



Clinical research

# Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations?

## The PRIME Study<sup>☆</sup>

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Received 14 February 2003; received in revised form 21 August 2003; accepted 5 September 2003

### KEYWORDS

Epidemiology;  
Primary prevention;  
Coronary heart disease;  
Risk function;  
External validation

**Aims** To assess whether the Framingham and PROCAM risk functions were applicable to men in Belfast and France.

**Methods and results** We performed an external validation study within the PRIME (Prospective Epidemiological Study of Myocardial Infarction) cohort study. It comprised men recruited in Belfast (2399) and France (7359) who were aged 50 to 59 years, free of CHD at baseline (1991 to 1993) and followed over 5 years for CHD events (coronary death, myocardial infarction, angina pectoris). We compared the relative risks of CHD associated with the classic risk factors in PRIME with those in Framingham and PROCAM cohorts. We then compared the number of predicted and observed 5-year CHD events (calibration). Finally, we estimated the ability of the risk functions to separate high risk from low risk subjects (discrimination).

The relative risk of CHD calculated for the various factors in the PRIME population were not statistically different from those published in the Framingham and PROCAM risk functions. The number of CHD events predicted by these risk functions however clearly overestimated those observed in Belfast and France. The two risk functions had a similar ability to separate high risk from low risk subjects in Belfast and France (c-statistic range: 0.61–0.68).

**Conclusion** The Framingham and PROCAM risk functions should not be used to estimate the absolute CHD risk of middle-aged men in Belfast and France without any CHD history because of a clear overestimation. Specific population risk functions are needed.

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<sup>☆</sup> Funding: The PRIME Study is organized under an agreement between INSERM and the Merck, Sharpe and Dohme-Chibret Laboratory.

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## Introduction

In western populations, assessment of the absolute coronary heart disease (CHD) risk is increasingly used to identify high-risk subjects who could benefit from primary prevention. The European Society of Cardiology has recently recommended the use of an algorithm derived from the Framingham risk function.<sup>1–3</sup> However, the relevance of the Framingham risk function in Europe is not well known. Few studies have explored this issue<sup>4–12</sup> and only a limited number have compared the predicted with the observed CHD events in a cohort study.<sup>4,5,8–12</sup> The results of such studies suggest that the Framingham risk function overestimates the CHD absolute risk in low risk populations from Southern Europe.<sup>4,5</sup> In high-risk populations from Northern Europe, however, mixed results were observed.<sup>8–12</sup> All these studies used earlier versions of the Framingham risk function. In 1998, a new version has been published including cholesterol sub-fractions and using blood pressure and lipids (cholesterol and sub-fractions) in several categories.<sup>13</sup> This version has the advantage to be based on relatively more recent data (1971–1974) than that of 1991 from which the algorithm of the ESC is derived. Moreover, its suitability in European populations has never been evaluated.

Recently, the German PROCAM risk function was proposed to estimate CHD risk in European men.<sup>14</sup> Similarly, its applicability to other populations has not yet been evaluated.

Therefore, our aim was to assess whether the Framingham and PROCAM risk functions were applicable to middle-aged men from two European countries (Northern Ireland and France) with contrasting CHD event rates.

## Methods

### The risk functions under evaluation

#### The Framingham risk function

The Framingham risk function estimates the probability of developing coronary death, myocardial infarction (recognized and unrecognized), angina pectoris or coronary insufficiency (total CHD end points) within 10 years, taking age, blood pressure, LDL and HDL cholesterol, cigarette use and diabetes as risk factors.<sup>2,3</sup> In this paper, we used the recently published version of the risk function in which blood pressure and LDL-cholesterol were categorised according to the US Fifth Joint National Committee on Hypertension (JNC-V) and the US National Cholesterol Education Program, Adult Treatment Panel II (NCEP-ATP II).<sup>13</sup> Although that risk function was based on a follow up of twelve years, results on CHD incidence were adapted according to the authors to provide a 10-year CHD risk of CHD.<sup>13</sup> Only the risk function for men was considered. It was developed from the CHD experience of a sample including the original Framingham cohort and the Framingham Offspring cohort. It consisted of 2489 men aged 30–74 years who were free of any cardiovascular disease at the time of their examination from 1971 to 1974.

