Clin. Cardiol. 26, 243–249 (2003)

Guideline Implementation in a Multicenter Study with an Estimated 44% Relative Cardiovascular Event Risk Reduction

ALTAN ONAT, M.D., FESC, INAN SOYDAN, M.D.,* LALE TOKGÖZOĞLU, M.D., FACC,† VEDAT SANSOY, M.D., FACC,‡ NEVRES KOYLAN, M.D., FACC,§ NERGIZ DOMANIÇ, M.D., DILEK URAL, M.D., ON BEHALF OF THE RISKBURDEN STUDY GROUP, TURKISH SOCIETY OF CARDIOLOGY, ISTANBUL, TURKEY

Istanbul University Cerrahpaşa, §Istanbul Medical Faculties, and ‡Cardiology Institute; *Aegean University Medical Faculty, Izmir; †Hacettepe University Medical Faculty, Ankara, Turkey

Summary

Background: The extent of cardiovascular risk reduction by implementing coronary prevention guidelines needs to be documented in various population samples.

Hypothesis: This is a multicenter study to assess the impact of risk reduction in cardiovascular events upon implementation of coronary prevention guidelines in patients with or at high risk for coronary heart disease (CHD) in the setting of clinical practice.

Methods: Enrolled volunteers numbered 2,021. Inclusion criteria postulated a minimum of 20–40% cardiovascular event risk in the subsequent 10 years as estimated from the risk table of the European Society of Cardiology (ESC) Guidelines. The estimated CHD risk reduction was assessed in terms of the Framingham risk scores at baseline and at 12 months, computed from the data of each individual. Data of the compliant group (making up half of the initial participants) at the end of the study, along with absolute and relative risk reductions in the compliant group, were analyzed.

Results: Mean global risk burden was 25.9% at baseline, reduced through multilateral preventive measures in absolute terms by 9.4% at 6 months and by 11.7% at 12 months; the latter represents a relative risk reduction of 44%. Independent variables determining the (enhanced) reduction in risk level at the end of 12 months included (high) level of baseline risk, (high) degree of compliance with treatment, younger age, female gender, smoking, and (high) baseline triglyceride/high-density lipoprotein cholesterol (TC/HDL-C) ratio.

While the relative reduction in patients with CHD amounted to 43%, a reduction of 46% ($p < 0.001$) was obtained in the setting of primary prevention. Diabetes emerged as a factor modestly limiting the extent of risk reduction. While subjects without hypertension revealed a decline of coronary risk by merely 8.7%, those with hypertension showed a decline by 12.7% ($p < 0.001$). Risk reductions were accompanied by a decrease of mean low-density lipoprotein cholesterol (LDL-C) level of 25.4%, a rise in mean HDL-C level of 5 mg/dl, a decrease in mean systolic blood pressure of 26 mmHg. Forty-five percent of smokers succeeded in discontinuing the habit.

Conclusion: By implementing standard prevention guidelines in the Turkish population among 1,000 compliant high-risk men and women and among 1,000 patients with CHD, prevention of cardiovascular events could be expected in 117 persons in the subsequent 10 years.

Key words: coronary risk reduction, guideline implementation, preventive cardiology

Introduction

In the past decade, continental,[1] international, and national[2] guidelines have been published by expert committees to assist physicians in the administration of proper evidence-based practice to eliminate or reduce cardiovascular risk factors. These actions were timely since cardiovascular disease has recently come to rank first among worldwide causes of death.[3] In view of a developing worldwide epidemic, a number of salient forums at the international[4] and European levels[5] have called for action by cardiovascular specialty societies, aiming to enhance efforts addressed to identification and improved treatment of cardiovascular risk factors in pa-

Address for reprints:

Altan Onat, M.D., FESC
Turkish Society of Cardiology
Nisbetiye cad. 37/24
Etiler 80630
Istanbul, Turkey
e-mail: tkd@ixir.com

Received: December 3, 2001
Accepted with revision: April 22, 2002

tients with vascular disease or in individuals who are at high risk for it. Studying the extent of implementation of current guidelines and assessing the outcome were important elements of this effort. A cohort-based model was recently used[6] to estimate the extent to which changes in secondary prevention treatment could further reduce coronary heart disease (CHD) mortality in Scotland. Yet, paucity of information still exists regarding the extent of cardiovascular risk reduction in clinical practice at large.

