

Meeting report on the Bellagio Conference 'prevention of vascular diseases in the emerging world: An approach to global health equity'

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Representatives from five international organizations (International Society of Nephrology, World Heart Federation, International Diabetes Federation, International Atherosclerosis Federation, and International Society of Hypertension) participated in a strategic planning workshop in December 2005 in Bellagio, Italy sponsored by the Rockefeller Foundation. There were equal representatives from developed and developing countries. Global perspectives on diabetes and cardiovascular and renal diseases were presented, with special emphasis on China, India, Latin America, and Africa. The rationale and effectiveness of preventive measures were discussed. It was apparent that measures for primary prevention and early intervention for all the chronic vascular diseases are similar. The five organizations agreed that an integrated global approach to chronic vascular diseases is needed. They resolved to collaborate and work towards an integrated approach to chronic vascular diseases with the establishment of a 5-year plan for the prevention and treatment of chronic vascular diseases, including public advocacy, advising international and national agencies, and improving education and the practice of established approaches.

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A landmark meeting funded by the Rockefeller Foundation was held in Bellagio, Italy in December 2005 to address the problem of chronic vascular diseases. Organized by John Dirks, Chair International Society of Nephrology COMGAN Michael Alderman, President International Society of Hypertension, and Giuseppe Remuzzi Chair ISN COMGAN Research Committee (Italy), participants included leaders from five international organizations, namely International Society of Nephrology (ISN), International Society of Hypertension, World Heart Federation, International Diabetes Federation, and International Atherosclerosis Society, and representatives of WHO and the European Commission. There were 24 participants with 11 from the developing world (Figure 1).

The meeting was structured over 3 days. Session 1 dealt with 'A Global Perspective on Cardiovascular–Diabetic–Renal Disease'. Session 2 dealt with 'Cardiovascular Disease in the Developing World: Why the Need for Prevention'. Sessions 3 and 4 examined 'Prevention of Kidney Disease and Diabetes in Developing Countries', and Session 5 addressed 'A Global Implementation Plan for Non-Communicable Diseases'. Session 6, 'The Challenge of Resources for Dealing with Chronic Diseases in the 21st Century', concluded with lively discussion resulting in a draft consensus statement concerning the global implementation of this integrated approach (Figure 2).

The objectives of this conference were to arrive at a consensus among five organizations dedicated to vascular disease and its complications and to develop a common agenda and strategies for global prevention of chronic vascular diseases, particularly in the developing world. The participating organizations, which are already involved in advocacy and/or prevention programs, believe that their overlapping science, such as risk factors, makes collaboration both practical and beneficial.

GLOBAL PERSPECTIVE ON DIABETES AND CARDIOVASCULAR AND RENAL DISEASE

Dirks (Canada) began with an overview on chronic diseases. In 2005, they caused over 35 million or 60% of all deaths

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Figure 1 | Five international organizations brought together representatives from the developing and the developed world in Bellagio, Italy to discuss an integrated approach to global prevention of chronic vascular diseases.



Figure 2 | After 3 days of intensive talks, the group resolved to work toward developing a consortium of six organizations and the establishment of a 5-year plan for the prevention and treatment of chronic vascular diseases.

worldwide. With the exception of sub-Saharan Africa, they have surpassed infectious diseases as the major cause of morbidity and mortality, the majority due to diseases affecting the vascular system.

Contrary to popular mythology, these diseases are not the revenge of the human body on a wealthy and overindulgent lifestyle, nor are they diseases of old age. Almost 80% of the deaths from chronic disease occur in countries with developing economies and half of them occur in people under 70 years of age.¹ Poor people have fewer choices regarding diet, living conditions, and access to education and health care. It is estimated that between 1990 and 2020, annual mortality rates from cardiovascular disease (CVD) alone will more than double within countries with develop-

ing economies.² Economic considerations alone would seem to make prevention an obvious approach to the growing prevalence of chronic diseases.

Unwin (UK) gave the WHO perspective, pointing out that health-care models in nearly all countries allocate virtually all their health-care dollars to treatment and very little to prevention. In the US, the ratio is 95% to 5%. The same lack of focus on prevention exists in emerging nations: in 2002, although development aid to the health sector was \$2.9 (US) billion, a scant 0.1% went to chronic diseases.³ WHO spent 3.5% of its 2002 budget on chronic diseases. It estimates that 80% of heart disease, stroke and diabetes could be prevented if the known risk factors were eliminated. Most importantly, this need not be a costly undertaking.