#### The PROCAM risk function

The PROCAM risk function estimates the probability of developing coronary death or first myocardial infarction (hard end-points) within 10 years, employing age, systolic blood pressure,

LDL and HDL cholesterol, triglycerides, cigarette use, diabetes and family history of myocardial infarction as risk factors.<sup>14</sup> The risk function was developed from a sample of men included in the PROCAM cohort. It consisted of 5389 men aged 35–65 years who were free of any cardiovascular disease at baseline between 1979 and 1985.

### The validation population

We used the Prospective Epidemiological Study of Myocardial Infarction (PRIME) cohort as the validation population. The recruitment and examination methods as well as the diagnostic procedures for CHD cases at entry and during follow-up have been previously described.<sup>15–17</sup>

#### Recruitment

Briefly, the recruitment of this cohort was done in centres in Belfast (Northern Ireland) and Lille, Strasbourg and Toulouse (France) and a Coordinating Centre in Paris. The sample was recruited to broadly match the social class structure of the background population. It consisted in workers in industry of various employment groups, general practitioners patients (Belfast) and volunteers attending health-screening centres. Initially, 10600 men aged 50–59 were recruited between 1991 and 1993. For the present analysis however, only the 9758 men who were free of any coronary heart disease at entry were included, consisting of 2399 men in Belfast and 7359 men in France. Subjects were considered free of coronary heart disease (CHD) at entry if they did not meet any of the following three criteria: (1) reported myocardial infarction and/or angina pectoris diagnosed by a physician; (2) evidence of a myocardial infarction on the standard 12-lead electrocardiogram (ECG) recorded at baseline and defined as a major or moderate Q waves coded using the Minnesota system; (3) a positive answer to the Rose Questionnaire.<sup>18</sup> As no retrospective checking of medical data from doctors and clinics was possible, a strict definition was chosen in order to exclude any subject with a suspicion of CHD.

#### Baseline measurements

Subjects who agreed to take part in the study were given a morning appointment and asked to fast for at least 12 h. A full description of clinical<sup>15,16</sup> and laboratory<sup>17</sup> measurements has been published elsewhere. Briefly, after fulfilling a self-administrated health questionnaire at home, trained interviewers checked at the clinic a broad range of clinical information including family and personal clinical history completed by the Rose Questionnaire,<sup>18</sup> tobacco consumption, drug intake. Diabetes mellitus was defined by the current take of oral hypoglycaemic or insulin. Blood pressure was measured on two occasions in the sitting position with the same automatic device (Spengler SP9). A 12-lead ECG was also recorded. Plasma lipids analyses were centralised (SERLIA INSERM U325, Institut Pasteur de Lille, France). Total cholesterol and triglycerides were measured by enzymatic methods using commercial kits in an automatic analyzer (Boehringer, Mannheim, Germany). High-density lipoprotein (HDL) cholesterol was determined after precipitation of apo-lipoprotein B by enzymatic method (Boehringer). Low-density lipoprotein (LDL) cholesterol was calculating according to the Friedewald formula.

#### Follow up and ascertainment of cases

After baseline measurements, subjects were followed for the occurrence of any clinical event including coronary death, myocardial infarction and angina pectoris. Subjects were contacted annually by letter and asked to complete a clinical event questionnaire. For all subjects reporting a possible event, clinical information was sought directly from the hospital or general practitioner records. All details of ECGs, hospital admissions, enzymes, surgical intervention, angioplasty, treatments, etc.,

**Table 1** Characteristics of the Framingham, PROCAM and PRIME cohorts

	Framingham <sup>13</sup>	PROCAM <sup>14</sup>	PRIME-Belfast <sup>15</sup>	PRIME-France <sup>15</sup>
Population	general population	workers	composite population <sup>a</sup>	composite population <sup>a</sup>
Geographic area	USA	Germany	Northern Ireland	France
Sample size	2489	5389	2399	7359
Age range	30–74	35–65	50–59	50–59
Time of recruitment	1971–1974	1979–1985	1991–1993	1991–1993
<b>Risk factors</b>				
Age	+	+	+	+
Systolic and diastolic blood pressure	+	+	+	+
LDL-cholesterol (Friedewald formula)	+	+	+	+
HDL-cholesterol	+	+	+	+
Triglycerides		+	+	+
Tobacco	+	+	+	+
Diabetes	+	+	+	+
Family history of myocardial infarction		+	+	+
<b>CHD end point<sup>b</sup></b>				
Follow up (years)	Total 10	Hard 10	Total and Hard 5	Total and Hard 5
Analytic form of the risk function	Cox model	Cox model	Cox model	Cox model
Number of CHD events	383	325	120	197

<sup>a</sup>Includes workers in industry from variant employment groups, general practitioners patients and volunteers attending a screening centre.

