INTER-HEART: A global study of risk factors for acute myocardial infarction

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Background Although declines in mortality rates have occurred in most developed countries, increases are being seen in developing countries. Our knowledge of risk factors for acute myocardial infarction (AMI) is largely derived from studies in the former. Applicability of these results to other populations is unknown. The objectives of INTER-HEART are to determine the association between risk factors and AMI within populations defined by ethnicity and/or geographic region and to assess the relative importance of risk factors across these populations.

Methods INTER-HEART is a study of 14,000 cases of AMI and 16,000 matched control patients from 46 countries, which was conducted with a standardized protocol. Questionnaires were translated into 11 languages; physical measurements were obtained, and 20 mL of blood was drawn and shipped frozen to a central laboratory in Canada. The study will evaluate the importance of conventional and emerging risk factors within each geographic region and whether their impact varies by region.

Results INTER-HEART is sponsored by the World Health Organization and the World Heart Federation and has received funding from several peer-reviewed agencies and many different pharmaceutical companies. A vanguard phase (February 1999 to 2000) enrolled 4000 subjects from 41 countries. Full data collection started in April 2000 and is expected to be completed by October 2002.

Conclusions Several years of targeted work have allowed the development of the concepts that were tested in the pilot studies. This has ensured the feasibility of INTER-HEART. This study has the potential to have a major impact in developing a worldwide strategy for cardiovascular disease prevention, especially in developing countries and nonwhite populations. [Am Heart J 2001;141:711-21.]
global strategy on the basis of an understanding of the importance of known and putative CVD risk factors in different geographic regions and ethnic groups.

The concept of risk factors (such as smoking, elevated cholesterol, or blood pressure) associated with CVD was derived from prospective epidemiologic stud-
ies conducted mainly in Western populations. Whether the conclusions derived from these studies are extrapolatable to people in developing countries that include individuals of different ethnic backgrounds is not clear. First, a particular risk factor may not be as strongly related to coronary heart disease (CHD) in some populations (eg, cholesterol levels may not be a strong predictor of CHD among South Asians3-5), and some populations may be more sensitive to specific risk factors (eg, South Asians show a strong risk associated with elevated glucose levels6; absolute risk of CHD at the same level of blood pressure varied substantially among different populations in the Seven Countries Study7). Second, even if the relation between a risk factor and CHD is similar, the population-attributable risk will differ with variations in prevalence of the risk factor (eg, mean cholesterol levels in China8 and some African9 countries are about 25% to 35% lower than in the West; therefore even if cholesterol levels are similarly related to CHD, the population-attributable risk would be lower in these countries). Third, the relative importance of risk factors may vary (eg, lower intake of vegetables or their prolonged cooking10 may lead to lower folate consumption and higher homocysteine levels in South Asians, whereas psychosocial stressors may play a larger role among Eastern Europeans11). Fourth, the prevalence of protective factors may vary between populations (eg, high fish intake among Chinese12). Fifth, some inherent tendency (eg, propensity for impaired glucose tolerance among South Asians13 and other migrant groups14) is accentuated by urbanization. Therefore a study aimed at discovering the relation between risk factors and CHD in multiple countries representing different regions and ethnic groups will have a profound influence in developing a global strategy for CVD prevention.

### Methods

**Options for study design and design overview**

Information on the importance of risk factors for CHD can be obtained by (a) prospective cohort studies in which risk factors are measured in a large group of individuals who are followed until a sufficient number of clinical events are recorded; (b) case-control studies in which distribution of risk factors is compared between diseased and nondiseased subjects; and (c) intervention trials in which specific risk factors are randomly assigned and incidence of clinical outcomes is compared. Each method has its strengths and limitations. Cohort and intervention studies have substantial methodologic advantages; however, they are relatively expensive and require a long duration of follow-up compared with a case-control study. Although conducting cohort studies within a particular country may be feasible, conducting a large global cohort study in several countries with adequate statistical power would be prohibitively expensive. Hence such studies are impractical at present, especially if they were to involve several developing countries in which the infrastructure for research is not as well established as in developed countries. A more efficient strategy is to conduct a simple, standardized, case-control study involving a large number of countries. Such a study would provide quick and reliable information on the importance of a range of risk factors for CHD.