In the Turkish community, in which the rate of smoking is high and physical activity habits leave much to be desired, the increasingly unhealthy habits of food consumption have all contributed in the 1990s to a rise in plasma triglyceride levels[7] and in the incidence of obesity, diabetes mellitus, and hypertension.[8] These factors, together with remarkably low mean high-density lipoprotein cholesterol (HDL-C) levels of the population,[9] have led to a high coronary mortality[10] in a population with a young structure, necessitating preventive measures. The Turkish Society of Cardiology therefore conducted a multicenter study in 26 clinics to examine the extent to which implementation of the Turkish guidelines for prevention of CHD[2] could reduce individual CHD risk among patients with CHD or subjects at an equivalent high risk for the disease.

Study Population and Methods

The study was conducted in 26 clinics of cardiology, internal medicine, and endocrinology located in various regions of Turkey. The participating centers and investigators are listed at the end of the text. The nucleus members of the Turkish Society of Cardiology's Working Group on Lipids formed the steering committee responsible for data, safety, and review. Data storage and statistical analysis of the study were performed by an independent contract research organization (CRO). Data monitoring was provided with the support of Merck-Sharp-Dohme Ltd., Co., Turkey, and interim analysis reports of the data from the CRO were presented to the primary investigator every 3 months.

Inclusion criteria: Individuals 40–70 years of age, who had CHD or plasma total cholesterol levels > 200 mg/dl, and who were in a risk category of > 20% according to the European Society of Cardiology (ESC) risk chart,[2] were included in the study if they had at least two of the following risk factors: (1) Age: men ≥ 45, women ≥ 55, or women who experienced menopause before 45 years of age; (2) smoking one or more cigarettes daily; (3) hypertension (> 140 and/or > 90 mmHg, or under treatment with antihypertensive drugs); (4) diabetes mellitus (DM); (5) low level of HDL-C (men < 35 mg/dl, women < 40 mg/dl); (6) family history of heart attack or sudden death occurring before the age of 55, or 65 years in first-degree male or female relatives, respectively.

The following adjustments were made in evaluating the risk level required for inclusion in the study for conditions not directly included in the CHD risk chart:[1] in the presence of a clinical vascular disease (e.g., arteriosclerosis obliterans, cerebrovascular accident), risk category was upgraded by one in accordance with the recommendations of the ESC Guidelines. Risk category was also upgraded by one compared with the chart if an individual had any two of the following: family history of premature clinical vascular disease, diabetes, familial hyperlipidemia, low HDL-C, or high (> 200 mg/dl) triglyceride levels.

Exclusion criteria: Individuals with New York Heart Association (NYHA) class II–IV cardiac failure, a malignant disorder that might affect morbidity and mortality in the intermediate period, hepatic or renal insufficiency, chronic inflammatory disease, secondary reasons for hyperlipidemia other than noninsulin-dependent DM, central nervous system disorders, or psychosocial incompatibility were excluded from the study.

Volunteers applying for treatment in the respective outpatient units of the centers were screened in accordance with inclusion and exclusion criteria. Minimal risk of CHD over the next 10 years was also required. Risk categories based on the ESC risk chart[1] were determined by computer software especially designed for this study, and high-risk patients for primary and secondary prevention, from whom informed written consents were obtained, were enrolled. Follow-up was set at 1 year. Risk category was assigned at each visit using the abovementioned program.

Investigators were informed at study commencement that all recommendations stipulated in the Prevention Guidelines[2] were to be implemented for risk reduction during the study and that treatment approaches to hyperlipidemia and hypertension were to be based upon the Guidelines.

Blood pressure measurements were performed at baseline and at each follow-up visit, and the average of at least two measurements was recorded. These measurements were taken while the individual was seated and resting for 5 min with the arm held at the heart level. Measurements were done in both arms, and the higher value was registered. Antihypertensive medication was not withheld at baseline or at subsequent visits.

Plasma total cholesterol (TC), HDL-C, low-density lipoprotein cholesterol (LDL-C), alkaline phosphatase, AST, ALT, creatine kinase, albumin, globulin, uric acid, blood glucose, blood urea and creatinine, and complete blood count values of all enrolled subjects were measured at baseline and at the 3rd, 6th, and 12th months. Measurements were taken after a 12-h fast at the laboratory of each study center. Physical examination of patients, including height and weight measurements, was performed and a 12-lead electrocardiogram (ECG) was recorded.

