypertensive patients, in both Northern and Southern Europe.

Methods

Study population

Among the 6321 patients included in the International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) intention-to-treat analysis [14,15], we selected all patients from Northern and Southern Europe, aged less than 75 years, and without a history of myocardial infarction, coronary heart disease, stroke or peripheral vascular disease. To ensure that our cohort was comparable to the Framingham population, 1491 patients were excluded because they did not satisfy the above criteria. Patients from the two INSIGHT study groups were included because the two antihypertensive drugs were shown to be equally effective.

INSIGHT study

Details of the INSIGHT protocol and the clinical outcomes have been reported previously [14,15]. Briefly, a double-blind randomized trial to compare the efficacy of two antihypertensive treatments (nifedipine and co-amiloride) in preventing major complications from hypertension was conducted in eight western European countries (UK, France, Spain, The Netherlands, Italy, Sweden, Denmark and Norway) and in Israel between 1994 and 1996. Patients were recruited from hospital hypertension centres in Israel and Italy and from general practice centres in the other countries. Inclusion criteria were men and women aged 55–80 years who had hypertension (blood pressure >150/95 mmHg, or systolic blood pressure >160 mmHg, regardless of diastolic pressure). Two or three blood pressure readings were recorded, with the patient in the sitting position with the arm resting on the armchair after at least 5 min rest. In addition, patients for inclusion were required to have at least one of the following risk factors: smoking, hypercholesterolaemia, diabetes mellitus, left ventricular hypertrophy, left ventricular strain confirmed by electrocardiography, family history of myocardial infarction, or personal history of coronary heart disease or peripheral vascular disease.

A total of 6321 patients were included in the intention-to-treat-analysis with a follow-up of at least 3 years. Primary outcomes (combination of death from any cardiovascular or cerebrovascular cause, and non-fatal stroke, myocardial infarction and heart failure) occurred in 200 patients (6.3%) in the nifedipine group and in 182 (5.8%) in the co-amiloride group (18.2 compared with 16.5 events per 1000 patient-years; relative risk 1.10, 95% confidence interval 0.91 to 1.34; $P = 0.35$).

Study design

Endpoints, follow-up, risk factors

Among the INSIGHT endpoints we selected the following: fatal and non-fatal myocardial infarction, cardiovascular death and angina pectoris for the CHD equation; fatal and non-fatal stroke, transient ischaemic attack and subarachnoid haemorrhage for the stroke equation. Fatal and non-fatal heart failure and cerebrovascular death of other origin were added to the events used for the CHD and stroke equations for the CVD equation. For the purpose of prediction, we used the date of the first occurrence of an event or the last follow-up date in the case of patients remaining event-free.

The independent risk factors recorded at entry to the INSIGHT study were included in the CHD, stroke and CVD Framingham models using the Framingham coding system. These were age in years, sex (male = 0, female = 1), systolic blood pressure (mmHg), ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol, smoking status (no = 0, yes = 1), and diabetes status (no = 0, yes = 1). We took the blood pressure value at inclusion, either without treatment or under the patient's current antihypertensive treatment. The blood pressure considered was the mean of the two or three blood pressure readings. The presence of diabetes was defined as patients treated with insulin or oral agents, or having a fasting glucose concentration of at least 140 mg/dl (7.8 ml/l). As left ventricular hypertrophy was not systematically assessed by central reading in all countries, this variable was set to absent for all participants.

Prediction

Using risk factors as defined in the Framingham equation, we estimated the risk equations predicting CHD, stroke and CVD in our population. As the Framingham group used different models to predict risk [4–6], we compared the results obtained in our population using logistic regression, and a Cox proportional-hazard model.

Using the risk equations predicting CHD, stroke and CVD described by the Framingham group in 1991 [4], we computed the individual risk of an event occurring within 3.7 years (our overall median study period), which can be considered to be valid because the Framingham group recommended use of the equations over intervals of between 4 and 12 years.

Because of the small number of events in Sweden, Denmark and Norway, data from patients in these three countries were pooled in one group, called Scandinavia. We then performed between-country comparisons. To assess if the effect of risk factors on outcome events was stable across European countries, we estimated an equation predicting CVD within each country. We did not perform this comparison separately for stroke and CHD, to avoid random variations as a result of the small number of events.

