

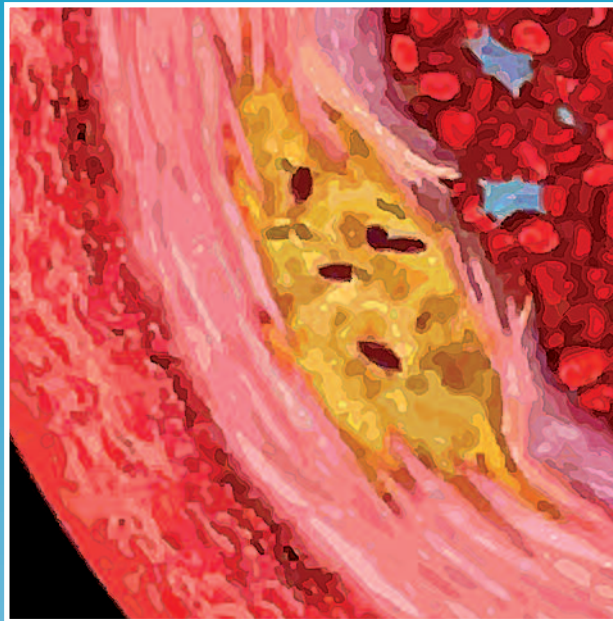


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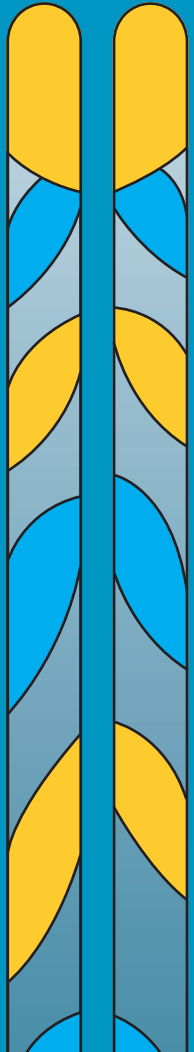
Conrado J. Estol
Marcelo Sánchez Sorondo

Atherosclerosis: The 21st Century Epidemic

*The Proceedings of the Working Group
31 May-1 June 2010*



VATICAN CITY 2011



Atherosclerosis: The 21st Century Epidemic

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*The Proceedings
of the Working Group on*

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Marcelo Sánchez Sorondo



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The opinions expressed with absolute freedom during the presentation of the papers of this meeting, although published by the Academy, represent only the points of view of the participants and not those of the Academy.

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PONTIFICIA ACADEMIA SCIENTIARVM • VATICAN CITY



In carrying out its distinctive service, the Pontifical Academy of Sciences always relies on the data coming from science and the Magisterium of the Church. In particular, concerning the present study group [on *The Signs of Death*], Christian Revelation also invites the man of our times, who in many ways seeks the real profound meaning of his existence, to face the theme of death casting his eye beyond human reality in its purest form and opening his mind to the mystery of God. Indeed, it is in the light of God that the human creature better understands himself and his final destiny, the value and meaning of his life, a precious and irreplaceable gift of the almighty Creator.

Benedict XVI, Letter dated 8 September 2006 to his venerated Brother H.E. Msgr. Marcelo Sánchez Sorondo, Chancellor of the Pontifical Academy of Sciences, concerning the working group on *The Signs of Death*, 11-12 September 2006.







Contents

Introduction	
H.E. Msgr. Marcelo Sánchez Sorondo, Conrado J. Estol	11
Programme	16
List of Participants	19
<i>Scientific Papers</i>	
▸ WORLD HEALTH ORGANIZATION: EPIDEMIOLOGY	
Epidemiology, Global Public Health; The Need for Equitable Action to Address Cardiovascular Diseases	
Shanthi Mendis	23
▸ DIABETES AND OBESITY	
The Importance of Diet, Obesity and Type II Diabetes for Vascular Disease	
Arne Astrup	37
▸ HYPERTENSION	
Hypertension: Why is it Poorly Detected and Poorly Treated?	
Conrado J. Estol	51
▸ LIPIDS	
Lipids: HDL, LDL, Role in Primary Prevention, the Message from Trials?	
Terje R. Pedersen	65
▸ RESEARCH NIH	
Vascular Disease: Ongoing National Institute of Health Research & Resources	
Walter J. Koroshetz	77
▸ HEART DISEASE	
Acute Myocardial Infarction: A Century of Progress	
Eugene Braunwald	89

