
**SECONDARY PREVENTION OF
NONCOMMUNICABLE DISEASES**
in **LOW- AND MIDDLE-INCOME COUNTRIES**
through **COMMUNITY-BASED & HEALTH SERVICE**
INTERVENTIONS

Report of WHO–Wellcome Trust Meeting of Experts

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Noncommunicable Diseases and Mental Health

WORLD HEALTH ORGANIZATION

Copies can be obtained from:

Cardiovascular Disease Prevention and Control
Management of Noncommunicable Disease Department
Noncommunicable Diseases and Mental Health Cluster
20 Avenue Appia
CH-1211 Geneva 27
Switzerland
OO 41 22 7914151
E-mail: mendiss@who.int

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SETTING THE SCENE

IN 1998, the World Health Organization (WHO) gave greater priority to the prevention and control of noncommunicable diseases (NCDs). At the same time, following a request made by the World Health Assembly, work began on developing a global strategy for the prevention and control of NCDs. The strategy, which was completed in November 1999, was discussed and endorsed by the 53rd World Health Assembly in May 2000. In the same session the Assembly passed resolution 53.17. The strategy summarizes the lessons learned from previous experience and outlines the major objectives for monitoring, preventing and managing NCDs with special emphasis on the four major disease groups that share many of the same determinants and risk factors, namely cardiovascular diseases, cancer, diabetes and chronic obstructive lung disease. The three key components of the strategy are surveillance; health promotion and primary prevention; and management and health care.

The roles of WHO, Member States and the international community in the implementation of the strategy are clearly defined. One of the major tasks of both WHO and Member States is to identify and provide cost-effective and equitable interventions for the management of the major NCDs and to improve health care for those affected at all levels of the health system. The strategy also places emphasis on the role of WHO in providing technical support to countries to build national capacity for secondary prevention and in working with local health authorities to ensure that effective programmes are put in place. The Resolution of the World Health Assembly further urges Member States to initiate community-based programmes for NCD control; to improve the effectiveness of their health systems in secondary and tertiary prevention; and to ensure that they provide appropriate health care based on cost-effective interventions and equitable access.

The Wellcome Trust, based in London, one of the world's largest biomedical research charities, has identified the need to respond to the emerging epidemic of noncommunicable diseases in developing regions as one of its most pressing priorities. In 1998, therefore, as part of its interest in health research in lower income countries, the Trust launched an initia-

tive (Programme on Health Consequences of Population Change) to encourage and facilitate high quality research into this important problem. Part of this initiative includes evaluating low cost interventions.

In the light of these common interests, WHO and the Wellcome Trust decided to collaborate and organized a meeting of experts to discuss strategies for secondary prevention of NCDs through community-based and health service interventions. The meeting was held in Cambridge from 1–3 August 2001. Participants included experts in the field of NCDs, representatives of low- and middle-income countries and WHO and Wellcome Trust staff members.

Objectives of the meeting

The broad objectives of the meeting were to promote secondary prevention of NCDs in developing countries and to discuss ways of assisting Member States to strengthen health care for NCDs, particularly coronary heart disease (CHD) and stroke, with emphasis on primary care and community-based action.

The specific objectives of the meeting were to: identify evidence-based and affordable interventions for the secondary prevention of these conditions; identify approaches to assess

the feasibility of interventions in developing countries and evaluate their impact on cardiovascular (CVD) risk factors and CVD outcomes; and to discuss sustainable strategies for integrating secondary prevention interventions into existing health care infrastructures and for capacity-building at a local and national level to meet health care needs in low- and middle-income countries.

In order to fulfil these objectives, it was intended that the meeting would develop a plan of action which would involve conducting demonstration research projects in selected low- and middle-income countries. These studies might generate important information of broad relevance to other low income countries thus promoting the adoption of evidence-based secondary prevention approaches.

WHO and Wellcome Trust staff welcomed participants to the meeting and outlined the roles and perspectives of their respective organizations in relation to the problem of NCDs. It was noted that the two organizations complemented one another in their functions and that this would be particularly beneficial when addressing the problem of NCDs: the Wellcome Trust has a long tradition of supporting high quality health research, while WHO has a broad remit to advise on health policy internationally, as well as extensive contacts with ministries of health across the world.

The Wellcome Trust

The Trust is an endowed, independent biomedical research charity based in London. Trust staff briefed participants on research opportunities offered by the Trust and more specifically on research into NCDs and health services.

► Some general points were made to provide an insight into the criteria used by the Trust when funding research. One of the goals of the meeting was to identify any gaps in data on the secondary prevention of NCDs which

might form the basis of specific research topics. Participants were asked to suggest short-, medium- and long-term research objectives. As a research charity the Trust cannot fund general surveillance activities. It can, however, support the collection of data on the incidence of disease if this data provides a platform for addressing

future key research questions. However, the nature of the next phase of research must be clear at the outset. The Trust recognizes that some research questions require a multidisciplinary approach and is therefore able to provide funds to

help bring together groups representing the different disciplines. It provides support for the best quality research proposals submitted by scientists. It is sensitive to the need to support the development of academics in less developed countries and, where appropriate, encourages collaborations with strong research groups in developed countries.

World Health Organization

WHO staff briefed participants on the organization's global strategy for NCD prevention and control, and highlighted WHO's increasing interest in developing good programmes for the secondary prevention of NCDs as part of its overall portfolio. Cost-effective schemes are needed. Current evidence suggests that in many countries, particularly in less developed ones, patients with CVD and other NCDs have poor access to care. There is strong evidence on the effectiveness of several secondary prevention interventions. However, despite the apparent benefits of such approaches and the generally low costs of the treatment required for some of these interventions, a substantial proportion of people worldwide who need secondary prevention do not have access to such treatment. In low- and middle-income countries, resources are generally scarce and many of the interventions currently being used are not cost-effective. There is therefore a need for a new initiative.

WHO and Wellcome Trust staff welcomed participants to the meeting and outlined the roles and perspectives of their respective organizations in relation to the problem of NCDs

SECONDARY PREVENTION OF MYOCARDIAL INFARCTION AND STROKE

Agreement of remit

Current evidence of cost-effective interventions for secondary prevention of myocardial infarction and stroke was presented and discussed. A series of overviews and perspectives were given about the problems and experiences encountered in various developing countries. A general discussion accepted the proposition that the focus of treatment should be on proven cost-effective interventions (medication and making changes to lifestyles). Such interventions should be considered when individuals seek treatment from the health care system for CVD such as a myocardial infarction, an ischaemic cerebral episode or stroke, or if they have developed angina or peripheral vascular disease. Since diabetes carries a substantive risk, middle-aged patients with diabetes should also be classified as at high risk of a CVD episode.

General strategies for the medical management of secondary prevention

It was recognized that medical professionals and the health care system are in an ideal position to help patients with CVDs. They play a crucial role in linking pharmacological and non-pharmacological methods for secondary prevention. It is now clearly evident that lifestyle changes such as smoking cessation, healthy dietary practices, weight control and regular moderate physical activity, can have a major impact on the development of CVDs and their recurrence.