To assess the predictive accuracy of the Framingham equations for each country, we classified the patient population of each country into the five quintiles of risk predicted by the Framingham equation at 3.7 years. We then computed the actual percentage of events within each of these quintiles from the data.

Statistical methods

The distributions of risk factors by country were compared using univariate analyses, χ^2 and analysis of variance. Odds ratios and risk ratios with their 95% confidence intervals were computed from the logistic regression and Cox models. A receiver operating characteristic (ROC) analysis was used to measure the extent to which the equation predicting CVD risk was able to separate true-positives (i.e. patients at high risk who had an event) from true-negatives (patients at low risk who did not have an event during the follow-up period). All calculations were performed using the SAS statistical software (SAS Institute, Cary, North Carolina, USA).

Results

Study population

A total of 4407 participants (2436 women and 1971 men) aged 55–74 years (mean age 64.1 ± 1.6 years) were included. Baseline characteristics of our population were: mean systolic blood pressure 166 ± 15 mmHg, total cholesterol/HDL cholesterol ratio of 5.1 ± 1.6, percentage of smokers 32%, and percentage with diabetes 19%. Table 1 shows the study population and the distribution of risk factors by country. We observed large between-country differences in the distribution of risk factors.

Cardiovascular events

In the total population, 231 CVD (5.2%), 124 CHD (2.8%) and 96 stroke events (2.2%) were observed. Table 2 shows the distribution of events over the median study duration by country. The incidence rate of cardiovascular events during the study period ranged

Table 1 **Characteristics of study population and distribution of risk factors by country**

	Italy ($n = 471$)	Spain ($n = 604$)	France ($n = 1206$)	Scandinavia* ($n = 277$)	The Netherlands ($n = 423$)	UK ($n = 1426$)	*P*
Men (%)	50	39	45	42	44	46	<0.001†
Age (years)	62.9 ± 5.4	64.1 ± 5.3	64.2 ± 5.6	64.1 ± 5.6	64.1 ± 5.7	64.3 ± 5.7	<0.001‡
SBP (mmHg)	161 ± 15	161 ± 16	164 ± 12	169 ± 19	169 ± 17	169 ± 15	<0.001‡
Smokers (%)	29	18	31	39	39	37	<0.001†
Diabetes (%)	21	26	21	20	16	15	<0.001†
Total cholesterol : HDL ratio	5.0 ± 1.4 ($n = 460$)	5.0 ± 1.2 ($n = 461$)	4.8 ± 1.5 ($n = 1180$)	5.4 ± 1.6 ($n = 271$)	5.5 ± 1.7 ($n = 393$)	5.3 ± 1.6 ($n = 1382$)	<0.001‡
Total cholesterol (mg/dl)	237.3 ± 44.0	247.7 ± 39.9	248.6 ± 44.1	252.4 ± 43.0	244.7 ± 43.5	255.1 ± 44.1	<0.001‡
HDL cholesterol (mg/dl)	49.8 ± 12.1	53.1 ± 12.4	55.2 ± 15.9	50.1 ± 15.0	48.1 ± 13.7	51.8 ± 14.7	<0.001‡

Values are as mean ± SD. *Scandinavia includes Sweden, Denmark and Norway. SBP, systolic blood pressure; HDL, high-density lipoprotein. †χ^2 test; ‡analysis of variance. §Cholesterol (mmol/l) = cholesterol (mg/dl) × 0.0259067. The ratios were calculated for each patient, it explains why the means of the ratios slightly differ from the ratios of the means

Table 2 **Number and type of cardiovascular events by country (incidence rates per 100 during the study period)**