<sup>b</sup>Total CHD end points refer to coronary death, recognized and unrecognized myocardial infarction, angina pectoris and coronary insufficiency in Framingham; in PRIME, it refers to coronary death, recognized myocardial infarction and angina pectoris; hard CHD end points refer to coronary death and myocardial infarction. (+) Indicates that the risk factor under consideration is available in the study.

were collected. Death certificates were checked for supporting clinical and post-mortem information on cause of death. Whenever possible, circumstances of death were obtained from the practitioner or the family. A Medical Committee comprising one member from each PRIME Centre and the Coordinating Centre and three cardiologists (two from France and one from the UK) was established, in order to provide an independent validation of coronary events in the PRIME Study. A description of the coronary end point definitions has been published recently.<sup>16</sup> Only the first coronary event among angina pectoris, myocardial infarction and coronary death for total CHD end points, and among myocardial infarction and coronary death for hard end points were kept for analysis.

At the time of the analysis, data from 5 years of follow-up were available and consisted of 317 CHD incident cases (120 first events in Belfast and 197 in France), and 167 were hard CHD incident cases (61 in Belfast and 106 in France).<sup>16</sup>

The main characteristics of the 4 cohorts are reported in Table 1.

## Statistical analysis

The applicability of the Framingham and PROCAM risk functions in PRIME was assessed in three steps.<sup>19</sup>

Firstly, in the PRIME population we calculated the multivariate relative risk for CHD (Cox model) associated with the risk factors used in the Framingham and in the PROCAM risk functions. Initially, these multivariate relative risks were estimated separately in Belfast and France (data not shown), but since similar estimates were obtained and in order to have more robust estimates, we calculated the relative risks in the PRIME cohort after adjustment for the centres. Adjustment for the centres was done by including three dummy variables in the multivariate Cox models. Then, we compared the magnitude of these relative risks among the cohorts (PRIME vs Framingham

and PRIME vs PROCAM). To this end, we compared the regression coefficients of the Cox model obtained in PRIME with those published in the Framingham and PROCAM risk functions with a z-test ( $P < 0.05$  for statistical significance).<sup>19</sup>

Secondly, we compared the predicted with the observed number of CHD events (calibration), respectively for the total CHD events (Framingham risk function) and the hard CHD events (PROCAM risk function). Since the Framingham and PROCAM risk functions yield an estimate of the 10-year absolute CHD risk for a given age and set of risk factors, we divided such an estimate by two in order to obtain a 5-year absolute CHD risk estimation for each PRIME participant. This approximation might result in slightly increasing the 5-year incidence rate for a given age and risk factor levels at entry but this bias is likely small as shown in the PROCAM population for which observed 5-year CHD rates were practically equal to half the 10-year rates.<sup>14</sup> We estimated the 5-year absolute CHD risk of each PRIME participant according to the Framingham and PROCAM risk functions and then ranked them into deciles (Framingham risk function) or quintiles (PROCAM risk function) of estimated risk. For the PROCAM risk function, we used quintiles rather than deciles of predicted events because of the limited number of events (120 hard events including 61 in Belfast). Then, within each decile (quintile), we computed the predicted number of CHD events as the sum of the individual absolute risks. We there after estimated the logarithm ratio of the number of predicted over observed CHD events within each decile (quintile) and calculated a global common log ratio as the weighted mean of the individual log ratios. Weights were the inverse of the variance of each log ratio as estimated by the number of observed cases (Poisson distribution); the variance of the common log ratio was calculated as the inverse of the sum of the weights.<sup>20</sup>

Thirdly, we estimated the ability of the Framingham and PROCAM risk functions to separate high risk from low risk PRIME subjects (discrimination). In this respect, we calculated the area