Health care systems in many countries need to recognize this and develop suitable

individually based, family-orientated and community-related strategies for changing the smoking habits and lifestyles of patients. Clinical trials have demonstrated the benefits of smoking cessation, healthy diet and physical activity, alone or in combination, on the reduction of recurrences in those with established CVDs. Community-wide changes in diet and smoking rates, encouraged by community involvement at a regional or national level but with medical support, can significantly lower the demand for clinical care, by bringing about a substantial reduction in the recurrence of events in patients with established CVDs. In many cultures, patients prove very responsive to explicit, simple and practical advice about smoking cessation, healthy diet and moderate physical activity.

Thus, policy-makers and professional groups involved in developing new systems of care and medical guidelines for dealing with the growing CVD epidemic need to incorporate these programmes into their national schemes.

Drug options for use in the secondary prevention of cardiovascular diseases

ASPIRIN

There is now overwhelming evidence to show that daily use of low-dose aspirin helps to reduce the risk of stroke, myocardial infarction (MI) or vascular death by one quarter (absolute risk reduction). This effect remains for as long as aspirin is taken. In high-risk patients who have not yet suffered a vascular episode, the benefit is

Lifestyle changes that have a major impact on secondary prevention of major CVDs:

- Smoking cessation
- Weight control
- Healthy diet
- Regular moderate physical activity

1% of lives saved per year. Aspirin is exceptionally cheap and effective so the implementation of lifestyle changes (avoidance of smoking, dietary changes, weight control and physical activity) plus the routine daily use of aspirin are within the reach of the poorest societies. Smoking cessation and other lifestyle changes can be promoted on a societal level as part of general health promotion, and smoking cessation and aspirin use should be clearly set out as a minimum requirement for the support of CVD patients by the Health Services.

OTHER DRUGS

The evidence clearly shows that the following categories of drugs are of proven efficacy: beta-blockers, angiotensin converting enzyme inhibitors (ACEI), statins, and thiazide diuretics. It has been shown that if these drugs are made available in a generic, non-patented form, many patients in middle-income countries can probably afford most, if not all, of them. The cost of statins will shortly come down as the patent on lovastatin expired in late 2001. Furthermore, as each category of drugs listed above operates through different pharmacological mechanisms, their combined use is of great potential value to many categories of CVD patient.

Secondary prevention of stroke

The use of a diuretic and, or, an ACEI is of proven value in stroke patients. Patients who have suffered an ischaemic, rather than a haemorrhagic, stroke have also been shown to benefit from aspirin. In many developing countries the rela-

tive proportion of ischaemic to haemorrhagic stroke patients is unclear and in many health systems clinical differentiation for therapeutic purposes is not possible. In the light of this, the combination of a diuretic and an ACEI should be considered a routine option for the treatment of hypertension in all patients who have had a cerebral episode, regardless of their blood pressure values. In a recent study, the benefits of blood pressure reduction in patients with a cerebral vas-

cular episode was evident in terms of reduced strokes and total death rates throughout the blood pressure range. These findings, if further substantiated by clinical trials, will open up the possibility for developing community-based projects, or possibly even of selling antihypertensives over-the-counter without the need for routine blood pressure monitoring. The thiazide diuretic, bendrofluazide, is as cheap as aspirin and generic ACEIs are now also cheap. Statins are also increasingly recognized as being effective in reducing stroke rates, regardless of the type of stroke. Furthermore, given their proven value in other CVDs, countries should now consider the additional use of a statin particularly in patients with elevated serum cholesterol.

Drug costs

The opportunities now exist for markedly reducing the costs of the five categories of beneficial drugs, provided: full use is made of local production systems; full quality assurance is safeguarded possibly with involvement of WHO; consideration is given to appropriate packaging; and systems are developed to al-

Daily use of low-dose aspirin reduces the risk of stroke and myocardial infarction or vascular death by one quarter

Effective medications for secondary prevention of myocardial infarction and stroke:

- Beta-blockers
- Statins
- Thiazide diuretics
- Angiotensin converting enzyme inhibitors

low appropriate combinations to be routinely administered. Some strategies put forward at the meeting proposed making drugs available over-the-counter, while others favoured the continued involvement of the medical establishment to allow physicians to monitor responses to therapy as well as susceptible groups for safety reasons.

Combination therapy

The use of multiple drugs might be more acceptable if they were to be combined into a single pill containing all four categories of drugs, for example, aspirin, a beta-blocker, an ACE inhibitor and a statin, and taken once a day. The use of a single pill could well encourage patients to adhere to treatment as well as seriously reduce the cost of the drugs.

With the exception of patients suffering from peripheral vascular disease who do not respond well to beta-blockers, the use of a combination (fixed-dose) pill could be considered and evaluated in patients suffering from all other cardiovascular conditions. It could be argued that there would be little need for monitoring—except of compliance with the drug regimen—however, this would require careful evaluation within different societies.

Such an evaluation could take five years or more to complete and would require careful assessment of the following:

- a) Stability testing.
- b) Bio-availability testing.
- c) Assessment of the short-term effects of the drugs on blood pressure, low density lipoprotein cholesterol and platelet aggregation, to ensure that the effects of the fixed-dose pill are similar to those obtained by the use of each individual drug, and that the effects are the same in developing country populations as those seen when the drugs were tested extensively in high-risk Caucasian populations.
- d) Assessment of safety and short-term symptomatic side effects. This need is well recognized and greater rigour can be applied to such an assessment if it is conducted as part of placebo

controlled trials. The inexpensive ACEIs currently available are known to have side effects in a small proportion of patients e.g. cough (5–10%) and dizziness with hypotension (<1%).

e) Study of the interactions and effects of a combination of drugs on physiological mechanisms.

f) Studies on adherence to treatment.

It was accepted that the rationale for this approach had to be set out in detail before it could be recommended to national professional groups and ministries. WHO has produced a useful preliminary overview of this approach.

Lifestyle changes

The focus on drug therapy for secondary prevention must not detract from the role of other interventions. Smoking cessation has a greater impact than any single drug even when the drug is administered appropriately. On a national level it was clearly recognized that promoting health measures, for example encouraging dietary change and physical activity, could be of great importance. While some participants in the meeting felt programmes to encourage smoking cessation and dietary and physical activity programmes should

Smoking cessation has a greater impact than any single drug even when the drug is administered appropriately

be an integral part of secondary prevention protocols, others felt that the impact of these additional measures, while very worthwhile, were either time-consuming or without the strength of evidence available for drug interventions. These differences notwithstanding, it was nonetheless agreed that the development of a strategy using a combination of pharmacological and non-pharmacological approaches would be valuable.

It is important to be aware that clinical trials such as those used to test drugs are not always possible when attempting to evaluate the impact of lifestyle changes such as dietary changes, increasing physical activity and weight control. It is therefore necessary to draw on available evidence from other sources, in particular, long-term prospective cohort studies.

Health system research

A dilemma arose because while the evidence of the efficacy of the specified drugs was overwhelming, the challenge was how to ensure that such regimens would be applicable in all WHO Member States and considered appropriate by the medical profession. Patients would also have to accept the need for therapy and for adherence to the proposed regimen. Great benefits in terms of outcome and recurrent CVD events are expected to be seen if there are rates of even 50% for patient compliance.