INTER-HEART is an international, standardized, case-control study, designed as an initial step to address the burden of CVD. This approach has been recommended by the Institute of Medicine/World Bank Report15 and the Global Health Forum. The objectives of INTER-HEART are to determine the strength of association between traditional (ie, smoking, hypertension, elevated cholesterol, diabetes) and emerging (glucose abnormalities, abdominal obesity, homocysteine, other

<table>
<thead>
<tr>
<th>IHD mortality estimates</th>
<th>Disability-adjusted life-years lost from IHD</th>
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<tbody>
<tr>
<td><strong>Projected increase (%) from 1990 to 2020 (men/women)</strong></td>
<td><strong>Men 1990/2020 (× 100,000) (men/women)</strong></td>
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<tr>
<td>46/32</td>
<td>54.2/73.1</td>
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<tr>
<td>51/25</td>
<td>42.6/60.9</td>
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<tr>
<td>127/114</td>
<td>56.0/138.4</td>
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<tr>
<td>108/79</td>
<td>32.7/74.0</td>
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<tr>
<td>152/139</td>
<td>21.2/52.9</td>
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<tr>
<td>144/116</td>
<td>10.9/25.2</td>
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<tr>
<td>144/141</td>
<td>16.4/39.0</td>
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<tr>
<td>171/148</td>
<td>29.7/82.3</td>
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<tr>
<td>100/80</td>
<td>263.7/545.7</td>
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nutritional, psychosocial) risk factors and nonfatal acute myocardial infarction (AMI) in the overall study population and within each population defined by ethnic group and/or geographic region, and the relative importance of risk factors across these different populations. The results and infrastructure of INTER-HEART will also provide an impetus for future cohort studies or intervention trials in a few selected countries.

Study patients and methods

INTER-HEART will study approximately 14,000 incident cases of AMI and 16,000 control patients matched by age (±5 years) and sex, with no prior history of heart disease. Women will make up 25% of all participants. Recruitment will take place in 260 centers from 46 countries in Asia, Europe, Middle East Crescent, Africa, Australia, and North and South America (Table II). The choice of countries for INTER-HEART represents a combination of a desire to represent each major region of the world and feasibility. Within each country, centers were chosen on the basis of practical considerations by an INTER-HEART National Coordinator based in that country. In some countries, the centers are distributed across the country (eg, Philippines, Thailand, China, Argentina, Brazil); in others they represent the entire country (Kuwait, Qatar, United Arab Emirates), and in others they are highly selective (eg, India, Pakistan) and represent centers that are specifically interested in the study.

All patients admitted to the coronary care unit or equivalent cardiology ward of participating centers are screened to identify incident cases of AMI. Cases are identified by means of standardized definitions and enrolled within 24 hours of onset of symptoms. At least 1 control patient per case is recruited with the use of specific criteria (Appendix C).

Ethics

At entry to the study, informed consent is obtained from each participant. The INTER-HEART protocol has been approved by appropriate regulatory and ethics councils in all participating countries and centers. All analyses will be conducted by INTER-HEART investiga-
tors, and no patient identifiers will be presented on any files transmitted to any committee or clinical center.

Data collection
Seven steering committee meetings have been held to develop study forms, review results of feasibility studies (addressing data collection, blood collection and processing, and data transfer protocols) in 22 countries, finalize the protocol before the start of the vanguard phase, and review progress as the study moves to full-scale recruitment.

The study questionnaire collects data on demographic factors (eg, country of origin, first language), socioeconomic status (education, occupation, income), lifestyle (tobacco use, physical activity, dietary patterns), personal and family history of CVD, and risk factors. Trained staff administer the questionnaire before the patient leaves the hospital. Data on medications (prehospital, in-hospital, and hospital discharge) are abstracted from charts. The questionnaire was compiled with the use of previously validated questions included in prior studies of CVD risk factors (Table III).16-26 The questionnaire was initially tested with 110 cases and 104 control patients from 20 countries in the INTER-HEART pilot study and modified as necessary. It has been translated into 11 languages (Chinese, English, Filipino, Hungarian, Italian, Japanese, Portuguese, Russian, Spanish, Swedish, and Urdu).

Standard but simple physical measurements are performed in duplicate by the same examiner on each participant: height, weight, waist and hip circumference, and heart rate. Waist and hip circumference are measured with a nonstretchable standard tape measure attached to a spring balance exerting a force of 750 g.