**Table 2** Multivariate-adjusted Relative Risk (RR) of total events<sup>a</sup> in Framingham and PRIME studies

	Framingham <sup>13</sup>		PRIME <sup>15</sup>		P <sup>b</sup>
	RR	95% CI	RR <sup>c</sup>	95% CI	
Age (year)	1.05	1.04–1.06	1.06	1.02–1.10	0.65
Blood pressure (mmHg) <sup>d</sup>					
optimal+normal	1.00	referent	1.00	referent	
high normal	1.32	0.98–1.78	1.40	1.00–1.96	0.80
stage I	1.73	1.32–2.26	1.58	1.18–2.13	0.65
stage II–IV	1.92	1.42–2.59	2.43	1.79–3.31	0.28
LDL-Cholesterol (mg/dl) <sup>e</sup>					
<130	1.00	referent	1.00	referent	
130–159	1.19	0.91–1.54	1.38	1.03–1.85	0.47
≥160	1.74	1.36–2.24	2.05	1.56–2.71	0.39
HDL-cholesterol (mg/dl) <sup>e</sup>					
<35	1.46	1.15–1.85	1.98	1.48–2.66	0.11
35–59	1.00	referent	1.00	referent	
≥60	0.61	0.41–0.91	0.72	0.51–1.02	0.54
Cigarette use (y/n)	1.71	1.39–2.10	1.70	1.36–2.13	0.97
Diabetes (y/n)	1.47	1.04–2.08	2.23	1.44–3.47	0.14

<sup>a</sup>Total events refer to coronary death, recognized and unrecognized myocardial infarction, coronary insufficiency and angina pectoris in Framingham. In PRIME, unrecognized myocardial infarction was not counted and only the first coronary event was considered.

<sup>b</sup>Comparison of the regression coefficients of each risk factor calculated in Framingham and in PRIME (z statistic).

<sup>c</sup>RR for the entire PRIME cohort adjusted for the centres and for age, blood pressure, LDL and HDL cholesterol, cigarette use and diabetes.

<sup>d</sup>Categories of the US Fifth Joint National Committee on Hypertension.

<sup>e</sup>Categories of the US National Cholesterol Education Program, Adult treatment Panel II.

under a receiving operative characteristics curve of the two risk functions (c-statistic).<sup>9,10,12,19</sup>

Statistical analysis was performed on SAS software (SAS Institute, Cary, USA).

## Results

### Description of the cohorts

Table 1 presents the baseline characteristics of the Framingham, PROCAM and PRIME cohorts and shows some inter cohort design differences. In the Framingham and PROCAM cohorts, the age range at entry was higher, the baseline measurements were made respectively 20 years and 10 years earlier and the duration of follow-up was twice as long as in the PRIME cohort. Differences in the population characteristics make difficult any strict comparison of the level of the underlying cardiovascular risk factors. However, their mean values were globally of similar order of magnitude in the three populations.

### Comparison of the relative risks attached to classical risk factors among cohorts

Table 2 shows the relative risks for total CHD events calculated in PRIME using the risk factors of the Framingham risk function. They were all significantly and independently associated with the occurrence of total CHD events. The magnitude of the relative risk associated with a given increase in these risk factors was of the same order as in the Framingham risk function. Table 3 shows the relative risks for hard events calculated in

PRIME using the risk factors of the PROCAM risk function. The findings were similar to those reported above for the Framingham risk function. However, the association between hard CHD events and triglycerides level was not significant in PRIME contrary to PROCAM.

### Calibration of the Framingham and PROCAM risk functions in PRIME

Figure 1a and Figure 1b show the predicted and observed numbers of CHD events in Belfast and France by deciles of Framingham estimated risk (Fig. 2a, Fig. 2b) and quintiles of PROCAM estimated risk (Fig. 2a, Fig. 2b). A positive linear relationship between predicted and observed CHD events (logarithmic scale) was observed with the Framingham risk function in Belfast and France, and with the PROCAM risk function in France. In Belfast, the relationship was not so clear in the first four quintiles of the PROCAM estimated risk, but all observed numbers of events were low (<10). The number of predicted CHD events estimated by the Framingham risk function (total CHD events) or the PROCAM risk function (hard CHD events) clearly overestimated that observed in Belfast and France. Overestimation was greater in France than in Belfast as indicated by the common ratio of predicted over observed CHD events of 2.35 vs 1.34 with the Framingham risk function, and of 2.76 vs 1.78 with the PROCAM risk function. Additionally, overestimation seems greater with the PROCAM risk function than with the Framingham risk function in Belfast (common ratio of 1.78 vs 1.34) as well as in France (2.76 vs 2.35).