Unfortunately the evidence suggests that the current systems of health care in both developed and developing countries have evolved over the decades on the assumption that the primary need is for a system geared to improving short-term, rapid response to acute illness. This is now considered, in both developed and developing countries, to be increasingly inadequate. The less developed nations continue to have to cope with pre-transition diseases such as infectious diseases and malnutrition. At the same time they are faced with the need to adopt a radically different approach to the long-term care of individuals suffering from chronic disease and multiple problems. These challenges are further compounded by inadequately resourced health care services.

A community-based, patient-oriented system needs to be developed where the patient is specifically engaged to take the initiative and become actively involved in self-management. Evidence suggests that such systems are much more effective in increasing the adherence of patients to chronic disease treatment and in achieving the required behavioural changes. It was therefore

seen as a limitation to focus exclusively on research approaches examining only the effectiveness of drug regimens. Identifying the most appropriate means of achieving maximal compliance was viewed to be equally important in health care terms. Health care research begs the question of equity and of making effective care available to all those in need. Nevertheless, it is important to be realistic and to work out which systems will allow the most cost-effective approach to be achieved in the different socio-economic and cultural environments.

Different country settings

The provision of funds for the health care system and for the support structure ensuring secondary prevention is crucial. Several countries have evolved health structures with a coherent primary health care system linked to secondary and tertiary referral systems which have popular appeal, community involvement and medical approval. There is therefore the need to consider controlled trials which involve randomising health care institutions or selective systems in order to test the validity of specific changes in the system. In other countries where regions are controlled by their own Health Ministers there is the option of trying different schemes in different regions. Some countries also provide settings with previous experience of community involvement in developing national, regional and local government links with management and preventive initiatives. In countries like China, the revolution now under-way in primary health care opens up opportunities for considering a variety of different approaches. In India, medical practice

Key areas for improving secondary prevention of major CVDs:

- Community-based approach
- Support for self-management
- Patient-oriented delivery system

is very different across the different states with a range of government, charitable and for-profit systems in existence. Thus any initiatives carried out must be adapted to the relevant medical structures within a country.

Health care initiatives that could be considered include: selective health personnel education, the provision of educational material to patients, the establishment of patient support groups, and the development of clinics at the primary care level to provide special care for CVD patients. Each of these initiatives requires proper testing. Evaluating the results of community-based health initiatives is as important as evaluating which drugs and doses are most appropriate under ideal conditions.

Several research approaches were proposed, including:

- a) A situational analysis, for example, a general assessment of the secondary prevention systems currently in place within a country: how many patients need treatment, what they are receiving, what are the critical pathways and what are the current barriers to secondary prevention.
- b) WHO and the Wellcome Trust could support the development of guidelines or principles for evaluating current secondary prevention systems, as well as the opportunities and bar-

Evaluating the results of community-based health initiatives is as important as evaluating which drugs and doses are most appropriate under ideal conditions

riers to improved care. It may be valuable to organize special meetings in selected developing countries with the support of dedicated senior leaders in this field from developed countries in order to engage in and support the establishment of a new programme of research.

- c) Special “demonstration” projects could then be developed to integrate the proposed secondary prevention interventions into health systems of selected countries. This in practice has a substantial health services research component related to specific outcomes. By refining these projects with different disciplinary inputs as well as with established medical expertise the legitimacy and standard of the proposals could be safeguarded.

- d) Exploring the possibility of developing and testing a single-dose pill of one or more types over the next 5 years. Such a combined pill should first be tested in settings with good facilities for carrying out controlled trials and for monitoring safety and side effects. Careful analyses would then need to be made of the feasibility of using such pills in low-income countries to ensure that the future use of a single combined pill with two or more drugs was economically justified, given competing health priorities and health care budgets available.

RECOMMENDATIONS FOR INTEGRATING SECONDARY PREVEN- TION INTERVENTIONS INTO HEALTH SYSTEMS IN DEVELOPING COUNTRIES

1 Secondary prevention as a key component of public health strategy

Secondary prevention of major cardiovascular events (fatal and non-fatal myocardial infarction; fatal and non-fatal stroke; sudden cardiac death, re-vascularization procedures) should be regarded as a key component of any public health strategy to reduce the rising burden of CVD in low and middle income countries. Evidence of effective interventions is available, which, if translated into a community-based secondary prevention programme, would prevent many deaths that occur in middle- and older age and substantially reduce disability related to CVD. Operational research to implement such programmes in low and middle-income countries should be a high priority.

► **Action:** WHO and Member States

2 Assessment of the current status of secondary prevention of major CVDs

Projects should be initiated, in selected developing countries with diverse health care systems, to assess the secondary prevention systems currently operating within certain countries. As part of these projects, the following items should be assessed:

a) estimated numbers of persons who require secondary prevention treatment (present; projected for 2010 and 2020) disaggregated by age, gender and socioeconomic status. Such estimates should identify the number of persons diagnosed with CVD or diabetes, the proportion of such persons who have been prescribed treatment that has been found to be effective for secondary prevention, and the proportion

of such persons who are regularly taking such treatment. This will also necessitate studies to confirm previous diagnoses of a cardiovascular event by a physician.

b) current practice patterns of management at different levels of health care.

c) beliefs and behaviours of patients and providers at different levels of health care.

d) capacity of existing health systems to integrate interventions and effectively implement a programme of secondary prevention (including drug availability and pricing).

e) barriers and opportunities for developing and delivering a programme of secondary prevention (including national health policies and the curriculum and training methods adopted by health care providers).

To facilitate this process, WHO (with assistance from the Wellcome Trust and/or other funding organizations) could organize workshops which would bring together multidisciplinary teams of investigators from selected developing countries to develop technically strong protocols to guide relevant research. Such workshops should ideally be conducted on a regional basis, tailored to the local settings and driven by local experts, with technical assistance from international experts identified by WHO and its partner(s).

► **Action:** WHO, Wellcome Trust, other research funding agencies and researchers

3 Initiatives for scaling up secondary prevention in countries

Based on the above assessment model, projects should be developed to integrate the proposed secondary prevention interventions into the health systems of selected countries. Context-

specific and resource-sensitive interventions to improve current practice patterns developed with the collaboration of local teams should be validated in these projects. Another component which should receive special attention in these projects is the non-pharmacological treatment provided after myocardial infarction and stroke. Particularly smoking cessation, physical activity, weight control and dietary change.

To facilitate this process, project development workshops may be convened by WHO (with assistance from the Wellcome Trust and other funding agencies). These workshops would bring together multidisciplinary teams of investigators, policy makers and local experts from selected countries, to develop programs appropriate in different settings as well as scientifically sound protocols for programme relevant research.