Nonfasting blood samples (20 mL) are drawn from each patient to be stored frozen for biochemical analyses (total cholesterol, high-density lipoprotein; apolipoprotein B, immunoglobulin G, and immunoglobulin A antibodies indicating infection with Chlamydia pneumoniae, glycated hemoglobin, homocysteine, serum folate, serum albumin, serum creatinine, and white blood cell count). Genetic materials (buffy coat) will also be collected to assess the relevance of candidate genes for AMI within each ethnic group. DNA samples will be used exclusively for genotyping related to cardiovascular risk factors. For cases, blood is drawn within 24 hours of onset of symptoms of AMI. All samples are centrifuged within 2 hours of collection and frozen immediately after processing. Samples are shipped by courier from each site to the National Blood Storage Site, where they are stored in liquid nitrogen (-196°C). Specimens are then shipped in nitrogen vapor tanks to the core laboratory at the Hamilton Regional Laboratory Medicine Program, Canada. The timing of all local and international shipments is guided by a specified schedule that is determined by local blood storage capacity (eg, blood samples will remain

<table>
<thead>
<tr>
<th>Table III. INTER-HEART questionnaire</th>
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<tr>
<td><strong>Domain</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Socioeconomic status</td>
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<tr>
<td>Physical activity</td>
</tr>
<tr>
<td>Alcohol</td>
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<tr>
<td>Smoking</td>
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<td>Nutrition</td>
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<tr>
<td>Psychosocial</td>
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<td></td>
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<tr>
<td>Medical and family history</td>
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<td></td>
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<td></td>
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<tr>
<td>Medications</td>
</tr>
</tbody>
</table>
at -20°C or -70°C for a maximum of 2 or 6 months, respectively). Laboratory specimens are being stored centrally in liquid nitrogen at the core laboratory, where analyses will be conducted by INTER-HEART investigators. Analyses will be limited to those that relate to CVD, its determinants, or cancer.

Data transfer and management

Data transfer for INTER-HEART was initiated in March 1999. Where toll-free lines exist, data are faxed directly from the countries to the Project Office. The computer system (DataFax) stores the optical image, and digital reading technology allows most of the information to be read and entered into a computer database directly. The results of the computer-read data are verified against a visual display of the faxed form by project office staff. Any discrepancies are organized into quality control reports and faxed back to the investigator at regular intervals. This management system enables us to have data entered into a central database within several days of collection. Where toll-free lines are unavailable, completed case-report forms are transported monthly by courier from each national coordinating center to the project office. The data are then entered into the data fax system and validated according to the specified protocol.

Training and standardization

A number of procedures have been incorporated to ensure standardization and high quality of data: (1) a comprehensive operations manual, (2) training workshops for national coordinators, (3) training video and instruction manual distributed to all centers, and (4) training workshops within each country. Several procedures are being used to maintain compliance and standardization: (1) center-specific pocket cards as data collection aids, (2) monthly newsletters, (3) provision of presentation materials for local meetings, (4) regular provision of quality-control reports to each center, and (5) prompt mail, telephone, or e-mail follow-up. In addition, a schedule of site visits has been initiated and visits to selected hospitals in Bahrain, Chile, Egypt, Kuwait, United Arab Emirates, Bangladesh, India, Nepal, and Thailand have already been completed.

Statistical considerations

The overall sample size for INTER-HEART is dependent on (1) the sample size requirements for each participating country or region (where smaller countries that are similar are clustered together) and (2) the ability to detect variations in the effect of a risk factor by region. The sample size per country was calculated on the basis of the following parameter specifications: (a) level of significance: 2-sided test at \( \alpha = .05 \); (b) power \( (1 - \beta) \): 80%; (c) effect size (minimum odds ratio [OR] considered to be clinically important is dependent on the risk factor of interest; for tobacco, smoking, and hypertension, ORs of \( \geq 2.0 \) are considered clinically significant); (d) exposure (Exposure rate in the control group was estimated on the basis of the prevalence in the general population from previous studies in each country; in some countries, two control patients are recruited for each case. This different ratio satisfies objectives for local, country-specific data collection and analysis.)

**Objective 1**

Objective 1 is to determine the strength of association between traditional and emerging risk factors and AMI within each population defined by ethnic group and/or geographic region. For common risk factors such as smoking, we have >80% power to detect a minimum effect size of 1.5 (OR). For less common risk factors such as diabetes, a minimum effect size of 2.0 is detected with >80% power within a geographic region (Table IV). In the case of continuous variables (eg, serum total cholesterol), we require 306 cases within each ethnic group to detect a minimum effect of 1.3 associated with a higher serum cholesterol level of 20 mg/dL.