**Table 3** Multivariate-adjusted Relative Risk (RR) of hard events<sup>a</sup> in PROCAM and PRIME studies

	PROCAM <sup>14</sup>		PRIME <sup>15</sup>		<i>p</i> <sup>b</sup>
	RR	95% CI	RR <sup>c</sup>	95% CI	
Age (year)	1.11	1.09–1.13	1.08	1.02–1.14	0.37
Systolic blood pressure (/10 mmHg)	1.10	1.05–1.17	1.09	1.02–1.17	0.84
LDL-cholesterol (/10 mg/dl, Friedewald)	1.13	1.10–1.16	1.07	1.02–1.11	0.06
HDL-cholesterol (/10 mg/dl)	0.73	0.64–0.82	0.78	0.67–0.91	0.52
Triglycerides (/mg/dl; log-transformed)	1.37	1.06–1.79	1.09	0.73–1.62	0.35
Current or past smoker (y/n)	1.93	1.55–2.41	1.65	1.21–2.26	0.42
Diabetes (y/n)	1.49	1.09–2.03	2.27	1.21–4.23	0.24
Family history of MI (y/n)	1.47	1.13–1.91	1.66	1.09–2.51	0.63

<sup>a</sup>Hard events refer to coronary death and myocardial infarction; in PRIME, the first event was counted.

<sup>b</sup>Comparison of the regression coefficients of each risk factor calculated in PROCAM and in PRIME (z statistic).

<sup>c</sup>RR for the entire PRIME cohort adjusted for the centres and for age, systolic blood pressure, LDL and HDL cholesterol, triglycerides, smoking status, diabetes and family history of MI.

### Discrimination of the Framingham and PROCAM risk functions in PRIME

Table 4 reports the ability of the Framingham and PROCAM risk functions to separate high risk from low risk subjects in Belfast and France through their c-statistics. The c-statistics ranged from 0.61 to 0.68, suggesting that the two risk functions had similar discriminatory power.

### Discussion

In middle-aged men from the PRIME cohort of Belfast (Northern Ireland) and France, the Framingham risk function seems to have general applicability for ordering individuals according to their absolute CHD risk. Similar finding was observed with the PROCAM risk function, especially in France. Moreover, both risk functions clearly overestimated the CHD absolute risk of these men since the estimated ratio of predicted over observed number of CHD events was 2.35 in France and 1.34 in Belfast using the Framingham risk function, and respectively 2.76 and 1.78 with the PROCAM risk function.

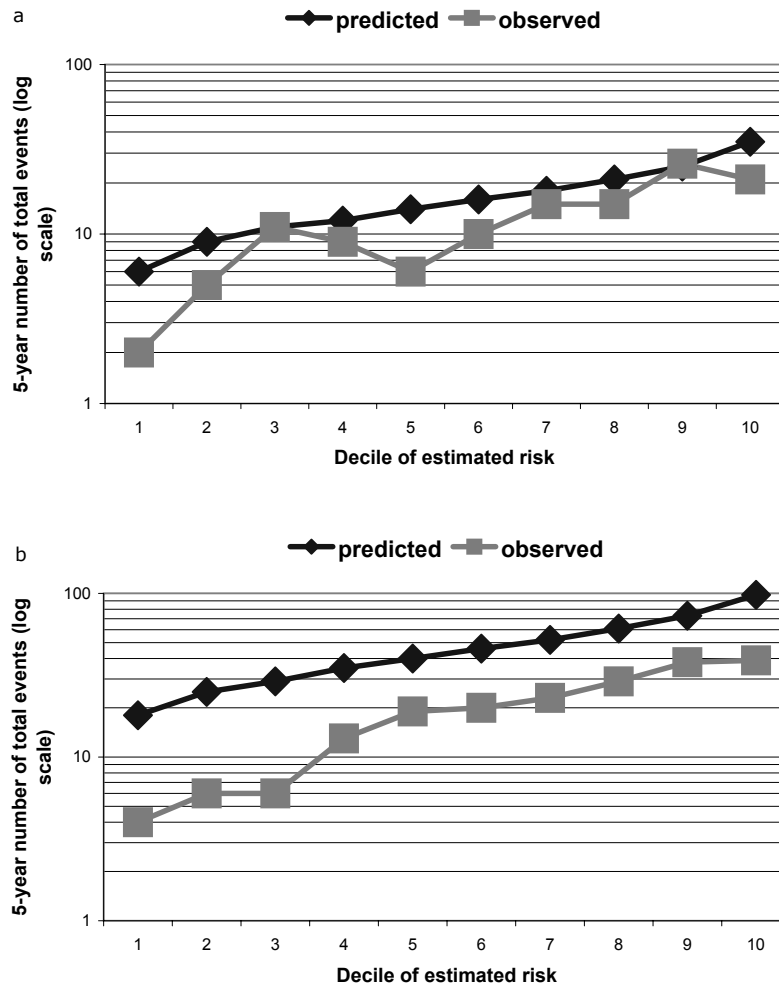
Coefficients of risk factors used in the Framingham and PROCAM risk functions were of the same order of magnitude to that observed in the PRIME Study. This is consistent with previous studies and confirms the universality and the robustness of the associations between classic risk factors and CHD.<sup>4,5,8,9</sup> For triglycerides however, there were no independent statistical association with hard CHD events in PRIME contrary to PROCAM, which is a relatively frequent finding.<sup>21</sup>