► **Action:** WHO

4 Health services

Health services at all levels of the health care system must become more responsive to the needs of managing noncommunicable diseases, and give high priority to the secondary prevention of CVD. WHO should recommend this to Member States, particularly low- and middle-income countries, as part of the reorganization of health services to manage noncommunicable diseases. Training of health care providers, coordination of chronic care programmes, integration of secondary prevention into primary health care, community education and multidisciplinary action to promote adherence are key elements of such a reorganization. Research must also focus on evaluating reforms at all levels of the health care system which can improve the effectiveness of secondary prevention programmes. Demonstration programmes should be set up at primary and secondary health care levels in different settings to test the efficacy of the reforms of the health service as well as to test the quality of interventions based on information obtained from the situational analysis and carried out by the health service. Model instruments and a process for research have already

been devised and WHO is currently testing them using several chronic disease conditions in less developed country settings.

► **Action:** WHO and Member States

5 Essential drugs

All five classes of drugs, whose efficacy as life-saving interventions is based on strong clinical trial evidence, should be included in the list of essential drugs which should be available in primary health care at low cost.

These are:

- Aspirin
- Beta-blockers (prototype drugs: atenolol, metoprolol)
- Thiazide diuretics (prototype drugs: hydrochlorothiazide, chlorthalidone)
- ACEI (prototype drugs: enalapril, ramipril)
- Statins (prototype drugs: lovastatin, simvastatin).

This will require the inclusion of statins in the list of essential drugs recommended by WHO and altering the prototype drugs currently identified in the list.

► **Action:** WHO

6 Guidelines

Health Professionals in developing countries should be provided with user-friendly guidelines for improving the practice of secondary prevention. Such guidelines should:

- a) Emphasize the benefits of smoking cessation.
- b) Encourage regular physical activity, weight control and healthy dietary practices, tailored to the clinical condition of the patient and the cultural context of the country.
- c) Recommend the use of effective drugs (identified above in Recommendation 5).

Based on a local appraisal of resources the guidelines should set out a modular programme of secondary prevention that begins with highly effective low-cost interventions such as smoking cessation and other lifestyle changes plus

the use of aspirin, and progressively adds other effective but more expensive interventions such as beta-blockers, ACEI and statins. A thiazide diuretic could also be included as an option where blood pressure control is a major goal and an important mechanism for risk reduction. Such guidelines should be prepared by WHO in collaboration with national experts.

► **Action:** WHO, international non-governmental organizations concerned with prevention and control of CVD diabetes, national associations of health professionals

7 Patient education programmes

Patient education programmes should be developed to promote informed self-care as a means of enhancing effective and sustainable chronic care. These programmes should be integrated into health care delivery systems at all levels of health care.

► **Action:** National associations of health professionals with assistance from WHO

8 National and regional policies

National and regional policies should be developed in order to enable greater access to secondary prevention by all individuals identified as being at high risk of major cardiovascular events, including:

- a) information on secondary prevention of cardiovascular events
- b) access to evidence-based treatment for addicted smokers (non-pharmacological and pharmacological)
- c) access to natural and processed foods which provide nutrition-based cardiovascular protection
- d) access to community-based facilities for promoting regular moderate physical activity
- e) access to essential drugs effective in secondary prevention.

► **Action:** WHO Member States

9 Partnerships

WHO should intensify its interaction with governments, the pharmaceutical industry and the World Trade Organisation Organization (WTO) to improve access to essential NCD drugs and to develop mechanisms that will promote the production and supply of these drugs (identified in Recommendation 5) and reduce their cost, so as to ensure that they are both available and affordable in low- and middle-income countries. Secondary prevention of CVD should be placed high on the agenda of discussions on essential drugs that WHO has initiated with the WTO as well as with the pharmaceutical industry.

► **Action:** WHO, World Trade Organization, pharmaceutical industry

10 Combination therapy

The development of combination therapy (fixed-dose) formulations of effective drugs should be considered as a means of overcoming poor adherence to treatment (due to the multiplicity of pills) and inadequate dosage (due to variations in the prescription practices of physicians). Such formulations should be evaluated in short-term studies on drug bio-availability, pharmacokinetics, biological effects on intermediate variables (risk factors) and safety of side effects. Such formulations, while attempting to combine as many of the effective drugs as feasible, should also provide flexible possibilities for treatment (two dosage levels for each drug and combinations of different drugs as appropriate to specific clinical and resource settings).

► **Action:** WHO in partnership with the pharmaceutical industry

After they have been developed and tested (as indicated above in Recommendation 10), combination formulations should be further evaluated for their cost-effectiveness in comparison with standard practice/usual care in randomized controlled trials or community-based demonstration projects. These evaluations should be carried out in settings with good systems in place to carry out controlled trials and for monitoring adverse effects and should use in-

intermediate variables (risk factors) to measure outcomes when assessing effectiveness.

► **Action:** WHO, Wellcome Trust and other research funding agencies

N.B. *In view of the Wellcome Trust's charitable status the Trust could only be involved in the development of applications for lower income countries where there are no commercial implications.*

SECONDARY PREVENTION OF MAJOR NONCOMMUNICABLE DISEASES THROUGH COMMUNITY-BASED AND HEALTH SERVICES INTERVENTIONS

A working paper for the WHO–Wellcome Trust Meeting on
Secondary Prevention, Cambridge, 1–3 August 2001*

* Prepared by Drs S. Mendis, A. Alwan and A. Mandil,
Management of Noncommunicable Diseases Department, WHO.

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1. Background

In 1999, noncommunicable diseases (NCDs) were responsible for approximately 60% of deaths in the world, and for 43% of the global burden of disease. Based on current trends, by the year 2020 these diseases are expected to account for 73% of deaths and 60% of the burden of disease (1). A substantial portion of this mortality and burden of disease can be attributed to cardiovascular diseases (CVD), cancer, chronic respiratory conditions and diabetes. In 1999, CVD alone was responsible for approximately half of all NCD deaths and one fourth of the global burden of disease (2). CVD, cancer, chronic respiratory disease and diabetes are the diseases that are being targeted by the WHO Global Strategy for NCD Prevention and Control, adopted at the General Assembly of the World Health Organization in May 2000 (1).

In 1998, NCDs were responsible for 54% of total mortality and 40% of the total burden of disease in low- and middle-income countries. Low- and middle-income countries also suffer the major burden of the CVD epidemic. In 1998, two-thirds of global CVD deaths and three quar-

ters of global DALYs occurred in these countries (2). It is also important to note that in low- and middle-income countries, unlike in established market economies, a higher percentage of cardiovascular deaths occur in those below 70 years of age. In 1998, about half (47%) of CVD deaths in low- and middle-income countries were below 70 years, compared to only 23% in established market economies (2).

Studies conducted in different parts of the world help to reveal the magnitude of the CVD problem in developing countries. A recent study in the Gambia showed that 24% of the adult population suffer from hypertension, and a substantial portion of the population is at risk of developing target organ damage (3). Similar and even higher figures have also been reported from several other low- and middle-income countries. Another study of blood pressure and its determinants found that hypertension affects 15% of the population in Nigeria and 26% of the population in Jamaica (4). Body mass index and salt intake were the major determinants of hypertension, and were reported to account for some 70% of the variation in hypertension prevalence (4). Not

only are CVDs such as hypertension important public health problems in developing countries, but they are also frequently associated with low levels of awareness and of treatment and control. Several factors may explain the propensity of developing nations to CVD. These include early life deprivation, the use of disposable income for deleterious health behaviours, and interactions between newly acquired health behaviours and genes (5).