	Italy ($n = 471$)	Spain ($n = 604$)	France ($n = 1206$)	Scandinavia* ($n = 277$)	The Netherlands ($n = 423$)	UK ($n = 1426$)	*P*
Cardiovascular disease	25 (5.3)	32 (5.3)	31 (2.6)	13 (4.7)	27 (6.4)	103 (7.2)	<0.001†
Coronary heart disease	10 (2.1)	18 (3.0)	16 (1.3)	9 (3.2)	10 (2.4)	61 (4.3)	<0.001†
Stroke	14 (3.0)	13 (2.2)	10 (0.8)	4 (1.4)	17 (4.0)	38 (2.7)	<0.001†
Study duration (median years)	3.47	3.43	4.22	3.20	3.53	3.72	

Values are number (%), or median. *Scandinavia includes Sweden, Denmark and Norway. Coronary heart disease includes myocardial infarction, coronary heart disease death plus angina pectoris and coronary insufficiency. Stroke includes transient ischemia. Cardiovascular disease includes all of the above plus congestive heart failure and peripheral vascular disease. †χ^2 test.

from 2.6% in France to 7.2% in UK. France had the lowest rate of both stroke and CHD. UK had the highest rate of CHD, and The Netherlands had the highest rate of stroke.

Risk models

In the 4147 participants in whom cholesterol values were available, the logistic regression and Cox models gave similar risk estimates (Table 3). Both models showed that male sex, age, ratio of total cholesterol to HDL cholesterol, smoking status and diabetes were significantly and independently related to CVD events. The coefficient for systolic blood pressure had only a marginal statistical significance in both models. Women had a 40% lower risk than men. Risk increased by approximately 4% per year of age, 0.8% per mmHg of systolic blood pressure, 25% per unit of total cholesterol to HDL cholesterol, 46% for smokers, and more than 48% in patients with diabetes. Similar results were obtained for CHD and stroke. The significant covariates were sex, smoking and the ratio of total cholesterol to HDL cholesterol for CHD (Table 3), and sex, age, diabetes and the ratio of total cholesterol to HDL cholesterol for stroke (Table 3).

All of the risk factors described in the Framingham study were significantly associated with the risk of CVD. The estimates of relative risks were of the same order of magnitude for the time-dependent model (Cox) and the logistic regression model. Therefore, we chose the Cox model for analysis by country, because of its non-parametric properties.

Table 4 shows the hazard ratios associated with each variable predicting CVD within each country. Although we observed some heterogeneity in hazard ratios for risk factors across countries, confidence intervals overlapped, which suggests that the effect of these risk factors is similar across countries.

Comparison of incidence rates of events with those predicted from the Framingham risk model and Cox model

We observed large between-country differences in the actual incidence rates of CVD events (from 3% in France to 7% in UK). Predicted risk of CVD using the study Cox model was close to the actual risk of CVD, whereas the Framingham model showed small between-country differences. The Framingham equation overestimated CVD risk in all countries (twofold higher in UK to fourfold higher in France). This was mainly attributable to CHD events (Table 5). The Framingham equation did not overestimate the risk of stroke compared with the actual risk (Table 5).

For CVD, patients in the highest quintile had a threefold greater risk compared with those in the lowest quintile. For CHD and stroke, the ratios of events in patients in the highest Framingham risk quintile compared with those observed in the lowest quintile were 3.9 and 2.6 respectively. Therefore, in western European countries, Framingham equations were able to stratify populations into groups of high and low risk (Table 6). However, as shown in Figure 1, the CVD risk equation derived from our data had only

Table 3 **Comparison of the logistic regression and Cox models to predict cardiovascular disease, coronary heart disease and stroke***