The graded increase of CHD incidence across the decile of Framingham estimated risk in Belfast and France and across quintile of PROCAM estimated risk in France underlines the ability of these risk functions to order individuals of these countries according to their estimated CHD absolute risk. In Belfast, the ability of the PROCAM risk function to ordering individuals was not so clear. However, this might be due to the limited number of observed hard CHD events (*n*=61), especially in the first four quintiles of estimated risk where there were all lower than 10.

In the present study, the Framingham risk function overestimates the CHD absolute risk in France. This is consistent with previous findings based on earlier versions of the Framingham risk function in countries with low CHD rates. For instance, overestimation of CHD events was described in a previous French cohort, the Paris Prospective Study.<sup>4</sup> Similarly, a marked overestimation of the 10-year absolute CHD risk of Italian middle-aged men of the Seven Counties Study was reported.<sup>5</sup> More recently, in the INSIGHT trial<sup>10</sup>-involving treated hypertensive patients from Northern and Southern Europe-the ratios of the predicted over observed total CHD event were respectively 7.0, 3.5 and 3.0 in France, Spain and Italy. It is very likely, however, that these ratios were overestimated given the very limited number of CHD events observed in these three countries. Outside Europe and using the most recent published Framingham risk function for the estimation of the 5-year risk of hard events,<sup>19</sup> a clear overestimation of observed events was also found in Japanese, Puerto Rican and Native American living in the USA, ethnics groups characterized by low CHD rates. All together, these results confirm that the Framingham risk function should be re-calibrated for countries with low CHD rates such as those of southern European countries.

The fact that the Framingham risk function also overestimates CHD risk in Belfast may indicate that its applicability in northern European countries may also be limited, at least in middle-aged men in the 1990s. The application of the Framingham risk function to northern European populations has yielded variable results. Close agreement between predicted and observed CHD events has been shown in German men of the PROCAM cohort and in Scottish men from the WOSCOPS Study.<sup>8,11</sup> However, a clear overestimation of observed CHD events was recently reported in the Glostrup cohort (Denmark),<sup>9</sup> in treated hypertensive patients (men and women) living in 5 northern European countries (The Netherlands, UK, Sweden, Denmark and Norway) from the INSIGHT trial<sup>10</sup> and in two German cohorts of men and women.<sup>12</sup> In the INSIGHT trial, the ratios of predicted over observed total CHD events were respectively 2.8, 2.3 and 2.0 in





**Fig. 1** a. Calibration of the Framingham risk function in Belfast. The common ratio of predicted over observed CHD events (95% CI) was 1.34 (1.12–1.60). b. Calibration of the Framingham risk function in France. The common ratio of predicted over observed CHD events (95% CI) was 2.35 (2.05–2.71).

Scandinavia (Sweden, Denmark and Norway), The Netherlands and UK. In the German study, the ratio of predicted over observed CHD events (myocardial infarction and coronary death) was around 2 in the Augsburg MONICA cohort as well as in the expanded follow up of the PROCAM Study.

The ability of the PROCAM risk function to estimate the absolute CHD risk in European men has never been evaluated so far. The present data indicate that this risk function clearly overestimates this risk in men from Belfast and France, overestimation being greater in France than in Belfast. It is surprising that the overestimation seems larger than that reported with the Framingham risk equation. However, the number of hard events (on which the PROCAM risk equation is based) in each cohort is low and no definite interpretation can be given.