Inequalities in health and in its determinants are deeply ingrained in the social structure of populations, in both developed and developing nations. In two large studies of civil servants in the UK, carried out twenty years apart, a consistent association has been shown between socioeconomic status and disease mortality and morbidity (6,7). In these cohorts, those in lower socioeconomic grades were at a higher risk of death from coronary heart disease, stroke, and chronic bronchitis (6,7). There is also a growing body of evidence that suggests that people in lower socioeconomic classes suffering from CVD receive poorer treatment than the general population (8–14). For example, despite being at greater risk of developing coronary heart disease and dying from it, patients in lower socioeconomic groups in the UK are less likely to be investigated once the disease develops, and are less likely to receive appropriate treatment once diagnosed (12–14). In both industrialized and less developed countries there tends to be a higher incidence of cancer and poorer survival rates among the lower social classes than among the higher social classes (15,16).

Actions to prevent common risk factors (primary prevention) and to provide equitable and cost-effective secondary prevention interventions have been given the highest priority in the WHO Global Strategy for the Prevention and Control of Noncommunicable Diseases (1). To assist Member States to develop effective programmes, the WHO has developed a protocol for establishing community-based integrated primary prevention projects that address the major NCDs with common risk factors namely: tobacco use, unhealthy diet, physical inactivity and overweight/obesity. There are also immense opportunities for reducing the impact of the NCD epidemic through cost-effective second-

ary prevention strategies. The WHO initiative proposes to combine both primary and secondary prevention interventions. However, given that the protocol outlining community-based primary prevention has already been developed, the present document will focus on the development of strategies for secondary prevention with special emphasis on the secondary prevention of the major CVDs, namely: coronary heart disease and cerebrovascular disease.

2. Potential for intervention

As indicated above, the root cause of the NCD epidemic is the increase in lifestyle-related risk factors and their environmental, economic, social and behavioural determinants. These modifiable risk factors include: tobacco use, physical inactivity, unhealthy diet, alcohol consumption and overweight/obesity.

A vast body of knowledge and experience now exists regarding the prevention of CVDs through a comprehensive long-term approach that effectively reduces risk factor levels (1). Prevention at the community-level is essential because modifiable causal risk factors are deeply entrenched in the social and cultural framework of society. Patients with established CVD constitute one of the highest risk groups. Secondary prevention involves identifying, treating and rehabilitating these patients to reduce their risk of recurrence, to decrease their need for interventional procedures, to improve their quality of life and to extend their overall survival

3. Effective interventions for secondary prevention of CVD

Several studies have demonstrated the effectiveness of secondary prevention interventions in the control of major NCDs, including CVD alone, or in people suffering from CVD and diabetes mellitus.

From the early 1980s the WHO–MONICA study monitored trends in coronary heart disease over 10 years, across 38 populations, in 21 countries. Data from this study indicate that secondary prevention and changes in coronary care are strongly linked with declining coronary endpoints (17,18).

Patients with established coronary heart disease or cerebrovascular disease are at the highest risk for subsequent coronary and cerebral events. Survivors of myocardial infarction (MI) are at increased risk of recurrent infarctions and have an annual death rate of at least five to six times that of people of the same age who do not have coronary heart disease (19). Similarly, patients who have suffered a stroke are at an increased risk of a further stroke, about 7% per annum (20), and are very likely to experience coronary heart disease. There is considerable scientific evidence to show that specific interventions can reduce the risk of further vascular events in patients with CVD and type-2 diabetes.

Despite known substantial benefits and generally low treatment costs, it has been reported that appropriate measures for secondary prevention after MI have been implemented in less than half of eligible patients, even in high-income countries (21,22). Because of inequitable and inaccessible health care systems, inefficient use of limited resources and the investment of already scarce resources in interventions that are not cost-effective, the availability of secondary prevention for CVD is likely to be far scarcer in low- and middle-income countries. Patients with established coronary heart disease and cerebrovascular disease experience recurrent morbid events such as stroke, myocardial infarction and heart failure that are costly to treat. However, they also provide the greatest potential for cost savings, through the use of cost-effective interventions (23–25). The results of cost-effectiveness analyses of secondary prevention measures indicate that secondary prevention measures for CVD are highly cost-effective when compared with many other routine medical interventions (23,24).

4. Scientific evidence of effectiveness of interventions

Interventions for secondary prevention of cardiovascular and cerebrovascular disorders include modification of risk behaviours (smoking cessation, promotion of healthy diet and of physical activity) and the use of medications which have been proven to be cost-effective. Examples of

the latter are: aspirin, beta-blockers, angiotensin converting enzyme inhibitors (ACEI), lipid lowering drugs and antihypertensives. Strong evidence for the efficacy of these drugs has been obtained from Randomized Clinical Trials (RCTs), which have mostly taken place in affluent societies (26–37). Unfortunately little evidence, if any, has come from studies conducted in low- and middle-income countries. Thus, many of the recommended medical interventions are based on RCTs carried out in developed countries and may cause economic hardship when applied in developing nations. Selected scientific evidence found in recent literature on cost-effective secondary prevention interventions for cardiovascular and cerebrovascular disorders is cited below. Evidence for pharmacological interventions is presented first (26–44), followed by that for behavioural risk factor modification (45–56).

4.1. ROLE OF PHARMACOLOGICAL TREATMENT IN SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

4.1.1 Aspirin in secondary prevention of CVD

The benefits of aspirin in the secondary prevention of myocardial infarction are well established and documented. In 19 791 patients who had myocardial infarction, reviewed by the Antiplatelet Trialists, low to medium doses of aspirin (75–325 mg/day) led to a 12% reduction in death, a 31% reduction in re-infarction and a 42% reduction in non-fatal stroke (26). Available evidence suggests that there are no added benefits from using daily doses higher than 325 mg. Currently, there is no clear evidence to suggest that any other anti-platelet regimen is more effective than aspirin.

One systematic review that compared anti-platelet treatment to a placebo suggested that at 6 months, 20 people would need to be treated with aspirin rather than a placebo to prevent one additional vascular event (27). With regard to cerebrovascular disease, RCTs have found that the routine use of prolonged antiplatelet treatment (aspirin 75 mg) is beneficial for the prevention of vascular events in people with a prior (presumed ischaemic) stroke or transient ischaemic attack, unless there is a clear con-

traindication against its use (26).

Bleeding is the most important adverse effect of aspirin. However, among people at high risk of cardiac events, the large absolute reductions in serious vascular events far outweigh any absolute risks (27).

Although aspirin, which prevents major vascular events by about 25% across various disease categories, is the drug of choice for secondary prevention, new evidence indicates that combining aspirin with clopidogrel leads to a further 20% risk reduction (28). However, the high cost of clopidogrel will limit its use to all but a small segment of the population in developing countries.

4.1.2 Beta-blockers in secondary prevention of CVD

Firm evidence from systematic reviews of RCTs also confirm that beta-blockers reduce the incidence of recurrent MI, sudden death and all cause mortality after myocardial infarction (29). Propranolol, timolol, metoprolol, atenolol and acebutolol have been shown to be highly beneficial. In long term trials the number needed to treat for 2 years to avoid a death is 42, which compares favourably with other treatments after MI (30). Serious adverse effects are uncommon with beta-blocker use (29).