Genetic and Environmental Factors for Ischaemic Heart Disease Attilio Maseri.....	99
Surgical Options in Myocardial Insufficiency Felix Unger.....	105
Cardiovascular Disease: From Treatment to Promoting Health; A Challenge for the Next Decade Jason C. Kovacic and Valentín Fuster.....	108
▮ CEREBROVASCULAR DISEASE	
Acute Stroke Treatment: A Window of Opportunity Werner Hacke.....	119
Frustrations in Cerebrovascular Disease Allan H. Ropper.....	132
Antiplatelet Agents, Anticoagulants: New Medical Strategies Geoffrey A. Donnan.....	135
Vascular Cognitive Impairment: An Overview John T. O'Brien.....	140
Cerebrovascular Disease: Lessons from the Past for the Near Future Louis R. Caplan.....	151
▮ STATEMENT	
Atherosclerosis: The 21st Century Epidemic - Concluding Statement Conrado J. Estol, Marcelo Sánchez Sorondo, Pierre Amarenco, Arne V. Astrup, Eugene Braunwald, Louis R. Caplan, Geoffrey A. Donnan, Valentín Fuster, Werner Hacke, Walter J. Koroshetz, Attilio Maseri, Shanthi Mendis, John T. O'Brien, Terje R. Pedersen, Allan H. Ropper, Felix Unger.....	171
Tables	177

Introduction

The Pontifical Academy of Sciences, whose purpose is to promote the progress of the sciences for the common good of the human person, in its Study Week of 31 May – 1 June 2010 at its headquarters in the Vatican, would like to focus on the wellbeing of the vascular system, taking into account the revolutionary contributions of the last century in relation to the human heart and brain.

Vascular Disease accounts for 15 million deaths per year worldwide. This represents 30% of all causes of mortality. Most vascular deaths are secondary to brain and heart infarctions. Stroke (cerebrovascular disease) ranks as 1st, 2nd and 3rd cause of death depending on the country or world region. Public recognition of cerebrovascular disease lags significantly behind identification of coronary artery disease.

Risk factors for Vascular Disease: known and treatable...

Genetic predisposition, hypertension, diabetes, cholesterol, smoking, lack of exercise and obesity are the main risk factors that predispose to the occurrence and progression of atherosclerosis.

Increased blood pressure causes heart, brain and kidney disease and accounts for 13% of all deaths worldwide. Hypertension is easily identified and treatable, yet only 2 out of 3 patients are diagnosed and up to 80% of those diagnosed are treated but do not reach target blood pressure goals. Hypertension accounts for 54% of stroke and 47% of coronary heart disease deaths. With 1 billion people affected, the prevalence of hypertension is increasing worldwide. Against deeply rooted medical traditions, recent data has shown that patients older than 80 years also benefit significantly from strict blood pressure management.

Actively screening and treating hypertension, cholesterol and diabetes are justified since more than 50% of vascular deaths are due to few risk factors. Moreover, different studies have shown that coronary heart disease and stroke share the same risk factors. Importantly, the most important vascular risk factor is a previously suffered vascular event. This emphasizes the importance of stringent medical treatment of conventional and other vascular risk factors once a cardiac, cerebral or other vascular event has occurred. Data from the Framingham study has shown that, counter intuitively, most vascular events occur in people with a moderate load of vascular risk factors.

How is Vascular Disease distributed throughout the world?

In low income countries, Vascular Disease accounts for 80% of all deaths (11 million per year). In these regions, cardiovascular disease occurs 1 to 2 decades earlier compared to developed countries. Sadly, because of a high case fatality rate, prevalence of cardiac and cerebrovascular disease in developing areas is lower compared to the developed world.

Epidemiological studies from developing regions are scarce and often of limited reliability. Good epidemiology studies are costly, complex and demanding and resources in developing countries are limited. The details on the distribution and characteristics of Vascular Disease in the developing world are needed to identify the areas in greater need to distribute resources accordingly. Surveillance data helps countries to develop, implement and monitor prevention programs.