In all, 2,021 persons from 26 clinics were enrolled; 1,008 were male and 1,013 were female. Mean ages were 56.2 ± 8 for men and 59.2 ± 7 for women; 57% of men and 42% of women had CHD. Baseline characteristics pertaining to demographics and risk factors of the volunteers with and without CHD are summarized in Table I.

Of the 1,018 subjects who needed primary prevention, 583 were female, and 491 of these belonged to the 20–40% risk category. Of 435 (63%) men in this group, 275 were in the 20–40% risk category. Of 430 female patients with CHD, 311 were in the 20–40% category and 94 in the > 40% category. Twenty-five patients (5.8%) were in the 10–20% risk category

TABLE I Baseline characteristics pertaining to demographics and risk factors in 2,021 volunteers

	Primary prevention (n = 1,018)		Secondary prevention (n = 1,003)	
Variable	Mean (or %)	SD (or %)	Mean (or %)	SD (or %)
Number of participants/center	39.2		38.6	
Age	57	8	58	8
Sex (M – F)	42.7	57.3	57.1	42.9
Presence of obesity	34.9		25.6	
Presence of hypertension	84.3		62.7	
Smoker	41.3		38	
Low HDL-C (M < 35, F < 40)	35.4		35	
Presence of diabetes	44.3		27.8	
Presence of family history	39.7			
TC (mg/dl)	282.6	49	260.5	42
LDL-C (mg/dl)	188.7	46	173.5	40
HDL-C (mg/dl) (n = 1927)	41.8	11	41.8	11
Triglycerides (mg/dl) (n= 1996)	252	138	226	128
TC/HDL-C ratio (n= 1918)	7.1	2.1	6.7	2.4

Abbreviations: SD = standard deviation, M = male, F = female, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TC = total cholesterol.

at baseline, but when projected to 60 years of age, belonged to the next higher risk category. Of 573 male patients with CHD, 32% were in the 20–40% and 68% in the > 40% risk category. Individuals included in primary prevention were clearly specifically selected from a high-risk group.

Forty-one percent of subjects without CHD and 38% of patients with CHD were smokers. Among individuals for primary prevention, 84% had hypertension, 35% were obese, and 44% had diabetes. Among patients with CHD, 63% had hypertension, 26% were obese, and 28% had diabetes.

Parameters such as the change in global risk, change in lipid and blood pressure levels, and the accomplishment of smoking cessation were assessed throughout the study, which was approved by an ethics committee of the Turkish Society of Cardiology and conducted in conformity with the revised (Hong Kong, 1989) version of the Helsinki Declaration.

Except for changes in the risk categories, the difference in the mean risk burden of certain subgroups between baseline and the following visits were assessed using the Framingham risk scoring method.[11] In the old Framingham formulation, the percentage risk of an individual for developing coronary artery disease in the subsequent 10 years depends first on systolic blood pressure, smoking, total cholesterol/HDL-C ratio, and left ventricular hypertrophy findings on the ECG, and then on gender, age, and the presence of diabetes.

Statistical analysis: The parameters at the end of the 6th and 12th months of the study were compared with baseline values by analysis of variance, *t*-test, chi-square test, and the subgroups by the Wilcoxon statistical analysis method. The difference among subjects with and without a risk factor at a certain visit in a subgroup was evaluated with the Mann-Whitney U test.[12]

In computing differences between variables measured more than once, differences between two measurements in the individual were calculated first, followed by reporting the mean differences. Since participants at subsequent visits were fewer than at baseline, the difference between means is not identical with the mean of differences. The actual absolute reduction resulted from the data of participants making both visits.

Results

Characteristics of Participants Not Completing the Study

The total follow-up period amounted to 1,245 patient-years. In all, 942 subjects (47%) completed the 12 months of the study. Compared with the latter, those who failed to come to the last visit had a slightly lower initial global risk burden in terms of the Framingham risk score ($p < 0.05$) because of a lower prevalence of diabetes mellitus ($p < 0.001$) and because women were included ($p = 0.052$). No significant difference existed with respect to age, family history, smoking, hypertension, nor in the mean concentrations of plasma lipids and lipoproteins.