4.1.3 ACE Inhibitors in secondary prevention of CVD

Systematic reviews have found that ACEI reduce rates of death, hospitalization for congestive heart failure, and recurrent non-fatal MI in people with left ventricular dysfunction who have suffered an MI (31). In addition, ACEI are also effective for reducing ischemic events after MI, as well as the risk of recurrent MI, unstable angina and death from recurrent MI (32). There may therefore be some rationale for using them in all patients who have suffered an MI because of their effect in reducing subsequent ischemic events.

A recent meta-analysis of four RCTs that included patients with type-2 diabetes, hypertension and a previous cardiovascular event who were randomized to an ACE inhibitor or an alternative drug, showed that ACEI may provide a special advantage in addition to blood pressure control (33).

Additional data from the Heart Outcomes and Prevention Evaluation (HOPE) study, have demonstrated that in high-risk patients with vascular disease, the administration of ramipril reduces the risk of myocardial infarction, stroke and cardiovascular death (34). The main adverse effects of ACEI include cough (5–10%), dizziness and hypotension (5–10%), hyperkalemia and renal impairment (less than 3%) (27).

4.1.4 Lipid-lowering agents in secondary prevention of CVD

Systematic reviews and large RCTs have also found that lowering cholesterol in people at high risk of ischemic coronary events substantially reduces the risk of CVD mortality and morbidity (35,36). There is insufficient evidence about the effects of routinely reducing cholesterol in patients who have suffered a prior stroke or transient ischemic attack (TIA). However, evidence from large RCTs suggests that there are benefits to be gained from using a statin to reduce cholesterol levels in people who have suffered a prior stroke or TIA, and who also have a history of coronary heart disease (37). Increased numbers of total non-cardiovascular events, cancers, accidents and violent deaths have been reported in statin trials. However, a systematic review of long-term statin trials found that there was no significant difference between the use of statins and a placebo in terms of non-cardiovascular mortality and cancer incidence during an average of 5.4 years of treatment (35).

4.1.5 Role of blood pressure control in secondary prevention of CVD

There is no direct evidence available from RCTs of the effects of lowering blood pressure in people with established coronary heart disease. However, observational studies and extrapolation of primary prevention trials of blood pressure reduction support the lowering of blood pressure in people at risk of ischemic events (38). A cohort study of 1032 Finnish subjects aged 70 years at baseline, and followed up for 6 years, indicated that poorly controlled hypertension, diabetes mellitus, previous stroke, smoking and male sex were all independent risk factors for stroke. It was therefore concluded

that poorly controlled hypertension was associated with an increased risk of stroke. Therefore, achieving good blood pressure control in elderly hypertensives receiving treatment has the potential of preventing stroke (39).

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) has recently provided evidence of the benefits of lowering blood pressure on the risk of stroke recurrence among patients with a history of cerebrovascular disease in the previous 5 years (40). In this study, 6105 patients were randomized to receive perindopril alone, perindopril plus indapamide, or placebo. The risk reduction in the perindopril group and combination group compared to placebo were 28% and 43% respectively.

As far as the prevention of vascular complications in diabetics is concerned, the United Kingdom Prospective Diabetes Study (UKPDS) has shown that in patients with type-2 diabetes, the risk of diabetic complications is strongly associated with raised blood pressure (41). Any reduction in blood pressure is likely to reduce the risk of complications, with the lowest risk being in those with a systolic blood pressure of less than 120 mm Hg.

There are many drugs available for the pharmacological management of hypertension. However, comparisons of different anti-hypertensives have shown that newer and more expensive drugs are not more effective than thiazides, diuretics and beta-blockers in reducing outcomes (42).

4.2 GLYCEMIC CONTROL AND DIABETES MANAGEMENT

In people with diabetes, available evidence indicates that glycemic control influences the rates of long-term complications. The Diabetes Control and Complications Trial (DCCT) shows that intensive treatment with the goal of maintaining blood glucose concentrations close to the normal range effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in type-1 diabetes (43). The UK Prospective Diabetes Study (UKPDS) compared the effects of intensive blood-glucose control, with either sulphonylureas or insulin, and conventional treatment on

the risk of micro-vascular and macro-vascular complications in people with type-2 diabetes. The study reported that intensive control of blood-glucose levels substantially decreases the risk of micro-vascular complications but not of macro-vascular disease (44).

4.3 ROLE OF MODIFICATION OF LIFESTYLE-RELATED RISK FACTORS IN SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE

In addition to pharmacological interventions for secondary prevention, evidence suggests that modification of CVD risk factors through smoking cessation, and encouraging a healthy diet and physical exercise can also significantly contribute to a reduction in cardiovascular mortality in people with established CVD (45–56).

4.3.1 Smoking control

Smoking is associated with approximately twice the rate of mortality from CVD and an even higher risk for cancer (45). Evidence from epidemiological studies indicates that people with coronary heart disease who stop smoking rapidly reduce their risk of recurrent coronary events or death (46). Angina patients who smoke have a greater risk of later infarction or death than do those who do not smoke. After coronary surgery reinfarction as well as new infarctions and angina pectoris are less common among patients who stop smoking than they are among those who continue to smoke (47).

Results of a meta-analysis of cohort studies suggest that smoking cessation after myocardial infarction is associated with a 50% reduction in mortality (48). The number needed to quit smoking to save one life is 13 assuming a mortality rate of 20% in continuing smokers. Smoking has also been shown to be a powerful predictor of recurrent heart failure and myocardial infarction as well as mortality in patients with left ventricular dysfunction. Quitting smoking appears to have a substantial and early effect (within two years) on decreasing morbidity and mortality in this patient group. The benefits of stopping smoking are therefore at least as important as those to be gained from recommended drug treatments in patients with left ventricular dysfunction (49).

In the case of stroke survivors, observational studies have shown that the excess risk of stroke among former smokers has largely disappeared 2–4 years after smoking cessation (50). Many randomized control trials have shown that counselling (51) and the use of the nicotine transdermal patch (52) are effective aids to quitting smoking. These findings reinforce the arguments for the incorporation and wider implementation in secondary prevention programmes of measures to promote smoking cessation, such as brief advice and nicotine replacement therapy.

4.3.2 Diet regulation

Diet regulation plays an important role in secondary prevention by modifying the CHD risk factors that are directly dependent on diet, primarily hypercholesterolemia, hypertension, overweight/obesity and diabetes.

Evidence from many studies demonstrates that the important goals of diet modification for secondary prevention of CVD, namely the prevention of thrombosis and the modification of blood lipid levels, can be achieved by adopting a Mediterranean or Asian-vegetarian type of diet (53,54). Many RCTs have found that advising people with coronary heart disease to eat more fish, fruit and vegetables, bread, pasta, potatoes, olive oil and rapeseed margarine results in a substantial survival advantage (55). Based on the above, current dietary advice should include reducing intake of total fat (not more than 30% of energy) and of saturated fat (less than 10% of energy) while maintaining intake of the essential omega-6 and omega-3 fatty acids, and increasing the intake of natural antioxidants, fruits and vegetable proteins (53–55). The main challenge is to adapt these scientifically quantified principles to the culture, ethnic origin and needs of individual patients and populations.