If Governments do not include health policy changes in their agendas, in the next five years non communicable Vascular Diseases will overcome infectious diseases (TB, HIV and malaria) as the number one cause of death in countries such as India and China. In the latter, there are about 300 million smokers, 160 million hypertensive people and 20% obese children between 7 and 17 years of age, something unknown to this region in the past.

Cognitive decline: a major health burden caused by Vascular Disease

Dementia poses a large burden of disease worldwide. Cerebral vascular injury causes cognitive impairment and dementia with a frequency similar to degenerative dementia. For a given load of neuropathology findings of Alzheimer's disease, the presence of cerebrovascular disease correlates with earlier clinical manifestations. Some authors have speculated and provided data to support that hypertension results in decreased cerebral blood flow in brain structures commonly affected by Alzheimer's disease predisposing a vulnerable state for the development of degenerative dementia. Increased blood pressure and cholesterol in the 4th and 5th decades of life correlate with dementia onset in the 7th decade.

There is a major 'implementation' problem by which the known measures and medications to prevent vascular disease are largely under-used

Prevention is the first step in the cure for Vascular Disease. Yet, there is a major gap between knowledge and the implementation of measures for primary as well as secondary Vascular Disease prevention. Effective treatments for the acute and chronic phases of coronary and cerebrovascular disease are largely underused. The scientific community and Governments through

their Ministries of Health are responsible for the effective implementation of policies that achieve lower smoking rates, increased physical activity, healthy eating habits, and high detection rates for hypertension, diabetes, abnormal lipids and other vascular risk factors. Stroke Units, proven effective by scientific evidence, should be available in most clinics/hospitals with Coronary Units.

There is no doubt that significantly more interest is devoted to acute and invasive techniques compared to prevention. And it is paradoxical that patients have artificial heart valves inserted with endovascular techniques and cerebral clots removed with cork-screw like devices, among other novel techniques, but various studies have shown that patients are frequently discharged from hospitals following a vascular event without the adequate dose of anti-thrombotic, anti-hypertensive or cholesterol-lowering medications. However, a measure as simple as counseling during hospitalization has been proven to increase adherence to treatment after discharge from the hospital. The general public and physicians need to be educated on the importance of vascular disease prevention. This teaching takes time but it is most effective when it starts as early as childhood. Healthy young adults must understand that a vast majority have vascular risk factors that justify treatment in the asymptomatic stage.

The challenge: effective prevention of Vascular Disease

The knowledge on Vascular Disease that has accumulated over the last decade is greater than that gained in the entire previous century. Commitment with Vascular Disease prevention has resulted in a 70% death reduction in the USA, Canada, Australia and the UK. Primary prevention provides an invaluable opportunity for early intervention. Unfortunately, data shows that the people at highest risk have the lowest knowledge about Vascular Disease. In one study following an education campaign in the year 2000, respondents could only name one warning sign of stroke. In one survey in India, close to 50% of respondents did not know that the brain is the affected organ in stroke. In countries from Africa and Latin America, up to 50% of patients go to alternate medical healers before consulting in a hospital. As an example, only 50% of people diagnosed with atrial fibrillation receive anticoagulants and just 1% of patients are treated among those who are candidates to receive thrombolytic therapy in the first few hours after occlusion of a cerebral vessel.

The pharmaceutical industry is a major player in the Vascular Disease battle. Many subsets of the world's population could benefit from a 'polypill'

simultaneously targeting various vascular risk factors. Among the important achievements to be expected in this sector is the production of affordable medications through the conduction of affordable trials. Large amounts of money are invested by the pharmaceutical industry and biotechnology companies in research and development of new therapeutic molecules. The scientific community should increase the interaction with the industry and influence the research lines likely to have a novel and higher therapeutic yield.

Conclusions

If the Vascular Disease burden could be reduced 2% per year, 36 million untimely deaths could be avoided by the year 2015. The World Health Organization has provided data showing that 80% of cardiac events and strokes could be reduced with diet, physical activity and smoking cessation. There is also data proving that 80% of stroke risk would be reduced with adherence to practice guidelines. A wealth of studies has proven the effectiveness of cardiac and stroke units. Yet, with the exception of a few developed countries heading in this direction, results in most world regions drift far from these projections.