The distribution of risk categories of the participants enrolled at baseline and at subsequent visits is shown in Figure 1, which illustrates a gradual and significant ($p < 0.001$) diminution. Reduction in risk categories among those who completed follow-up was also significant in each gender ($p < 0.001$). The reduction was also valid for the mean Framingham risk scores: the 10-year probability of coronary event risk among all individuals of the cohort, initially 25.4%, was reduced to 14.2% at the end of the study. Women achieved a greater reduction (44.8%) than men (41.4%) ($p < 0.04$) (Table II). Among participants followed up for 12 months (Table II), smokers at baseline displayed a greater decline in the mean risk score (47.9%) than nonsmokers (40.3%). Although cigarette smok-

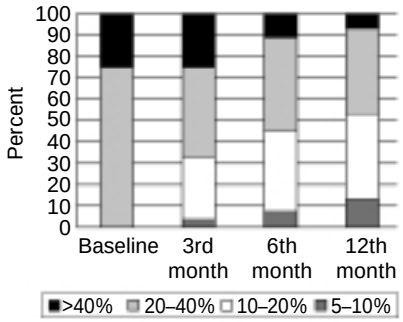

FIG. 1 Distribution of risk categories among participants at baseline, and after 3, 6, and 12 months.

ers comprised 39.6% at baseline, 193 men and women forming 21.4% of those followed up continued to smoke; in other words, recommendations met success in 45% of smokers. No nicotine replacement therapy was used. Failure to discontinue smoking reached 64% among women, while it remained at 44% in men. Mean coronary risk in primary prevention declined by 46%, from baseline 28.4% to 15.3% at end the of study (Fig. 2); in secondary prevention, likewise, the initial 23.2% mean risk declined by 43.5% to 13.1% after 12 months.

In patients with hypertension and no CHD, the initial risk of 28.4% was reduced by 47.1% at 12 months, and in individuals with neither CHD nor hypertension risk was reduced from 25.2% by a relative 40%, ($p < 0.01$ vs. normotensive subjects)

TABLE II Mean risk score and its changes at different visits by gender and smoking status

		Women				Men		
	Month	n	Mean	SD	p Value	n	Mean	SD
Risk percentage	0	963	24.5	11.1	0.0002	955	26.4	11.5
	12	495	13.7	7.9	0.04	448	14.8	8.5
Absolute reduction	12	474	11.7	7.8	0.98	428	11.7	8.7
% reduction	12	474	44.8	22.7	0.04	428	41.4	27.2
		Nonsmokers				Smokers		
Risk percentage	0	1165	23.9	10.8	< 0.0001	753	27.8	11.7
	12	581	14.2	7.7	0.94	362	14.2	8.9
Absolute reduction	12	555	10.5	7.8	< 0.0001	347	13.6	8.7
% reduction	12	555	40.3	23.8	< 0.0001	347	47.9	26.1

Abbreviation: SD = standard deviation.