Jamison (US) attributed 10–15% of the economic growth in developing countries to improvements in population health.⁴ The increase in the prevalence of chronic diseases, however, is a growing threat to their economies. The Developing Countries Priorities Project, second edition estimates the cost effectiveness and impact of single and multiple interventions. An analysis of the disease burden in selected low- and middle-income countries showed that CVD and stroke ranked second and fourth among all diseases in terms of disability-adjusted life years.⁵ The study compared the efficacy (disability-adjusted life years averted) of taxation of tobacco products versus various treatment interventions and found that taxation would be the most effective single undertaking, and at the least cost.

Alderman (USA) pointed out that hypertension now affects 26% of the world's population⁶ and is increasing. Although rates are expected by 2025 to increase by just over 28% in developed countries, they will almost double in the Middle East and sub-Saharan Africa, and increase substantially in India, Latin America, and South East Asia. Furthermore, although treatment is both efficacious and available, control levels remain stubbornly low, ranging from about 6 to 27% in the developed world.⁷ He reported that currently 68% of disability-adjusted life years attributable to non-optimal blood pressure occur in developing countries, and 43% in people 30–59 years of age. Studies have shown that the risk of cardiovascular (CV) events is linear from a systolic reading of 115 mm Hg, which suggests that the current definition of hypertension may not be useful because risk levels of blood pressure are continuous.

Smith (USA) confirmed that coronary heart disease is now the leading cause of mortality in every area of the world except sub-Saharan Africa. In the developing world, there is a correlation between urbanization and the increase in coronary heart disease. In addition, tobacco use has surpassed human immunodeficiency virus and diarrheal diseases as a major cause of death. To assist efforts to prevent CVD in developing countries, the World Heart Federation has published principles⁸ for national and regional guidelines on CVD prevention, indicating that strategies should be

based on epidemiologic risk factor data appropriate to the population to which it is applied.

Remuzzi (Italy) described an array of ISN-supported screening and interventional studies in developing countries. Investigators are trained in a Western country, and upon returning home lead the local study in tandem with their Western partners, resulting in significant capacity building in nephrology epidemiology. He has concluded that research capacity in vascular disease should be coordinated so that various specialists work together. Centers of excellence in selected sites in the developing world, linked with developed centers, could advance international vascular research.

Remuzzi estimates that there are 60 million individuals worldwide with early kidney disease to end-stage renal disease. However, after a 20-year increase, kidney disease in the USA has begun to level off as a result of improved clinical strategies including increased prescription of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers.

Unwin showed that diabetes is increasing most in developing countries. Seven of the top 10 countries whose 35- to 64-year-old population suffers from the disease are in the low- and middle-income group (i.e. Brazil, India, Indonesia). By 2030, WHO estimates that 366 million people will have diabetes, overwhelmingly Type II. Of these, up to 40% will develop diabetic nephropathy, 25% visual impairment, 33% peripheral neuropathy, and 66% will die of CVD. An estimated 2.9 million people aged 35–64 died from diabetes in 2000.⁹ Although there is a lack of data from many countries, WHO estimates that diabetes accounts for 2.5–15% of national health-care budgets. In many, diabetes can be delayed or prevented through weight loss, diet adjustment, and increased physical activity as shown in the Finnish diabetes prevention study, which resulted in a 50% reduction in the control group.¹⁰

Nine recognized risk factors account for 90% of CV events: hypertension, smoking, abdominal obesity, physical inactivity, APoB/APoA, diabetes, psychosocial factors, insufficient fruit and vegetables, and alcohol. Metabolic syndrome, prevalent in all countries, has been identified as a multi-dimensional risk factor for CVD (Grundyl, USA). It increases with abdominal obesity but it is unclear whether this or insulin resistance is its underlying cause. It leads to increased risk of diabetes mellitus (five-fold) and CVD (1.5- to three-fold), with greater risk for South Asians.

Yusuf's 52 country *Interheart* Study¹¹ has established waist-to-hip ratio as a better indicator for acute myocardial infarction risk than body mass index (BMI) categories. This is true of all ethnic groups, leading him to believe ethnicity is a better marker of lifestyle differences than genetic differences. He questions the descriptive categories of BMI, pointing out that there are probably no healthy adults in North America with a BMI of ≤ 20 . This leads to the question, What is normal? His study indicated that within a given population, obesity accounts for 34% of the risk for acute myocardial infarction, which in developed countries is higher than smoking.

CVD IN THE DEVELOPING WORLD: WHY THE NEED FOR PREVENTION?