Several reasons may explain that the Framingham and PROCAM risk functions overestimate CHD absolute risk in our population.

Firstly, the heterogeneity of the end points definitions across studies must be considered. For instance, unrecognized myocardial infarctions (silent myocardial in-

farcction) were included in the Framingham risk function but not in PRIME. Similarly, the definition of angina pectoris in PRIME (angiographic and scintigraphic criteria in addition to usual criteria) was more specific and restrictive than in Framingham, resulting in lesser events in PRIME than in Framingham.

Secondly, the use of the PRIME cohort as an external validation population representative of the general population of Northern Ireland and France is a matter of concern. As many examination surveys with recruitment based on a voluntary basis, acutely ill people as well as subjects with poor health status were not included in the PRIME study. This bias is illustrated by the comparison of the estimated 5-year official mortality rates of the two countries according to age in 1991–1993 with that observed in PRIME. The 5-year official mortality rates were 6.3% in Northern Ireland and 6.1% in the French regions whereas the corresponding rates in PRIME were respectively 2.9% and 2.0%.<sup>16</sup>

In contrast, the incidence of coronary hard events in PRIME was more comparable to that observed in the same MONICA regions.<sup>16</sup> The incidence of hard events in the four MONICA regions over the period 1991–1993 by 5-year

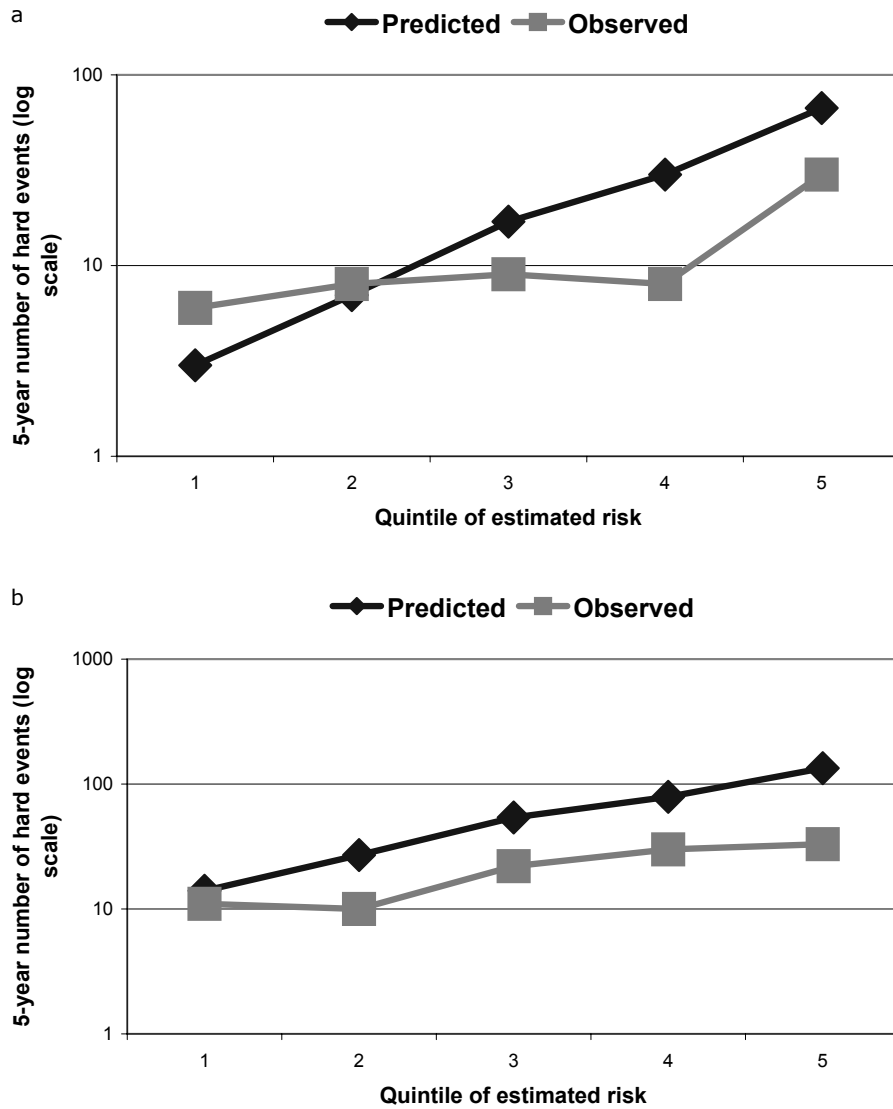


Fig. 2 a. Calibration of the PROCAM risk function in Belfast. The common ratio of predicted over observed CHD events (95% CI) was 1.78 (1.38–2.28). b. Calibration of the PROCAM risk function in France. The common ratio of predicted over observed CHD events (95% CI) was 2.76 (2.28–3.34).