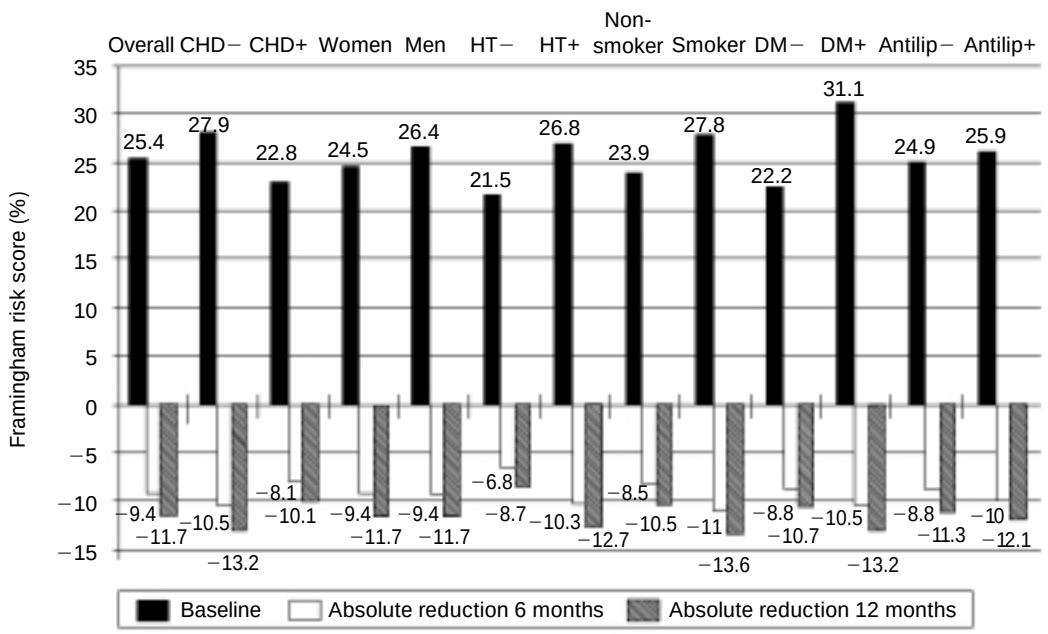

FIG. 2 Framingham risk score among participants with respect to six risk variables at baseline and absolute reduction after 6 and 12 months. CHD = coronary heart disease, HT = hypertension, DM = diabetes mellitus, Antilip = antilipidemic.

TABLE III Mean risk levels and changes therein in hypertensive and nonhypertensive subjects by primary and secondary prevention groups

		Nonhypertensives				Hypertensives		
	Month	n	Mean	SD	p Value [a]	n	Mean	SD
Primary prevention								
Risk percentage	0	154	25.2	10.0	0.0007	823	28.4	11.0
	12	79	14.9	8.6	0.65	411	15.4	8.7
Absolute reduction	12	77	10.6	8.0	0.003	399	13.6	8.0
% Reduction	12	77	40.1	27.2	0.01	399	47.1	21.8
Secondary prevention								
Risk percentage	0	348	19.9	9.2	< 0.0001	593	24.6	11.9
	12	156	11.9	6.9	0.01	297	13.7	7.7
Absolute reduction	12	144	7.7	7.1	< 0.0001	282	11.3	8.4
% Reduction	12	144	35.6	31.5	0.01	282	42.4	23.7

[a] Refers to the difference between the groups with and without the risk variable.
Abbreviations as in Table II.

(Table III). Absolute and relative mean risk reductions during the 12-month period in those receiving antihypertensive medication were significantly greater than in those not requiring such drugs.

Table IV summarizes the baseline risk with respect to presence or absence of diabetes, as well as the risk reduction in those followed up to the end of the study, among whom the baseline risk decreased in nondiabetics from 22.2 to 11.6% (by 45%) compared with a decline from 31.1 to 18.2% in diabetic individuals (by 40.5%, $p < 0.01$).

Magnitude of Changes in Lipids and Lipoproteins

Significant changes occurred in the concentrations of plasma lipids and lipoproteins during 12 months in response to the measures taken in both genders. In men, mean TC declined by 20.9%, LDL-C by 24.9%, and TC/HDL-C ratio by 34%, while HDL-C levels rose by 17%. In women, average TC decreased by 21.4%, LDL-C by 25.9%, and TC/HDL-C ratio by 31%, whereas HDL-C increased by 15%. Although LDL-C was reduced by a mean of 23.8% in persons not taking lipid-lowering drugs, a more pronounced decline of 27.3% ($p < 0.001$) was achieved in those receiving such drugs.

Multivariate Analysis of Reductions in Risk and Lipid Levels

Factors influencing the reduction in the Framingham risk score from baseline to 12-month follow-up were evaluated in 884 participants completing the study by multiple regression analysis in a model that included 21 variables. The following 10 factors were found to be significant independent determinants: (1) baseline Framingham risk score, (2) female gender, (3) absence of diabetes, (4) smoking, (5) age, (6) TC/HDL-C ratio, (7) patient compliance at second visit, (8) baseline risk category, (9) presence of hypertension, and (10) absence of lipid-lowering treatment.

Mean Framingham risk score was reduced at the end of 12 months in a similar proportion regardless of requirement for lipid-lowering drugs ($p = 0.97$, Fig. 2), presumably because individuals who were not on lipid-lowering therapy benefited from antihypertensive or other therapy.