Reddy (India) focused on the role of socio-economic gradients in the risk factors for CVD using as examples India and China. A study within 10 industries in India showed a direct correlation between educational status and five risk factors for CVD, namely smoking, regular physical activity, diabetes, hypertension, and metabolic syndrome. In four educational groups (post-graduate, graduate, high school, primary/illiterate), the five risk factors were inversely related to the levels of education.¹² In China, where acute coronary events increased between 1984 and 1997 at a rate of 1.7% a year, a study on women aged 15–69 years at three different educational levels yielded similar results.¹³

Rodriguez-Iturbe (Venezuela) reported that there is significant disagreement in reported studies about the prevalence, treatment, and control of hypertension in Latin America. Variable diagnostic criteria are used and data sampling techniques are not always consistent.¹⁴ In some countries, there are no statistics available on prevalence, treatment, or control.

Forrester's (Jamaica) presentation on the African American Diaspora Study, the International Collaborative Study on Hypertension in Blacks, compared 9577 black adults in four West African sites, three Caribbean sites, and one American site for prevalence of hypertension.¹⁵ He found that prevalence of hypertension increased with per capita GNP, from 16% in West Africa to 26% in the Caribbean to 33% in the USA. Environmental factors, specifically obesity, and sodium and potassium intake vary with the prevalence of hypertension.

Tobacco is the second leading cause of mortality worldwide and its use remains high in the developing world. In China 70% smoke, and in Indonesia 60% use tobacco, including 16% of children 13–15 years old. Zaman (Bangladesh) demonstrated the high opportunity costs for the population (50%) that uses tobacco. When the revenue from taxes and tobacco-related employment are set off against direct and indirect medical costs, tobacco costs the country US \$44 million per year.¹⁶

Smoking cessation provides the best example of how effective a concerted national program of education and prevention can be in changing behaviors. In developed countries where such programs have been in effect for over 20 years, smoking rates have dropped significantly through a combination of media campaigns, smoking restrictions, advertising bans, and increased taxes. The tax increase has been particularly effective among teenagers, a price-sensitive group, as would presumably be the case within other low-income populations.

PREVENTION OF KIDNEY DISEASE AND DIABETES IN DEVELOPING COUNTRIES

One of the more animated discussions took place over de Zeeuw's (The Netherlands) presentation on albuminuria as a marker for CVD and kidney disease. According to his

RENAAL study, the more the albuminuria in the urine, the more the risk for chronic kidney disease (CKD), CVD, and diabetes. In the IRMA study,¹⁷ reducing proteinuria through treatment with sartans achieved a risk reduction of 70% for diabetic nephropathy. The PRIME study showed that earlier interventions are better. In controlled studies in the USA and Groningen (The Netherlands), mild renal dysfunction (albuminuria plus decreased glomerular filtration rate) were found in 11 and 10.5%, respectively. In several studies, microalbuminuria was found in 5–7% of the 'healthy' population, 20–30% of the hypertensive population, and up to 40% of diabetics.

In the PREVEND study, albuminuria was found to predict moderate (Stage 3) CKD.¹⁸ Preliminary data from the same study showed that high albuminuria concentrations could be a better predictor of CV mortality than hypertension.¹⁹ Treatment of albuminuria with angiotensin-converting enzyme inhibitors showed a risk reduction for CV mortality of 40–44% over 40 months,²⁰ a cost-effective treatment. Discussion indicated that cardiologists remain uncertain about the additive value of microalbuminuria to standard CV risk factors, and questions remain to be answered about the pathogenic process by which protein leakage affects the vascular system. De Zeeuw called for a working party from the participating societies to standardize the measurement and definition of albuminuria, and its use in CVD and CKD assessment.

In Africa, intervention to prevent or slow kidney disease is the only economically viable approach, according to Naicker (South Africa). A survey of 16 Sub-Saharan African countries indicates the prevalence of end-stage renal disease from a high of 75.5 patients per million of population in South Africa to a low of 1.6 in Ghana. There is a correlation in most developing countries between average income and rates of reported end-stage renal disease, suggesting that the variability has more to do with economics than true prevalence. There is a shortage of general physicians as indicated by a WHO survey of 27 African countries indicating that 17 countries have fewer than nine physicians per 100 000 people. Ghana, Togo, and Zambia have only two nephrologists and two dialysis units each. Where available, dialysis is usually unaffordable. For instance, in Nigeria, Ghana, Senegal, and Togo, it costs \$100 per dialysis, more than in most developed countries and far more than the average monthly income of most Africans. Latin America (Rodriguez-Iturbe) shares many issues with Africa, to a lesser degree. With the exception of Uruguay, Chile, Costa Rica, and Mexico, CKD is both underreported and undertreated. Diabetic nephropathy and hypertension are the main causes of CKD, reflecting a more 'Western' profile.