In summary, preventive measures that should begin during childhood are needed to educate individuals on how to avoid the most common risks of Vascular Disease. In addition to the former, disease specific information should be provided to the population as a whole. Behavioral changes at the community level could be expected following effective education and information programs. Active Government participation and commitment with the appropriate health policies are a sine-qua-non to achieve these goals. The Health System, Unions, and other health players should understand the social and financial benefits of Vascular Disease screening and prevention programs.

Vascular Disease is the field of interest for Cardiologists, Vascular Neurologists, Diabetes, Lipid, Genetics and Nutrition experts, Epidemiologists, Vascular Surgeons, and Endovascular specialists. They all have an increasingly larger number of specialty meetings and seldom participate in strongly integrated conferences. Pulling the rope in the same direction will surely increase the yield in the battle against Vascular Disease. A closer cooperation among the different vascular specialties should be encouraged and the integrated meeting of most vascular disciplines at the Pontifical Academy of Sciences is a significant contribution to this endeavor.

The moral imperative of our meeting is to make people and private and public institutions, at the national and international level, aware, as was done in the case of alcoholism, drug addiction and smoking, that most risk factors are either under treated or simply not treated, and convince them to adopt adequate precautions in order to avoid premature death or survival with physical and/or mental impairments.

■ + MARCELO SÁNCHEZ SORONDO, CONRADO J. ESTOL

Programme

► MONDAY, 31 MAY 2010

8:30 *Introduction and Welcome*

World Health Organization: Epidemiology

9:00 *Epidemiology, Global Public Health; The Need for Equitable Action to Address Cardiovascular Diseases*
Shanthi Mendis

Diabetes and Obesity

9:45 *The Importance of Diet, Obesity and Type II Diabetes for Vascular Disease*
Arne Astrup

Hypertension

10:30 *Hypertension: Why is it Poorly Detected and Poorly Treated?*
Conrado Estol

11:15 Coffee break

Lipids

11:45 *Lipids: HDL, LDL, Role in Primary Prevention, the Message from Trials?*
Terje R. Pedersen

Research Nih

12:30 *Vascular Disease: Ongoing National Institute of Health Research & Resources*
Walter Koroshetz

13:15 Lunch at the Casina Pio IV

Heart Disease

15:00 *Acute Myocardial Infarction: A Century of Progress*
Eugene Braunwald

15:45 *Genetic and Environmental Factors for Ischaemic Heart Disease*
Attilio Maseri

16:30 Coffee break

- 17:00 *The Heart and the Brain: AF, CHF, PFO, the Aorta*
Pierre Amarenco
- 17:45 *Surgical Options in Myocardial Insufficiency*
Felix Unger
- 18:30 *Cardiovascular Disease: From Treatment to Promoting Health; A Challenge for the Next Decade*
Valentin Fuster
- 19:15 General Discussion
- 20:15 Dinner at the Casina Pio IV

► **TUESDAY, 1 JUNE 2010**

Cerebrovascular Disease

- 8:00 Guided tour of the Vatican Museums, including the Sistine Chapel
- 9:00 *Acute Stroke Treatment: A Window of Opportunity*
Werner Hacke
- 9:45 *Frustrations in Cerebrovascular Disease*
Allan Ropper
- 10:30 *Antiplatelet Agents, Anticoagulants: New Medical Strategies*
Geoffrey Donnan
- 11:15 Coffee break
- 11:45 *Vascular Cognitive Impairment: An Overview*
John O'Brien
- 12:30 *Lessons from the Past for the Near Future*
Louis R. Caplan
- 13:15 Lunch at the Casina Pio IV
- 14:15 Round Tables
- Top 5 priorities for the next 5 years
 - Focus on:
 - Education/Cultural
 - Health Politics
 - Medical Goals: Polypill
 - Low Income/High Income Countries

- 18:00 Departure from the Casina Pio IV by bus to attend the concert at Prince Boncompagni's residence at Villa Aurora
- 19:00 Private concert of baroque music offered to the participants by Prince Boncompagni at his residence
- 22:00 Bus leaves Prince Boncompagni's residence to take participants back to their hotels

► **WEDNESDAY, 2 JUNE 2010**

- 9:30 *General Audience with the Holy Father. Open to all Participants.*

List of Participants

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Chairman, TIMI Study Group
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Boncompagni-Ludovisi**

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Property Developer
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President, European Academy
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(Austria)