Validating the estimation: The baseline risk burden of the cohort was estimated as 25.4 coronary events per 1,000 patient-years, indicating that during a follow-up of 1,245 patient-years, approximately 32 cardiovascular events would be anticipated. Of these, 14 would be predicted to be prevented,

TABLE IV Mean risk score of diabetic and nondiabetic participants at baseline and absolute and relative risk reductions

		Nondiabetics				Diabetics		
	Month	n	Mean	SD	p Value [a]	n	Mean	SD
Risk percentage	0	1224	22.2	10.3	< 0.0001	694	31.1	10.9
	12	564	11.6	6.9	< 0.0001	379	18.2	8.3
Absolute reduction	12	542	10.7	8.0	< 0.0001	360	13.2	8.4
% Reduction	12	542	45.0	27.3	0.008	360	40.5	20.6

[a] Refers to the difference between the groups with and without the risk variable.
Abbreviations as in Table II.

resulting in an anticipated 18 coronary deaths or events during the follow-up. Information obtained from 17 participating centers, comprising 64% of the total follow-up period, indicated the development of 11 cardiovascular events. Thus, the calculated and the materialized numbers of cardiovascular events largely coincided.

Discussion

The primary endpoint of this prospective multicenter prevention study was demonstration of the extent of the estimated coronary event risk reduction among high-risk individuals in need of primary and secondary prevention by implementing measures recommended in the National Prevention Guidelines. It is worth emphasizing that to obviate comparison of a compliant group of individuals with a mixed group at outset, comparisons in terms of risk reduction from baseline as well as the multivariate analysis are made only in subjects completing the study. This approach precludes bias, yet results cannot be anticipated to be applicable to the whole population. It is difficult to convince a substantial proportion of Turks with few or no symptoms to comply with measures and medication lasting for 12 months; hence the high drop-out rate. Absolute reduction in estimated CHD risk in participants was 9.4% at 6 months and 11.7% at 12 months. Expressed in terms of the baseline risk burden, an impressive 44% decline was accomplished at 12 months. Among risk parameters, substantial improvements were observed in this period in blood pressure, plasma TC, body mass index, and in HDL-C levels in association with risk reductions.

The Framingham risk score, upon which the risk estimation was based, is not necessarily optimally valid for the Turkish population. In fact, the Framingham risk function-based coronary risk chart in the 1998 version of the European Joint Task Force[13] was shown to overestimate absolute coronary risk in an Italian population.[14] However, since change in risk was primarily under study here, utilizing the Framingham score seems to reflect appropriately the magnitude of changes in risk in the present investigation. Worthy of emphasis is the fact that the estimated risk diminution assumes sustenance of the modified risk profile for 10-years' duration.

Other than female gender and age, independent variables in the multivariate analysis in the investigated risk reduction included the baseline risk level, absence of diabetes, smoking, TC/HDL-C ratio, patient compliance, presence of hypertension, and absence of lipid-lowering treatment. This finding underlines the risk-reduction potential of eliminating any of the coexisting mentioned factors. Presence of CHD in the individual and of family history and (solely) HDL-C level did not appear to be independent determinants of risk reduction. The significantly higher reduction in coronary risk attained in women compared with men was a finding consistent with that of the Cholesterol and Recurrent Events (CARE) study,[15] an observation supporting the finding that the yield of risk reduction efforts in women may be somewhat greater.

It is quite plausible that a high score in terms of treatment compliance has a beneficial effect on risk reduction. A 7% risk reduction (32.3% relative reduction) was achieved in nonsmokers without hypertension, while an 11.3% reduction in absolute risk was observed in subjects who did not require a lipid-lowering medication, that is, in hypertensive individuals who smoked. This group has obviously benefited from measures such as antihypertensive treatment, weight reduction, control of diabetes, and cessation of smoking. The finding that patient compliance was an independent determinant of risk reduction, is both a message to patients and indicative of the crucial importance of the physician's skill in ensuring patient compliance.

Participants not subjected to lipid-lowering drugs have recorded an LDL-C reduction significantly less than those treated with such drugs, although their LDL reduction by 23.8% is more than one anticipates without the use of drugs. The combined effect of diet and weight reduction might possibly account for this observation.

Smoking was another independent determinant that affected the risk reduction positively on multivatiate analysis. This observation can probably be accounted for by the relative success in quitting smoking, which was a considerable share of the risk burden. Of individuals who attended the last visit, 45 of every 100 smokers at the onset of the study had succeeded in smoking cessation. The failure rate was slightly higher in the context of primary prevention, and especially among women. These observations were in line with the EuroAspire survey,[16] in which 4,000 patients with CHD from nine European countries were followed up; this survey reported that 34% of patients had been smokers prior to a coronary event, and 41% of them were continuing to smoke 1 to 2 years after the event.[16, 17]

The comparatively small difference in coronary risk reduction in diabetics (40.5 vs. 45%) suggests that the diabetic individual may benefit from preventive measures to an extent not unlike that of other subjects. Both the presence of hypertension and its severity were among the significant independent determinants of risk reduction at 12 months. The decline in risk was associated with an average reduction by 26 ± 25.9 mmHg, from 157 mmHg. The HDL-C levels rose by approximately 5 mg/dl (from a mean of 41.8 mg/dl) among subjects who had completed the study, associated with a decline in the proportion of patients who had body mass index levels of obesity, from 30.3% at baseline to 20.1%.