4.3.3 Promotion of physical activity

Although the role of exercise alone in reducing cardiovascular outcomes is not clear, systematic reviews of RCTs have found that cardiac rehabilitation which includes physical exercise improves coronary risk factors and reduces the risk of major cardiac events in people after MI (27). Although there are no satisfactory RCTs of

the effects of physical activity, a recent systematic review has summarized the large amount of evidence obtained from prospective cohort studies (56). These studies demonstrate that physical inactivity is a major risk factor for CVD and that changing levels of activity can improve health outcomes, even in the elderly.

5. Health Economics of secondary prevention

CHD and stroke place a large economic burden on developed countries, and are becoming increasingly important in developing countries. In developed countries like the USA secondary prevention has contributed substantially to the dramatic decline in mortality rates witnessed in the second half of the 20th century.

In order to be widely useful interventions for secondary prevention of CVD need to be effective in reducing disability and prolonging life. At the same time they need to be cost-effective. A full appraisal of the economic burden of recurrent vascular events in stroke and CHD patients and of the economic consequences of implementing strategies for secondary prevention will require future research since data in this area are extremely sparse, particularly in developing countries.

Within this framework there is a vital need to generate data to assist health care decisions with regard to secondary prevention in different settings. Any strategy for assessing both the effectiveness and the economics of programmes to manage cardiovascular disease should have four discrete, mutually reinforcing aims: (1) to identify the technologies that need to be assessed, (2) to collect data on the selected technologies, (3) to synthesize the data collected, and (4) to disseminate the information collected. The present project proposal will endeavour to address these issues in order to develop a firm foundation for health care decisions in Member States.

6. Compliance with treatment

Compliance with treatment regimens for CVD, whether pharmacological or non-pharmacological, plays a pivotal role in the success of such interventions and in influencing CVD outcomes.

Many studies have used a variety of cognitive, educational and behavioural strategies to improve compliance with both pharmacological and non-pharmacological regimens for reducing cardiovascular risk (57). These studies have demonstrated that patient-focused strategies such as behavioural skill training, self-monitoring, telephone/mail contact, self-efficacy enhancement and external cognitive aids are useful methods of improving adherence of patients (58).

Successful management of chronic diseases such as CVD, as opposed to acute infections, involve long-term follow-up and care and are closely linked to issues of adherence. The current health systems in most countries, particularly those in developing countries, are not geared to cater to these requirements. Many organizational changes will be required in existing health services to make them more receptive to the needs of those suffering from NCDs.

7. Policies on drugs for secondary prevention

Drug costs make up a substantial part of the direct costs of secondary prevention programmes. The success of secondary prevention programmes is therefore, heavily dependent on national drug policies and on the quality, rational use and safety of the relevant drugs. WHO has developed an effective strategy to improve access to essential drugs. The main components of this strategy are (i) rational selection, (ii) affordable prices, (iii) sustainable financing, and (iv) reliable health and supply systems.

(i) Key actions recommended to ensure rational selection include: linking treatment guidelines with essential drug lists, regular updating of such lists based on best evidence, and using such lists for supply, reimbursement, and training.
 (ii) To ensure affordable prices, proposed key actions include: encouraging competition, using generics, and equity pricing of newer essential drugs.
 (iii) For sustainable financing, the proposed actions include: increasing public funding for cost-effective drugs, expanding drug benefits in health insurance, and seeking external funding for the poorest communities.

(iv) For reliable health and supply systems, the strategy proposes integrating supply management into health system development, developing an efficient mix of public-private systems, and maintaining quality in distribution channels.

8. Overall aim of the project

The overall objective of this initiative is to assist Member States to strengthen health care for people with major CVDs, by supporting the implementation of cost-effective secondary prevention interventions, with emphasis on primary health care and community-based action [Objective 3 of the Global Strategy for the Prevention and Control of Noncommunicable Diseases (1)].

The Management of the Noncommunicable Disease department will work jointly with other concerned departments from the Noncommunicable Disease and Mental Health Cluster, as well as with the Tobacco Free Initiative and Noncommunicable Disease Advisers in the six Regional Offices to provide the technical support required for the planning and implementation of the project.

8.1 Specific objectives

The specific objectives of the initiative are:

To develop and test protocols for community-based projects using evidence-based and affordable secondary prevention interventions aimed at controlling the major CVD risk factors and reducing cardiovascular outcomes. Such interventions will be tested in pilot projects in selected Member States, and then implemented on a wider scale.

To evaluate the impact of such interventions on the levels of major risk factors as well as on cardiovascular outcomes.

To develop sustainable strategies for integrating secondary prevention into the existing health care infrastructure and build national capacities to meet the needs of health services in the prevention and management of CVDs.

9. Approach

9.1 PHASE 1: IDENTIFICATION OF INTERVENTIONS AND DEVELOPMENT OF PROJECT PROTOCOLS

During this phase, an essential package of evidence-based, cost-effective interventions for secondary prevention of CVD (coronary heart disease and stroke) will be identified. A general protocol for a multi-country pilot project that integrates secondary prevention into community-based primary prevention programmes will be developed. Organizational models for implementing the protocol with particular reference to primary care will be proposed. Individual studies will be designed by local principal investigators in response to country/region-specific circumstances, with the collaboration and advice of other international scientists where appropriate.

Proposed activities:

1. Establish a Steering Committee, including staff/external experts, for planning, quality assurance and monitoring purposes.
2. Organize a consultation with international experts and potential investigators from developing countries to discuss the following issues:
 - (i) To identify cost-effective interventions for the secondary prevention of CVD that can be integrated into the health systems of developing countries.
 - (ii) To identify mechanisms and tools to assess the feasibility of these interventions and their impact on major risk factors and selected cardiovascular outcomes.
 - (iii) To develop a plan of action for the development of a general protocol for community projects on evidence-based, cost-effective interventions aimed at controlling the major NCD risk factors and reducing cardiovascular outcomes.
 - (iv) To discuss strategies for integrating secondary prevention into the existing health care infrastructure and build national capacity to meet health services needs for the secondary prevention of the major NCDs.
3. Develop the protocol for the pilot project

which identifies the target population, methodology, indicators for evaluation and defines organizational models for implementation.

4. Identify the basic requirements of the health system for incorporating the selected interventions into primary health care (e.g. training, logistics, referral system and other relevant components). Issues that need to be considered include the cost of relevant drugs in different countries, other direct and indirect costs, implications for the health system, and the role of the various levels of health professionals.

9.2 PHASE 2: PILOT TESTING OF PROJECT

- (i) Pilot testing will be carried out in selected countries from the 6 WHO Regions.
- (ii) Identify countries and potential local investigators, adapt the protocol developed in phase 1 and train local teams.
- (iii) Implement the basic changes required in the infrastructure of the existing health system in the pilot areas.

9.3 PHASE 3: IMPLEMENTATION

- (i) Implement pilot projects.
- (ii) Monitor process and outcomes.