Scientific Papers

► WORLD HEALTH ORGANIZATION: EPIDEMIOLOGY

EPIDEMIOLOGY, GLOBAL PUBLIC HEALTH; THE NEED FOR EQUITABLE ACTION TO ADDRESS CARDIOVASCULAR DISEASES

■ SHANTHI MENDIS

The magnitude of the cardiovascular disease burden

Cardiovascular diseases (CVD) are responsible for nearly 50% (17.3 million) of deaths due to noncommunicable diseases (NCDs) (Table) [1]. Out of the 17.3 million deaths, heart attacks and strokes account for 7.3 million and 6.2 million respectively. Projected estimates reveal that in 2030 coronary heart disease and cerebrovascular disease will continue to be the leading causes of the global disease burden [1]. Cardiovascular diseases once associated with affluence are now increasingly affecting low income groups due to the reversal of social gradients of risk factors including tobacco use [1–4]. Although almost 80% of the CVD burden is in low and middle income countries (LMIC) (Table 1) policy makers do not seem to give adequate attention to them, partly due to the unfortunate misconception that no affordable solutions are available.

Powerful global forces are shaping the health and disease profiles in the world. Ageing, rapid unplanned urbanization, and the globalization of unhealthy lifestyles such as tobacco use, unhealthy diet, inadequate physical activity and harmful alcohol use are increasing the prevalence of major metabolic risk factors; blood pressure, blood sugar and blood cholesterol. These risk factors are mostly asymptomatic. They are detected late only when they present to health facilities with complications such as heart attacks, strokes, heart failure, renal failure and amputations. This is the case particularly in disadvantaged groups who have inadequate access to health

DALYS	Low Income	Middle Income	High Income
Cardiovascular diseases	57,258	76,204	17,583
Cancer	18,982	40,975	17,826
Respiratory diseases	22,706	29,045	7,266
Diabetes	5,991	10,080	3,623

Table 1. The disease burden due to cardiovascular disease and other major noncommunicable diseases in high, middle and low income countries (DALYs thousands 2004).

care [5]. The resulting costs to individuals, families and the productivity of the society are high and are unacceptable but avoidable [5,6].

Developing countries have the greatest vulnerability and the least resilience. They have limited capacity to cope with CVD. Attention paid to CVD is minimal partly due to competing health priorities such as communicable diseases and maternal and child health that consume most of the meagre resources available for health care. Rising CVD trends also have a negative impact on poverty-reduction strategies as out of pocket expenditure and catastrophic costs of treatment for heart attacks, strokes and other complications drive many households below the poverty line each year. In addition, the fast growing CVD epidemic is also an impediment to economic development due to its impact on labour productivity and escalating public sector expenditure on health [7].

What needs to be done to address the cardiovascular epidemic?

There are evidence-based primary prevention interventions available to reduce behavioural and metabolic risk factors both at population and individual levels. They are cost effective and are applicable to LMIC [3,5,8]. Very cost-effective interventions are also available for prevention of recurrent cardiovascular events in those with disease [5,9]. All these interventions have been implemented effectively in many developed countries resulting in a downward trend in coronary heart disease mortality [10]. In developed countries, frameworks for addressing cardiovascular disease recognize the importance of prevention approaches and primary care as well as the contribution of the more specialized services. They offer a range of actions to help people so that they can avoid getting heart disease and stroke. In addition they provide high quality treatment and care for those who develop coronary heart disease or cerebrovascular disease including early diagnosis, prompt and effective ambulance and emergency services, high quality nursing, medical, surgical, specialist services including vascular surgery and rehabilitation.

Providing such a comprehensive framework is beyond the reach of LMIC due to limitations in resources, health systems and the health workforce. As a result, at present, many LMIC focus primarily or only on the care of acute cardiac or vascular events or complications of CVD. These patients usually have advanced disease that require sophisticated and costly technologies and treatment. Prevention and simple inexpensive interventions which can be implemented in primary care are thoroughly under-utilized. As a result of this short-sighted approach LMIC are experiencing upward spiralling of their health care budgets particularly due to hospital care.