Among subjects followed up for 12 months, the high baseline TC/HDL-C ratio (6.94) was greatly decreased to 4.7 but still did not reach the optimal ratio of < 3.5. By specifically optimizing treatment for every individual, the global risk might be somewhat further diminished. In fact, the mean LDL-C value at 12 months only attained a value of 131 mg/dl. As suggested in guidelines, this value could beneficially be decreased by an additional 10–15 mg/dl in this cohort at high coronary risk. The discontinuance, toward the end of the study, of the required lipid-lowering medication by some individuals and treatment at suboptimal doses in others may explain the efficacy gap with regard to target levels. Were such potential limitations not to exist in practice, the extent of estimated risk reduction might have been augmented. Yet human nature and/or physicians' practice habits preclude the elimination of these restrictions in other countries as well.[16]

Based on the Framingham risk scoring,[11] it may be estimated that for every 1,000 men and women who have a risk burden similar to that of the cohort included in the Riskburden study and in whom National Guidelines were implemented, 254 cardiovascular events will occur in the subsequent 10 years of life. Based on the 11.7% risk reduction achieved by maintaining 1 year of treatment for 10 years, it may be predicted that the development of cardiovascular events in 117 of every 1,000 individuals, who comply with the treatment, would be prevented. The fact that the numbers of cardiovascular events, both by estimation and by observation during the follow-up period, were consistent with each other is indicative of the validity of risk reduction estimated in the study. The relatively high estimated number of coronary events prevented may be accounted for by the implementation of multifaceted measures in our study. Given that the risk burden of nonsmokers is between 35 and 40%[18] and 48%[19] lower than that in smokers, taking into account that the mean 26 mmHg reduction in systolic blood pressure herein achieved would provide a further 20–25% reduction in cardiovascular risk, and adding the beneficial effects of lipid-lowering measures, the impressive decline accomplished in global relative risk by as high as 44% may be apparent.

Results obtained from this study on national implementation of recommendations of prevention guidelines reveal that in high-risk individuals or in patients with CHD, it is feasible to reduce the relative global cardiovascular event risk by as much as 44% in those who comply with implementation of preventive cardiology measures.

Members of the Riskburden Study Group

Centers and investigators participating in the study (in order of the number of enrolled subjects): *GATA (A. Yönem), GATA Haydarpaşa (M. Coşkun, M. Uslu), Osmangazi U. (B. Timuralp, Y. Çavuşoğlu), Izmir Devlet Hosp. (H. Ari), Çukurova U (E. Acartürk, F. Akgül), Kardiyoloji Inst. (D. Güzelsoy, V. Sansoy, S. Karcier, H. Yüksel, Z. Yiğit), Ankara Nümune (S. Karaahmetoğlu, N. Yilmaz), Ege U (I. Soydan, M. Kayikçioğlu), Haseki Devlet Hosp. (M. Yenigün, I. Hatemi), Celal Bayar U (B. Kiliççioğlu, B. Özmen, T. Parildar, G. Göksel), Erciyes U (A. Ergin), Ondokuz Mayis U (O. Sağkan), Cerrahpaşa (N. Domaniç), Uludağ U (J. Cordan, K. Gemici, D. Yeşilbursa, S. Güllülü), S. Ersek (T. Ulusoy, H. Akgöz), Hacettepe U (O. Gedik, A. Gürlek, N. Başcil), Gazi U (M. Aslan, A. Karakoç), Istanbul Tip (E. Sencer, E. Algül), Hacettepe U (L. Tokgözoğlu, G. Kabakçi, A. Yildirir, N. Özer), T. Yüksek Ihtisas Hosp. (H. Şaşmaz, Y. Balbay, R. Atak), Gazi U (H. Dörtlemez, Ö. Dörtlemez, R. Yalçin), Dokuz Eylül U (Ö. Kozan), Ankara U (G. Akgün, O. Döven), Başkent U (H. Müderrisoğlu, S. Topçuoğlu, A. Ertürk), Şişli Etfal Hosp. (H. Şenli, Ç. Yazici-Ersoy), Ankara U (G. Erdoğan).