**Objective 2**

Objective 2 is to determine the relative importance of risk factors across different populations (grouped by geography). The OR for each risk factor as derived on the basis of the above analysis will be compared across regions. Table V reveals sufficient study power to detect an interaction effect of 1.5 to 2.0 (ratios of ORs) between regions for the association of smoking and hypertension with disease. A similar approach will be taken for other risk factors.

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**Table IV. Study power to detect minimum effect size of 1.5 for smoking and 2.0 for diabetes, \( \alpha = .05 \) (2-sided) for selected countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Cases/control patients</th>
<th>Smoking/diabetes</th>
<th>OR of 1.5 or 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>720/720</td>
<td>31* [27]/4.2 [28]</td>
<td>96/87</td>
</tr>
<tr>
<td>India</td>
<td>400/800</td>
<td>17.5 [29]/11.5 [30]</td>
<td>76/99</td>
</tr>
<tr>
<td>Italy</td>
<td>400/400</td>
<td>32 [27]/8.3 [30]</td>
<td>79/88</td>
</tr>
<tr>
<td>Egypt</td>
<td>1000/1000</td>
<td>20 [27]/4.3 [31]</td>
<td>97/96</td>
</tr>
<tr>
<td>Brazil</td>
<td>600/600</td>
<td>32.6 [27]/7.1 [30]</td>
<td>92/95</td>
</tr>
<tr>
<td>Colombia</td>
<td>320/640</td>
<td>21.4 [32]/8.0 [30]</td>
<td>81/89</td>
</tr>
<tr>
<td>United States</td>
<td>500/500</td>
<td>25.5 [33]/7.0 [30]</td>
<td>83/90</td>
</tr>
</tbody>
</table>

*Study power [%].
†Prevalence factor in population.
Objective 3

Objective 3 is to determine the strength of association between traditional and emerging risk factors and nonfatal AMI in the overall population. With the projected sample sizes per region (Table II) and based on local estimates of prevalence, we have sufficient statistical power to detect an effect size of 2.0 (OR) within a region for several risk factors. Therefore the power will be even higher to detect a similar overall effect.

Conditional logistic regression will be used to assess (1) the relation between AMI and (a) conventional and (b) emerging risk factors within countries or regions and (2) the relation between risk factors and disease across countries or regions. Provided that there is no strong variation of effect of risk factors by regions, overall effect estimates will be derived from the region-specific estimates by means of a mixed-effects model.34 The overall effect estimation is dependent on the assumption of absence of strong variation of effect of risk factors by region.

A priori–identified confounding variables will be adjusted for in the analysis, and other potential confounders will be assessed empirically. An extraneous variable that does not satisfy both the empiric criteria of confounding and effect modification as assessed at the $\alpha = .1$ level of significance will be considered for inclusion in the final model on the basis of gain in precision.

Sponsorship

INTER-HEART is sponsored by the World Health Organization and the World Heart Federation and has received funds from the Canadian Institute of Health Research, Heart and Stroke Foundation of Ontario, the International Clinical Epidemiology Network, and 8 pharmaceutical companies. For the majority of countries, national coordinators have raised funds to cover patient costs and costs of local coordination (Appendix B). Most have secured at least one funding source and have approached multiple additional sources.

Study organization

INTER-HEART includes 260 centers from 46 countries (a list of investigators is provided in Appendix A). The study is coordinated by the Canadian Cardiovascular Collaboration Project Office and the Population Health Research Institute of McMaster University and the Hamilton Health Sciences Research Center. The key element of this organization is the collaboration of health professionals in the design and conduct of large studies. The project office is responsible for the overall protocol development, study coordination, and international meetings. INTER-HEART national coordinators are responsible for local coordination: (1) raising funds for data collection, (2) site recruitment and training of study staff, (3) liaison between sites and project office, and (4) monitoring data collection, storage, and transfer. Annual meetings with national coordinators are held to discuss the study and provide an educational forum. The organization of INTER-HEART has ensured the development of a protocol that is both feasible and efficient in multiple countries.