	Logistic regression		Cox model	
	OR (95% CI)	*P*	HR (95% CI)	*P*
Cardiovascular disease				
Sex (male = 0; female = 1)	0.604 (0.453 to 0.806)	0.001	0.616 (0.466 to 0.814)	0.001
Age (years)	1.038 (1.011 to 1.065)	0.005	1.038 (1.012 to 1.064)	0.003
Systolic blood pressure (mmHg)	1.008 (0.999 to 1.017)	0.094	1.008 (0.999 to 1.016)	0.088
Smoker (no = 0; yes = 1)	1.459 (1.081 to 1.971)	0.014	1.448 (1.084 to 1.934)	0.012
Diabetes (no = 0; yes = 1)	1.487 (1.066 to 2.075)	0.020	1.473 (1.070 to 2.028)	0.018
Total cholesterol : HDL ratio	1.249 (1.154 to 1.350)	<0.0001	1.236 (1.149 to 1.331)	<0.0001
Coronary heart disease				
Sex (male = 0; female = 1)	0.508 (0.340 to 0.757)	0.001	0.519 (0.350 to 0.769)	0.001
Age (years)	1.012 (0.977 to 1.048)	0.504	1.013 (0.979 to 1.048)	0.465
Systolic blood pressure (mmHg)	1.008 (0.996 to 1.020)	0.182	1.008 (0.996 to 1.020)	0.181
Smoker (no = 0; yes = 1)	1.701 (1.142 to 2.534)	0.009	1.692 (1.145 to 2.499)	0.008
Diabetes (no = 0; yes = 1)	1.235 (0.768 to 1.986)	0.384	1.244 (0.782 to 1.979)	0.356
Total cholesterol : HDL ratio	1.341 (1.213 to 1.481)	<0.0001	1.324 (1.205 to 1.456)	<0.0001
Stroke				
Sex (male = 0; female = 1)	0.639 (0.414 to 0.987)	0.044	0.647 (0.421 to 0.993)	0.046
Age (years)	1.062 (1.021 to 1.105)	0.003	1.063 (1.022 to 1.105)	0.002
Systolic blood pressure (mmHg)	1.006 (0.993 to 1.019)	0.384	1.006 (0.993 to 1.020)	0.372
Smoker (no = 0; yes = 1)	1.217 (0.763 to 1.940)	0.409	1.221 (0.771 to 1.935)	0.394
Diabetes (no = 0; yes = 1)	1.667 (1.028 to 2.704)	0.038	1.668 (1.037 to 2.683)	0.035
Total cholesterol : HDL ratio	1.144 (1.011 to 1.295)	0.034	1.144 (1.013 to 1.292)	0.031

*Models calculated among the 4147 individuals with cholesterol values available. OR (odds ratio) and HR (hazard ratio) giving the increase (or decrease) in risk observed for a change of one unit of measurement for each risk factor (i.e. 1 year of age, 1 mmHg of systolic blood pressure, etc.). CI, confidence interval; HDL, high-density lipoprotein.

Table 4 Hazard ratios using Cox models to predict risk of cardiovascular disease by country*

	Hazard ratio (95% confidence interval)					
	Italy	Spain	France	Scandinavia	The Netherlands	UK
Sex (male = 0; female = 1)	0.720 (0.302 to 1.717)	0.411 (0.159 to 1.059)	0.478 (0.223 to 1.025)	0.421 (0.135 to 1.311)	0.376 (0.161 to 0.877)	0.807 (0.539 to 1.208)
Age (years)	1.034 (0.961 to 1.113)	1.067 (0.981 to 1.160)	1.066 (0.997 to 1.141)	0.991 (0.893 to 1.100)	1.096 (1.016 to 1.181)	1.011 (0.975 to 1.049)
Systolic blood pressure (mmHg)	1.000 (0.972 to 1.028)	1.014 (0.987 to 1.042)	0.988 (0.960 to 1.018)	1.000 (0.970 to 1.031)	0.999 (0.977 to 1.022)	1.011 (0.999 to 1.024)
Total cholesterol : HDL ratio	1.303 (1.045 to 1.625)	1.364 (1.002 to 1.858)	1.083 (0.866 to 1.354)	0.919 (0.630 to 1.340)	1.295 (1.063 to 1.578)	1.221 (1.099 to 1.356)
Smoker (no = 0; yes = 1)	2.124 (0.912 to 4.946)	1.256 (0.404 to 3.910)	1.482 (0.670 to 3.275)	1.783 (0.579 to 5.490)	1.444 (0.643 to 3.242)	1.248 (0.811 to 1.920)
Diabetes (no = 0; yes = 1)	1.270 (0.496 to 3.254)	1.174 (0.449 to 3.071)	2.850 (1.351 to 6.013)	1.187 (0.319 to 4.423)	0.925 (0.309 to 2.773)	1.640 (0.983 to 2.733)

*Models were calculated for each country among the subgroups of individuals with cholesterol values available. Hazard ratio (with 95% confidence interval) giving the increase (or decrease) in risk observed for a change of one unit of measurement for each risk factor (i.e.: 1 year of age, 1 mmHg of systolic blood pressure, etc.). HDL, high-density lipoprotein.