**Table 4** Five-year discriminatory ability (c-statistic) of the Framingham and PROCAM risk functions in Belfast and France in PRIME

	Risk function	Framingham <sup>13</sup>	PROCAM <sup>14</sup>
PRIME <sup>15</sup>	Belfast	0.66	0.61
	France	0.68	0.64

age groups in men without a history of coronary heart disease was used for comparison. According to the choice of the definition of coronary events in MONICA, the estimated 5-year incidence rates (per 1000 person-year) ranged from 5.0 to 6.4 in Belfast and from 2.6 to 3.4 in France compare to the 5.2 and 2.9 observed in PRIME respectively.<sup>16</sup> Comparison of hard CHD incidence rates

in MONICA Augsburg and PROCAM cohorts in the recent work of Hense et al.<sup>12</sup> shows that the observed incident event rates (hard event) in men of 45–54 and 55–64 years were 30% to 46% higher in PROCAM than in the Augsburg MONICA cohorts. These opposite discrepancies in comparison with MONICA data might contribute to the overestimation of hard CHD incidence rate when the PROCAM risk function is applied to the PRIME population. However, no other results on the applicability of the PROCAM risk function in another independent cohort seem available.

Thirdly, the decrease in CHD incidence and mortality rates since 1980 in Western countries could also explain why 'old' risk functions (initial data gathered before 1974 and 1985 respectively in the Framingham and the PROCAM studies) overestimate CHD absolute risk in a more recently examined population such as PRIME.<sup>22</sup> This reason may be especially important for the Belfast

population since the downward trend in CHD incidence in MONICA was particularly important in countries at high CHD risk such as the northern European countries.<sup>22</sup>

Recalibration of the Framingham and PROCAM risk functions might be a way to reduce the overestimation of the absolute CHD risk in PRIME.<sup>19,23</sup> At the time of analysis however, there were not enough events to recalibrate and assess the applicability of the 'modified' risk functions separately in Belfast and France.

In our population, the Framingham and PROCAM risk functions had similar abilities to separate high risk from low risk subjects in Belfast and France. It is likely that the c-statistic range (0.61–0.68) also reflects the short duration of follow up of our cohort (5 years) and not just a poor discriminative power. This is consistent with the c-statistic of the Framingham risk function reported (0.66) in the INSIGHT trial<sup>10</sup> in which the length of follow up was 3.7 years. Conversely, in the Glostrup cohort (10 years of follow up), the MONICA Augsburg men cohorts (median duration of follow up of 13.2 years and 7.8 years) and PROCAM men cohort (median duration of follow up of 11.1 years), the c-statistic of the Framingham risk function was 0.75, 0.78 and 0.73 respectively.<sup>9,12</sup>

In conclusion, the present study shows that while the use of Framingham and possibly PROCAM risk functions may be suitable for ordering individuals according to their estimated CHD absolute risk, their use seems inappropriate to estimate CHD absolute risk of healthy middle-aged men from low risk (France) and high-risk (Belfast) populations since it leads to a clear overestimation. This study highlights the fact that the use of one single risk function is not an acceptable target and that the development of specific-population risk functions is necessary.

## Acknowledgements

We thank the following organizations which allowed the recruitment of the PRIME subjects: the Health screening centers organized by the Social Security of Lille (Institut Pasteur), Strasbourg, Toulouse and Tourcoing; Occupational Medicine Services of Haute-Garonne, of the Urban Community of Strasbourg; the Association Inter-entreprises des Services Médicaux du Travail de Lille et environs; the Comité pour le Développement de la Médecine du Travail; the Mutuelle Générale des PTT du Bas-Rhin; the Laboratoire d'Analyses de l'Institut de Chimie Biologique de la Faculté de Médecine de Strasbourg; the Department of Health (NI) and the Northern Ireland Chest Heart and Stroke Association.

## Appendix A

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