Progress and timetable

Data collection began in January 1999 in a limited number of centers. Gradual start-up has allowed us to ensure that all data collection transport and communication protocols work for every geographic region. Full recruitment commenced in April 2000 and will continue for approximately 2.5 years. As of December 2000, data have been collected centrally from more than 8000 subjects. Mean age of cases enrolled is 57 years, and more than 20% of subjects recruited are women. Expected trends in the prevalence of risk factors are already apparent. For example, approximately 45% of cases and 26% of control patients are current smokers. Smoking rates ranged from 12% of control patients in South America to 38% of control patients in Sub-Saharan Africa. Prevalence of known diabetes and hypertension is also higher among cases than among

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**Table V. Illustrative example of study power (percentage) to detect interaction effect sizes of 1.5 and 2.0 (ratio of ORs) between regions for selected risk factors based on $\alpha = .05$ (2-sided)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>South Asia</th>
<th>Africa</th>
<th>Middle East</th>
<th>South America</th>
<th>North America</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking 1.5†</td>
<td>84</td>
<td>100</td>
<td>88</td>
<td>100</td>
<td>93</td>
</tr>
<tr>
<td>Hypertension 2.0†</td>
<td>50</td>
<td>94</td>
<td>69</td>
<td>99</td>
<td>72</td>
</tr>
</tbody>
</table>

*Interaction effect of 1.5 implies that effect of smoking in Africa is 1.5 times its effect in South Asia, that is, 1.5 × 1.5 = 2.25.
†Minimum effect of 1.5 to 3.0 (OR) of smoking and hypertension is assumed in South Asia.
control patients (diabetes has been reported in 24% of cases and 10% of control patients; hypertension has been reported in 38% of cases and 15% of control patients).

Results will be published at periodic intervals. Initial results based on the overall population will be reported when data on at least 10,000 individuals have been collected (mid 2001 onward). A second series of publications based on geographically grouped data will be available when data on at least 20,000 individuals have been completed (mid 2002 onward). Publications based on data by country will only be available at the end of the study (mid 2003 to 2005). Analyses based on frozen blood and DNA will also only be available in 2003 onward.

Potential limitations of the study

A case-control methodology has been previously found to be useful for all of the risk factors that we are measuring and has provided comparable estimates to cohort studies for these risk factors. However, where appropriate, the study has been designed to minimize biases, and additional care will be taken during analysis.

For example, the occurrence of AMI may change some of the risk factors being studied. After the first 24 hours after AMI, cholesterol levels can drop. The protocol therefore emphasizes that all blood measurements be taken within 24 hours of onset of symptoms. Median time between onset of symptoms and arrival at the hospital for patients recruited to date in the vanguard phase is 3.5 hours (range, 2.5 hours in the Middle East to 6.0 hours in South America); therefore, it is feasible in most cases to collect blood within the 24-hour window. Such an approach has provided valid results in the large ISIS case-control study of 12,000 cases and 24,000 control patients relating lipids to AMI (R. Collins, Oxford University, unpublished data) and case-control studies conducted by INTER-HEART investigators in India, South America, and Italy. Data will also be analyzed, stratified by time from the onset of the symptoms, to examine if there is a change in the relation between those hospitalized early versus those hospitalized late for a given risk factor. In a retrospective study, the occurrence of AMI may influence responses to questions about stress, which would result in an overestimation of the effect. In INTER-HEART, stress will be measured primarily by accumulation of major life events (eg, death of spouse), which is a more objective measurement. Other psychosocial factors such as years of education, job status, and income are unlikely to be affected immediately after an AMI. We are uncertain about the effects of the AMI on lipoprotein (a) and coagulation markers and will await the results of a pilot study with serial blood analysis to assess any confounding. Only if this indicates no impact of the AMI on these parameters will we measure them in INTER-HEART.

The preferred control patients are community based. However, hospital-based control patients are allowed as an alternative. The advantages of using hospital-based control patients include enhanced motivation of patients and study feasibility. A potential disadvantage is that this control population may not be representative of the general population. For INTER-HEART, sources for hospital-based control patients have been carefully designed to reduce this bias. For example, there is no known relation between cardiac risk factors and refractory problems or cataracts. The broad list of hospital-based control sources for recruitment could result in biases, depending on the strategies adopted by centers. However, by using different approaches to selecting control patients for cases, we will be able to test the robustness of our findings across different recruitment strategies. We expect that the results will be consistent for different methods of recruitment.

Conclusions

Seven years of related work and 2 years of targeted pilot work have allowed us to develop the concepts and protocols and to ensure feasibility of this ambitious global project. The methods are based on our experiences from several case-control studies conducted by INTER-HEART investigators. As stated in excerpts from the Consultation on Research Initiative for CVD Control in Developing Countries convened by the World Health Organization and the Global Forum for Health Research and confirmed by sponsorship from the World Health Organization and the World Heart Federation, INTER-HEART is already recognized as a project that could have a major potential impact in developing a worldwide strategy for CVD prevention, especially in developing countries and nonwhite populations.