An ISN early detection and intervention program in Morocco (de Broe) will identify at-risk patients through community-wide (100 000 people in two communities) screening programs. It will examine the role of occupational exposure and traditional medicines in the development of CKD. The protocol is based on the ISN 'Program for

detection and management of chronic kidney disease, hypertension, diabetes and cardiovascular disease in developing countries', a flexible model applicable according to local conditions.

In India's rapidly growing cities, diabetes rates are double the USA rates. Ramachandran's (India) study showed that both the age and the BMI threshold for diabetes are lower in Indians (23) compared to Europeans (27.5). Another observed characteristic is that Indians have higher central obesity and fat mass for a given BMI. It is speculated that this results in high rates of insulin resistance (16.8% in 2000).

A control trial on primary prevention of diabetes on subjects with impaired glucose tolerance found that the conversion rate of impaired glucose tolerance to diabetes is high (55% in 3 years). Conversion rates were reduced by 28.5% using lifestyle modifications other than weight loss, and by 26.4% using metformin. There was no added benefit to using both.²¹

Ramaiya (Tanzania) reported that in Africa, diabetes medications are often unavailable and usually unaffordable. The complications of diabetes are high; ketoacidosis is common and contributes to the high mortality (25% in Tanzania, 33% in Kenya). Retinopathy is also high (21–25% of Type II patients in South Africa); 35% of all dialysis patients have diabetes; and 40–60% of non-traumatic amputations are diabetes related.

A study by Cardoso (Brazil) of 471 Type II diabetics of Japanese descent over a 5-year period in Brazil reported 121 deaths over 5 years, 36% from CVD and 33% from infection.²² We conclude that both prevention and treatment of diabetes is a worldwide problem.

A GLOBAL IMPLEMENTATION PLAN FOR NON-COMMUNICABLE DISEASES

Unwin presented the WHO plan for reducing the chronic disease burden by 2% annually over the next decade. Nine of 10 lives saved would be in low- and middle-income countries, resulting in massive savings: over \$35 billion in China, nearly \$20 billion in Russia, and almost \$15 billion in India. The WHO Stepwise framework involves a comprehensive and integrated action plan, including (1) estimating the population need and advocating for action, (2) formulating and adopting prevention and control policies, and (3) identifying the policy implementation steps at the national, sub-national, and individual level. It begins with interventions using existing resources, proceeds to interventions with realistically increased resources, and finally moves to evidence-based interventions beyond the reach of current resources.

Jamison described the mission of the Ellison Institute (Harvard), to improve population health and the efficiency of health system resources. It will seek out and make available credible, comprehensible, and comparable information where it is lacking. Partnerships with 15–20 low-, middle-, and high-income countries will be established to undertake capacity building to match the analytical agenda in each one. Potential areas of activity include health intervention delivery, burden

of disease and comparative risk assessment, population health, system efficiency, and policy analysis.

Alderman said that lack of research within the emerging world is a major problem, exemplified by the fact that 82 of 192 countries published nothing on CVD in major international peer-reviewed journals between 1991 and 2001.²³ Over half the International Medical Graduates in North America, the UK, and Australia come from developing countries. This brain drain has had a negative effect not only on patient care but also on the establishment of role models, mentorship and training programs, and research capacity.

Yusuf described international research being undertaken by the Population and Health Research Institute (Hamilton, Canada). It has undertaken a number of global epidemiological studies including the Interheart Study (on risk factors for acute myocardial infarction) on 30 000 people in 52 low-, middle-, and high-income countries, and the PURE (prospective urban rural epidemiologic) study, which looked at the impact of risk factor modification on myocardial infarction in 135 000 people in 15 low-, middle-, and high-income countries.

He described the problems of conducting research in low- and middle-income countries – limited funds, lack of recognition of chronic diseases, personnel shortages, few role models, and a limited culture of research. The practical challenges of such research include regulatory difficulties, lack of local expertise and equipment, the integrity of drugs and blood, and maintaining long-term follow-up. However, he stressed the positive advantages to locals who are trained by being involved in his projects. Local principal investigators who are knowledgeable about research and local issues are needed. Yusuf iterated that international research has scientific, cultural, political, and health benefits for developing countries and benefits developed countries by providing understanding of the evolution of chronic disease.

A program called Heartfile has been developed by Nishtar (Pakistan). Its purpose is to improve CV outcomes in less well-resources settings. Heartfile has laid out an economically and socially viable blueprint for health systems and community demonstration projects generating the evidence for advocacy and advocacy for chronic diseases.