Table 5 Comparison of incidence rates of events of cardiovascular disease, coronary heart disease and stroke in each country, with those predicted by the Framingham equation and the INSIGHT Cox models*

	Risks (%)						
	Italy ($n = 460$)	Spain ($n = 461$)	France ($n = 1180$)	Scandinavia ($n = 271$)	The Netherlands ($n = 393$)	UK ($n = 1382$)	All ($n = 4147$)
Cardiovascular disease							
Predicted by†:							
Framingham equation	12	11	12	14	14	14	13
INSIGHT Cox model	4	4	2	4	4	6	4
Observed	5	5	3	5	6	7	5
Predicted/observed‡	2.4	2.2	4.0	2.8	2.3	2.0	2.6
Coronary heart disease							
Predicted by†:							
Framingham equation	7	6	7	8	8	8	7
INSIGHT Cox model	1	1	1	2	1	3	2
Observed	2	2	1	3	2	4	3
Predicted/observed‡	3.5	3.0	7.0	2.7	4.0	2.0	2.3
Stroke							
Predicted by†:							
Framingham equation	1	1	2	2	2	2	2
INSIGHT Cox model	2	2	1	1	3	2	2
Observed	3	2	1	1	4	3	2
Predicted/observed‡	0.3	0.5	2.0	2.0	0.5	0.7	1.0

*Medians of risk calculated among the 4147 individuals with cholesterol values available. †Median value of 3.7-year risk (3.7 years was the median follow-up in this population). ‡Ratio of the incidence predicted using the Framingham model to that actually found: a ratio >1 indicates an overestimation by the Framingham equation; a ratio <1 indicates an underestimation.

a poor discriminative value at the individual level (area under the ROC curve 66.1 ± 0.2%).

Discussion

In a population of European patients who were treated for hypertension in a multicentre therapeutic trial, we showed that the Framingham equation largely overestimates CHD risk in all countries, with large inter-country differences. As expected, this overestimation was greater in southern countries with low incidence rates. Therefore, the large discrepancy between the actual and the predicted risk of CHD in each country precludes the use of a single 'European' threshold to define patients at high risk. However, we demonstrated that it was possible to classify patients into risk groups using the Framingham risk model, provided that patients were classified according to the thresholds defined within each country. It must be underlined that the risk ratio is high despite the fact that we had a population of treated hypertensive patients belonging to a high-risk group of patients.

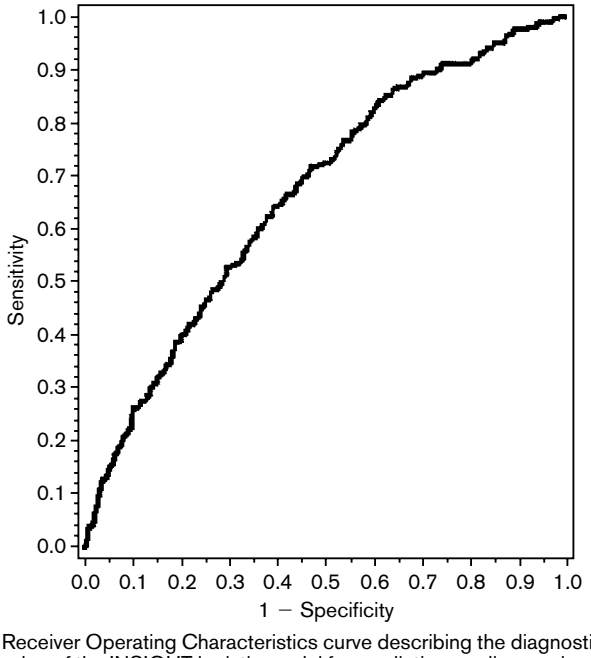
The validity of our findings depends on several factors, including the unbiased recruitment of patients, their classification according to the outcome measures, and the accuracy of risk factor measurements. In such a randomized trial, selection bias cannot be excluded; the INSIGHT cohorts are probably not representative of