*Follow-up of the majority of patients was provided by the first seven institutions listed.

Acknowledgment

The authors wish to thank Ebru Çapanoğlu, M.D., for her valuable contributions in monitoring the study and are indebted to Merck-Sharp-Dohme Ltd. Co. for providing logistic support.

References

1. Pyörala K, De Backer G, Graham I, Poole-Wilson P, Wood D: Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclorosis Society, and European Society of Hypertension. *Eur Heart J* 1994;15: 1300–1331
2. Türk Kardiyoloji Derneği: Koroner Kalp Hastaliğindan Korunma ve Tedaviye Ilişkin Ulusal Kilavuz. Istanbul: Türk Kardiyol Dern, 1995
3. Murray CJL, Lopez AD: Alternative projections of mortality and disability by cause 1990–2020: Global burden of disease study. *Lancet* 1997;349: 1498–1504
4. Pearson TA, Smith SC Jr, Poole-Wilson P: Cardiovascular Specialty Societies and the emerging global burden of cardiovascular disease: A call to action. *Circulation* 1998;97:602–604
5. European Forum on the Prevention of Coronary Heart Disease in Clinical Practice (19–21 February 1999). Newsletter by European Society of Cardiology, 1999 (May); vol. 8 (no. 2)
6. Capewell S, Pell JP, Morrison C, McMurray J: Increasing the impact of cardiological treatments: How best to reduce deaths. *Eur Heart J* 1999;20: 1386–1392
7. Onat A, Sansoy V, Ince E, Dönmez K, Keleş I, Ökçün B, Kahraman G, Dursunoğlu D: Türk erişkinlerinde kanda kolesterolde istikrar, trigliseridde yükselme. Türk Kardiyol Dern Arş 1996;24:392–398
8. Onat A: Risk factors and cardiovascular disease in Turkey. *Atherosclerosis* 2001;156:1–10
9. Mahley RW, Palaoğlu KE, Atak Z, Dawson-Pepin J, Langlois A-M, Cheung V, Onat H, Fulks P, Mahley LL, Vakar F, Özbayrakçi S, Gökdemir O, Winkler W: Turkish Heart Study: Lipids, lipoproteins and apolipoproteins. *J Lipid Res* 1995;36:839–859
10. Onat A, Dursunoğlu D, Sansoy V: Relatively high coronary death and event rates in Turkish women: Relation to three major risk factors in five-year follow-up of cohort. *Int J Cardiol* 1997;61:69–77
11. Anderson KM, Wilson PWF, Odell PM, Kannel WB: An updated coronary risk profile: A statement for health professionals. *Circulation* 1991;83: 356–362
12. Dawson-Saunders B, Trapp RG: *Basic and Clinical Biostatistics*. Englewood Cliffs, N.J.: Prentice-Hall International Inc., Appleton & Lange
13. Wood D, De Backer G, Faergeman O, Graham I, Mancia G, Pyörala K: Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of the European and other societies on coronary prevention. *Eur Heart J* 1998;19:1434–1503
14. Menotti A, Puddu PE, Lanti M: Comparison of the Framingham risk function-based coronary chart with risk function from an Italian population study. *Eur Heart J* 2000;21:365–370
15. Sacks FM, Pfeffer MA, Moyé LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnicka JW, Arnold JMO, Wun C-C, Davis BR, Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009
16. EUROASPIRE Study Group: EUROASPIRE: A European Society of Cardiology survey of secondary prevention of coronary heart disease: Principal results. *Eur Heart J* 1997;18:1569–1582
17. van Berkel TFM, Boersma H, De Baquer D, Deckers JW, Wood D, on behalf of the EUROASPIRE Study Group: Registration and management of smoking behaviour in patients with coronary heart disease. The EUROASPIRE Survey. *Eur Heart J* 1999;20:1630–1637
18. Shepherd J: A call to action. *Eur Heart J* 1998;19(suppl M):M2–M7
19. Assmann G, Cullen P, Schulte H: Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the Prospective Cardiovascular Münster (PROCAM) study. *Circulation* 2002;105: 310–315