Steyn (South Africa) pointed out that AIDs care is forcing poor countries to develop models for chronic disease care, which provides an opportunity to links that care for all patients with chronic conditions.

THE CHALLENGE OF DEALING WITH CHRONIC DISEASE

Falling death rates for CVD in developed countries over the last 30 years suggest that with an effective, well-funded action plan, large improvements can be made in developing countries.

Remuzzi established the correlation between poor health and poverty. Several speakers (Unwin, Zhao, Jamison) referred to the threat that chronic diseases cause to economic development through projected foregone national income. In China, WHO estimates US\$550 billion will be lost as a result of diabetes, heart disease, and stroke between 2005 and 2105.

Although few emerging countries have the resources to deal with chronic disease, the large international agencies have concentrated solely on communicable diseases. Over the past 5 years, the World Bank has provided US\$4.25 billion in loans to countries for health sector work, but only US\$106 million to non-communicable disease prevention and control programs.²⁴

With the exception of tobacco control, WHO spends 1/15 as much on chronic diseases as on communicable diseases in spite of its own Commission on Macroeconomics and Health (WHO, 1999) which recommended that developed countries should quadruple their donations to developing countries for health promotion.

An international strategy including governments, international agencies, international scientific societies, academic centers, foundations, and pharmaceutical companies is required. Remuzzi pointed out that the latter are the most profitable economic sector (18.6% as compared to 11.7% for telecommunications, the next highest)²⁵ led by drugs for chronic vascular diseases. Given that they are not included in the Millennium Development Goals, Remuzzi urged the creation of a Global Fund to fight chronic diseases. Such a fund must be used to activate or implement prevention/education programs and increase capacity, particularly at the primary care level. Remuzzi suggested that creating centers of excellence within emerging countries would be an appropriate approach.

Paehler described the research and policy direction for chronic diseases announced by the European Commission,²⁶ which has established health as one of nine thematic priorities. The three pillars underlying their program include (a) biotechnology, generic tools and technologies for human health, (b) translating research for human health, and (c) optimizing delivery of health care to European citizens.

Bengoa (WHO) said, 'Let's get beyond the documentation of the chronic disease burden. It's insufficient to bring about change'. He presented on the need for refined health-care systems that will respond better to chronic disease by intervening across the entire disease continuum, bringing together public and clinical perspectives and implementing evidence-based models of care (i.e. connect broader population upstream intervention (primary and secondary care) on populations with downstream intervention on individuals).²⁷ The system must treat the patient continuously and not sporadically. A study on shortfalls in care for diabetes (blood sugar not normalized for 24%) showed 26 000 going blind and 29 000 with kidney failure. Similarly, in hypertensive patients (where less than 65% received appropriate care), the toll was 68 000 deaths.²⁸

Where there are health-care providers with defined goals, outcomes appear to be improved. An excellent example is the Washington State Collaboratives.²⁹

Bengoa concluded by stressing sharper asset planning to build an integrated system for diabetes, CVD, and kidney disease. The skill is to take the coalition of special societies and work out a single system for chronic vascular care.

Advocacy and awareness building are necessary precursors to any program for prevention, particularly in developing countries. International medical societies are uniquely positioned to play an effective role because of their global membership networks, international partnerships, screening and intervention studies, establishment of practice guidelines, and their long-term commitments within the developing world. ISN (Couser) with over 8000 members is affiliated with 70 national societies; World Heart Federation's network involves 186 national society and foundation members in 100 countries; International Society of Hypertension has 800 members in 64 countries; International Diabetes Federation is an umbrella organization of over 190 diabetes organizations; and International Atherosclerosis Society has 55 member societies worldwide.

CONCLUSION

The focus of the Bellagio meeting was encapsulated by two questions posed during its very first session: (1) why are we not moving towards more assistance for chronic diseases, and what can this group do about it; and (2) what is the right policy response to increasing numbers of people needing treatment for chronic diseases? (This meeting created a platform for a more integrated approach to vascular diseases. The participants resolved to work jointly and to collaborate on developing a 5-year plan to increase prevention activities including formal goals, a strategy, and a time line with milestones to assess progress. Stroke-associated societies should also be included.

There was a clear consensus that chronic diseases have been underfunded by international agencies and have lacked advocates to bring them to the world's attention. Yusuf said the mindset to date, which must be changed, has been to fund either chronic diseases or communicable diseases but not both. Furthermore, all agreed that tackling the risk factors rather than the diseases themselves would yield better results. The meeting ended on a note of high optimism that such an approach can be effective when a number of organizations collaborate to work towards an integrated approach to chronic vascular diseases.

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