Table 6 **Percentage distribution of actual events by quintile of risk at median study duration (quintiles defined per country) defined by Framingham equation for cardiovascular disease, coronary heart disease and stroke***

	Distribution (%)						
	Italy ($n = 460$)	Spain ($n = 461$)	France ($n = 1180$)	Scandinavia ($n = 271$)	The Netherlands ($n = 393$)	UK ($n = 1382$)	All ($n = 4147$)
Cardiovascular disease							
1st quintile	2.2	2.2	1.7	1.9	3.8	3.6	2.2
2nd quintile	3.3	1.1	1.3	1.9	2.5	5.8	3.3
3rd quintile	4.3	5.4	2.1	9.3	5.1	5.4	4.9
4th quintile	7.6	7.6	3.0	5.6	7.6	11.6	6.5
5th quintile	8.7	7.5	5.1	5.5	12.7	9.7	9.0
Ratio 5th : 1st	4.0	3.4	3.0	2.9	3.3	2.7	4.1
Coronary heart disease							
1st quintile	2.2	1.1	0.4	–	–	2.2	1.1
2nd quintile	–	–	0.8	5.6	–	1.4	1.0
3rd quintile	2.2	1.1	–	7.4	2.6	5.1	2.2
4th quintile	3.3	2.2	1.7	1.9	3.8	4.7	3.7
5th quintile	3.3	7.5	3.8	1.8	5.1	7.9	5.8
Ratio 5th : 1st	1.5	6.8	9.5	–	–	3.6	5.3
Stroke							
1st quintile	–	2.2	1.3	–	2.6	1.4	1.4
2nd quintile	2.2	1.1	–	–	–	1.8	1.0
3rd quintile	3.3	1.1	0.8	3.7	5.1	2.5	2.4
4th quintile	4.3	3.3	0.8	–	6.3	3.6	3.0
5th quintile	4.3	3.2	1.3	3.6	6.3	4.0	3.0
Ratio 5th : 1st	–	1.5	1.0	–	2.4	2.9	2.1

*Models calculated among the 4147 individuals with cholesterol values available.

Fig. 1



Receiver Operating Characteristics curve describing the diagnostic value of the INSIGHT logistic model for predicting cardiovascular disease.

the population aged 55–74 years of the respective countries. However, as the same procedure was performed in all countries, this potential selection bias could not explain the large inter-country differences in actual risk. Conversely, an advantage of the present study over comparison of national cohorts is the similar measurements of risk factors and the classification of events by the same independent critical events committee. Therefore, the between-country differences cannot be explained by different definitions of events, or by the use of different methods to measure risk factors.

The discrepancy between the Framingham risk prediction and the actual risk could be explained by a change in the weighting of the common risk factors. However, although direct comparison of regression coefficients with those of the Framingham model was not possible, the same risk factors were predictive of CVD events in our study and in the Framingham study, in spite of their great differences (participants in the Framingham study belong to a different generation, and were mostly without disease at entry). Hazard ratios estimated in each country for the various risk factors were compatible, with a common effect of each of these factors on cardiovascular risk. Similar findings have been reported in a comparison of the cardiovascular risk factors in a French cohort and those of several American cohorts [8], and in a more recent comparison of three northern and 10 southern European cohorts [11].

Two factors may explain the relatively low risk in our patients. First, the major difference between our patients and those in the Framingham cohort was blood pressure values. Patients were untreated in the Fra-