References


Appendix A

INTER-HEART Project Office Staff, National Coordinators, and Investigators

Project office staff: S. Yusuf, principal investigator; S. Öunpuu, J. Keys, study coordinators; S. Hawken, statistician; C. Wright, R. Mayhew, S. Rangarajan, research assistants; L. Westfall, P. Mackie, D. Cunningham, data management.


Appendix B

Summary of sponsorship and funding

The INTER-HEART study is funded through unrestricted grants from several pharmaceutical companies (with major contributions from Astra Zeneca, Novartis, Hoechst Marion Roussel, Knoll Pharmaceuticals, Bristol-Myers Squibb, and Sanofi-Synthelabo), the International Clinical Epidemiology Network, Canadian Institutes of Health Research, Heart and Stroke Foundation of Ontario, and various national bodies in different countries.

Argentina: INCLEN, OASIS-4; Australia/New Zealand: OASIS-4; Botswana: Astra South Africa; Brazil: OASIS-4; Cameron: INCLEN; Canada: OASIS-4; Chile: INCLEN, Universidad de la Frontera, Sociedad Chilena de Cardiologia Filial Sur; Colombia: Colciencias, Ministerio de Salud; Croatia: Croatian Ministry of Science and Technology; Czech Republic: OASIS-4; Germany: OASIS-4; Greece: OASIS-4; Hungary: ASTRA Hassle, National Health Science Council, OASIS-4; Iran: Iran Ministry of Health; Italy: OASIS-4; Japan: Sankyo Pharmaceutical Co, Merck Japan, Astra Japan; Kuwait: Endowment Fund for Health Development in Kuwait; INCLEN; Netherlands: OASIS-4; Pakistan: ATCO Laboratories, Philippines: Philippine Council for Health Research and Development, INCLEN, Pfizer Philippines Foundation, Inc, Astra Pharmaceuticals (Philippines), Inc, Astra Fund for Clinical Research and Continuing Medical Education, Pharmacia and Upjohn Inc; Poland: OASIS-4; Singapore: Singapore National Heart Association; South Africa: MRC South Africa, Parke-Davis Pharmaceuticals, Aventis, OASIS-4; Spain: OASIS-4; Sweden: Swedish Heart and Lung Foundation Grant from the Swedish State under LUA Agreement; Thailand: INCLEN, The Heart Association, Thailand Research Fund; United States: OASIS-4; Zimbabwe: INCLEN.

Appendix C

Criteria for recruitment of cases and control patients

Cases. AMI was defined as clinical symptoms plus electrocardiogram demonstrating significant changes such as new pathologic Q waves or 1-mm ST elevation...
in any 2 or more contiguous limb leads or a new left bundle branch block or new persistent ST-T wave changes diagnostic of a non–Q-wave myocardial infarction. Criteria for subsequent confirmation include significant enzyme elevation (>2 times normal) or evolution of electrocardiographic changes.

Exclusion criteria were failure to provide informed consent; potential cases who have cardiogenic shock or a significant chronic medical illness (eg, liver, untreated hyperthyroidism or hypothyroidism, kidney disease or malignancy, or who are pregnant) will also be excluded because their condition may change lifestyle or alter the risk factors for AMI.

**Control patients.** First control per case was an attendant or relative of a patient from a noncardiac ward or an unrelated (not first-degree relative) attendant of a cardiac patient. Second control per case was (a) preferred: patients attending the hospital or outpatient clinic for the following reasons: 2.1, refraction and cataracts; 2.2, physical check-up; 2.3, routine pap smear; 2.4, routine breast examination; 2.5, elective minor surgery for conditions that are not obviously related to coronary heart disease or its risk factors; and 2.6, elective orthopedic surgery; (b) acceptable: patients attending the hospital or outpatient clinic for the following reasons: 3.1, outpatient fractures; 3.2, arthritic complaints; 3.3, plastic surgery; 3.4, hemorrhoids, hernias, hydrocele; 3.5, routine colon cancer screening; 3.6, endoscopy; 3.7, minor dermatologic disorders.

Exclusion criteria for control patients are identical to those described for cases, with the additional criterion that control patients have no previous diagnosis of heart disease or history of exertional chest pain.