9.4 PHASE 4: EVALUATION

Evaluate the process of the programme, the short-term impact of the interventions, and the suitability of the programme to serve as a demonstration project for the establishment of other national programmes.

10. Expected outcomes

- (i) The implementation of context-specific, resource-sensitive, high-impact and cost-effective secondary prevention interventions for cardiovascular disease in low- and middle-income populations (WHO publication).
- (ii) Pilot projects that integrate the secondary prevention of CVD into existing health systems through health service interventions in selected countries.
- (iii) Evaluation of the feasibility and sustainability of secondary prevention programmes in

low- and middle-income countries.

(iv) Recommendations on effective and applicable approaches to the secondary prevention of CVD.

(v) The establishment of model intervention sites for use as demonstration projects and for national policy development.

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LIST OF PARTICIPANTS

WHO/WELLCOME TRUST MEETING OF EXPERTS
ON SECONDARY PREVENTION OF
NONCOMMUNICABLE DISEASES IN
LOW- AND MIDDLE-INCOME COUNTRIES THROUGH
COMMUNITY-BASED & HEALTH SERVICE INTERVENTIONS

HINXTON, CAMBRIDGE, UK
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Professor Rory Collins
CTSU
Harkness Building
Radcliffe Infirmary
Oxford, OX2 6HE, UK
+44(0)1865404834
Fax: +44(0)1865558817
Email: gale.mead@ctsu@ox.ac.uk

Professor Shah Ebrahim
Department of Social Medicine
Canynges Hall
Whitelanes Road
Bristol, BS8 2PR UK
+44(0)1779257350
Fax: +44(0)1179287325
Email: shah.ebrahim@bris.ac.uk

Professor Philip James
Public Health Policy Group
10TF/IASO, 3rd floor
231 North Gower Street
London, NW1 2NS, UK
+44(0)2076911800
Fax: +44(0)2073876033
Email: jeanHJames@aol.com

Professor Liming Li
Chinese Academy of Preventive
Medicine
27, Nan Wei Road
Beijing 100050, China
+86 10 83163186
Fax: +86 10 63163746
Email: cchp@public3.bta.net.cn

Dr Hossein Malek Afzali-Ardakani
Ministry of Health
Research Department
Tehran, Islamic Republic of Iran
+98 21 933751
Fax: +98 21 923840
Email: afzali@hbi.or.ir

Dr Curtis Meinert
John Hopkins Centre
for Clinical Trials
6/5 N. Wolfe Street, Room 5010
Baltimore, MD 21205, USA
+1 410 9558198
Fax: +1 410 9550932
Email: cmeinert@jhsph.edu

Dr Hector Moguilevsky
Ministerio de Salud
Avenue 9 de Julio 1925
Buenos Aires C1073 ABA, Argentina
+54 11 43799011
Fax: +54 11 93799151
Email: moguilev@satlink.com

Professor V. Mohan
Madras Diabetes
Research Foundation
6B Conran Smith Road
Gopalapuram
Chennai 600086, India
+91 44 8200703
Fax: +91 44 8258935
Email: mvds@vsnl.com

Professor Richard Peto
CTSU
Radcliffe Infirmary
Oxford, OX2 6HE, UK
+44(0)1865404801
Fax: +44(0)1865404801

Professor K. Srinath Reddy
Department of Cardiology
All India Institute
of Medical Sciences
Ansarinager
New Delhi 110029, India
+91 11 6167459
Fax: +91 11 6167397
Email: ksreddy@satyam.net.in

Professor Gerry Shaper
Royal Free and University
Medical School
8, Wentworth Hall
The Ridgeway
Mill Hill
London NW7 1RJ, UK
Fax: +44 20 89598742
Email: agshaper@wentworth.u-net.com

Dr K.T. Shenoy
Director, M. Phil Programme
Clinical Epidemiology
Research and Training Centre
Medical College
Thiruvananthapuram
695011 Kerala, India
+91 471 528241
Fax: +91 471 448825
Email: ktshenoy@md3.vsnl.net.in

Dr Chaisri Supornsilaphachai
Social & Behavioural Medicine
Division

Department of Medical Services
Ministry of Public Health
Tivanond Road
Amphur Muang
Nonthaburi 11000, Thailand
+662 5033702

Fax: +662 5033720
Email: chaisri@health.moph.go.th

Dr Krisela Steyn
Medical Research Council
Chronic Diseases & Lifestyle Unit
WHO Collaborating Centre

PO Box 19070
Tygerberg 7505, South Africa
+27 21 9380345

Fax: +27 21 9335519
Email: Krisela.Steyn@mrc.ac.za

Dr K.R. Thankappan
Achutha Menon Centre
Health Science Studies
Sree Chitra Tirunal Institute for
Medical Sciences and Technology
Trivandrum, India

+91 471 524231
Fax: +91 471 446433
Email: thank@sctimst.ker.nic.in

Dr Salim Yusuf
(by Conference line)
237 Barton St. E
McMaster Clinic, Room 252
Hamilton General Hospital
Hamilton, Ontario L8L 2X2,
Canada

+1 905 5277327
Fax: +1 905 5211166
Email: yusufs@mcmaster.ca

THE WELLCOME TRUST

Miss Sam Balakrishnan
183 Euston Road
London, NW1 2BE, UK
+44(0)207 6117236
Fax: +44(0)207 6117288
Email: s.balakrishnan@wellcome.ac.uk

Dr Catherine Davies
183 Euston Road
London, NW1 2BE, UK
+44(0)207 6118692
Fax: +44(0)207 6117288
Email: c.davies@wellcome.ac.uk

Dr Wendy Ewart
183 Euston Road
London, NW1 2BE, UK
+44(0)207 6118406
Fax: +44(0)207 6117288
Email: w.ewart@wellcome.ac.uk

Miss Michelle Honey
183 Euston Road
London, NW1 2BE, UK
+44(0)207 6118246
Fax: +44(0)207 6118237
Email: mhoney@wellcome.ac.uk

Dr Richard Lane
183 Euston Road
London NW1 2BE, UK
+44(0)207 6118854
Fax: +44(0)207 6110681
Email: r.lane@wellcome.ac.uk

Dr Jacob Sweiry
183 Euston Road
London NW1 2BE, UK
+44(0)207 6118321
Fax: +44(0)207 6117288
Email: j.sweiry@wellcome.ac.uk

THE WORLD HEALTH ORGANIZATION

Dr Ala Alwan
Avenue Appia 20
1211 Geneva 27, Switzerland
+41 22 7914619
Fax: +41 22 7914259
Email: alwana@who.int

Dr Raphael Bengoa
Avenue Appia 20
1211 Geneva 27, Switzerland
+41 22 7912410
Fax: +41 22 7914769
Email: alwana@who.int

Dr Shanthi Mendis
Avenue Appia 20
1211 Geneva 27, Switzerland
+41 22 7913441
Fax: +41 22 7914151
Email: mendiss@who.int

Dr Pekka Puska
Avenue Appia 20
1211 Geneva 27, Switzerland
+41 22 7914703
Fax: +41 22 7914186
Email: puskap@who.int