mingham study, whereas patients in the INSIGHT study were treated throughout the trial and physicians had to achieve a predefined target blood pressure for their patients. Consequently, systolic blood pressure decreased by 30.9 mmHg during the trial period in our patients [15]. This probably explains the marginal significance of the systolic blood pressure coefficient in the INSIGHT equation and may partly explain the lower risk in the INSIGHT population. This is consistent with the finding in the treated group of the Systolic Hypertension in Europe Trial Investigators; systolic blood pressure at the time when patients were allocated to groups did not significantly predict cardiovascular risk in the treated group [16]. Second, left ventricular hypertrophy may have been present in some patients, and may also have caused underestimation of the risk by the Framingham equation. However, the previous limitations apply to the entire population and, once again, cannot explain the between-country differences. It should also be underlined that only CHD, but not stroke, was overestimated by the Framingham equation. This is not completely unexpected, because when mortality data are used there is much less between-country difference in stroke mortality than in CHD mortality, the USA having one of the lowest stroke death rates among industrialized countries [17]. Finally, the between-country risk difference was not attributable to the difference in the level of risk factors observed in the various countries, because they were taken into consideration in both the INSIGHT and the Framingham risk equations. In this respect, the present study confirms the well-known heterogeneous baseline risk of CVD, particularly between northern and southern European populations, which is a reflection of differences in the genetic and cultural backgrounds, which are not taken into account in risk prediction equations.

Using predicted risk for individual decision-making implies that the prediction is both accurate (it predicts a risk of the same order of magnitude as the actual risk), and discriminant (the difference in actual risk between patients at high and low predicted risk is large enough to be clinically useful). A comparison of the Munster, UK, England and Wales, and Framingham risk equations showed that the Framingham equation was accurate and able to identify patients at high- and low-risk CHD [12]. However, the four risk functions were described in countries with populations at high cardiovascular risk, and were not validated against the actual number of events that occurred in the study population. Moreover, although several guidelines for CHD management and prevention, based on the Framingham model, are currently used to stratify patients into risk categories in the UK (Sheffield table) [18], USA [19] and Europe [20], the Framingham model has been shown to be accurate only in the USA [21] and in a limited number of countries at high risk of cardiovascular events, such as Scotland [22]. In the last of these studies, the classification provided by the Framingham model was observed both in treated and in untreated hypercholesterolemic patients, the latter situation being strictly comparable to that of the present study. In contrast, our finding that the predicted CVD and CHD risks were twofold greater than the percentage of events observed in our population suggests that the original Framingham model is not applicable in Europe. This is further supported by a recent study of the Framingham group which showed that, although the Framingham functions performed reasonably well for prediction of CHD events in white and black American men and women outside the Framingham setting, they systematically overestimated the risk among Japanese American and Hispanic men and Native American women [23]. In our study, although the Framingham model overestimated the risk in all countries, the overestimation was far greater in southern European countries than in the northern countries.

Despite both the overall overestimation and large differences between countries in absolute risk, the variation in the risk ratios from 1.8 to 4.0 between the first and the fifth quintiles according to the country shows that the classification was accurate enough for identification of subgroups of risk, provided thresholds are defined within each country. However, as shown by the low area under the ROC curve, the quality of prediction remains insufficient for individual risk prediction.

A 4-year follow-up time could be considered too short for being used for decision-taking purposes. However, the Framingham risk functions were recently updated because they could not be used to predict short-term risk (between 1 and 4 years) [6]. Moreover, this short-term prediction can be used to identify those high-risk patients who will benefit most from interventions, having demonstrated their usefulness in randomized trials that also usually lasted 4–5 years. The models provided in the present work could be used for optimizing treatment in already-treated patients – who represent a large proportion of hypertensive patients nowadays – in European countries.

Our study, along with other studies [8,9,11,23] demonstrate that a 'universal' prediction of cardiovascular risk using absolute risk remains difficult, because of the heterogeneous baseline risk among populations. Although separate risk charts for northern and southern Europe have been proposed by Menotti *et al.* [11], their study included only men, and the equation did not include HDL cholesterol and diabetes, which are two major risk factors used in the Framingham equation.

The present use of the original Framingham model with a single threshold to define high-risk patients in European countries is inappropriate, as it could lead to over- or undertreatment of patients, depending on the underlying cardiovascular risk of the population to which they belong. Use of the cohorts followed up in each country to recalibrate prediction functions for differing underlying rates of events is possible, as recently shown by the Framingham group [23]. This recalibration of the Framingham model to European country-specific conditions may broaden the applicability of this widely used model, without the need for new cohorts.

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