The only lasting solution for the cardiovascular epidemic is one that is grounded in public health. Such an approach has to modify and monitor behavioural risk factors and determinants that lie outside the health sector. People have to be provided enabling environments and opportunities for healthy eating and physical activity [11]. Deterrents for tobacco use and harmful use of alcohol need to be embedded in policy actions such as banning of advertising and levying tax on these products [12,13]. In addition universal access to at least essential cardiovascular interventions needs to be ensured through a primary health care approach [5,14].

Global action and roadmap to address cardiovascular disease

The mandate of the World Health Organization is to strengthen the capacity of all countries to realize the full potential of CVD prevention and curtail unnecessary human suffering caused by disease through equitable and sustainable policies and disease control programs.

An action plan for implementation of a Global Strategy for prevention and control of NCDs including CVD was endorsed by the World Health Assembly in 2008 [2,4]. It provides a roadmap for the work of the World Health Organization, its Member States and international partners. The six main objectives and progress in the implementation of the Global Action Plan are outlined below.

Objective 1. Embedding NCD/CVD prevention in the development agenda, and in policies across all government departments.

The World Health Organization (WHO) is joining efforts with all partners to get NCD/CVD on the global health and development agenda. Regional Ministerial Meetings were held in Beijing, in April 2009 and in Qatar, in May 2009. At the latter meeting the Doha Declaration was issued which called for 'raising the priority accorded to NCDs on the agendas of relevant high level meetings of national, regional, and international leaders'. The Economic and Social Commission (ECOSOC) Ministerial Roundtable Meeting on NCDs was held at the ECOSOC High-level Segment on Global Health held in Geneva in July 2009. In addition, at the Commonwealth Heads of Government Meeting in Trinidad and Tobago in November 2009, a statement was issued on Commonwealth Action to combat NCDs.

More recently, the United Nations General Assembly Resolution A/RES/64/265 was adopted in May 2010, which calls for specific actions to address NCDs including convening a high-level meeting of the General Assembly in September 2011, with the participation of Heads of State and Government. The UN resolution further requests the Secretary-General to

submit a report to the General Assembly at its sixty-fifth session in collaboration with Member States, the World Health Organization and the relevant funds, programmes and specialized agencies of the United Nations system, on the global status of NCDs, with a particular focus on the developmental challenges faced by developing countries.

Objective 2. Establishing and strengthening national policies and programmes

WHO is promoting integrated NCD policy frameworks in alignment with national health strategies. National programs with performance targets are been established under these overarching policy frameworks for monitoring of risk factors, early assessment of cardiovascular risk and management of CVD/NCDs. A package of essential NCD interventions and the Global Price Tag for its implementation are been developed.

Objective 3. Reducing and preventing risk factors

Prevention of behavioural risk factors is a public health priority reflected in the global public health instruments such as the Framework Convention on Tobacco Control (FCTC) [11] and global strategies for Diet, Physical Activity and Health [12] and against the harmful use of alcohol [13]. They call for appropriate policy actions and intersectoral approaches to curb the rising trends in tobacco and alcohol use and obesity. The WHO Framework Convention on Tobacco Control (WHO FCTC) [12] is a regulatory strategy to reduce the demand for tobacco (through price, tax and other measures) and to address supply issues such as illicit trade, sales to minors, and economically viable alternatives to tobacco. The WHO FCTC has 168 Signatories and many countries have shown good progress in tobacco control through its implementation.

There is strong evidence of the link between intake of *trans* fat, high salt consumption, low consumption of fruits and vegetables and CVD [12]. Strategies to reduce population-wide salt and *trans* fat intake are cost-effective and applicable worldwide [12,2,4]. The average daily salt consumption in most populations exceeds recommended amounts [15]. WHO is providing guidance to Member States to interact and negotiate with food manufacturers to reduce salt in processed food. Many developed countries are actively pursuing policies for reducing consumption of industrially produced *trans* fat and salt [15,16].

Objective 4. Prioritizing research on prevention and health care

There is a clear need for bridging gaps in knowledge about what works in NCD prevention and control. A prioritized research agenda which addresses

the priority needs of CVD prevention and control will be finalized in 2010 [17]. The aim is to provide guidance to developing countries on implementation research for effective translation of already available scientific evidence.

Objective 5. Strengthening partnerships

The recently established global NCD network (NCD net) and NCD alliance have facilitated partnership processes across diseases linking CVD advocates with their colleagues from cancer, diabetes and lung diseases, to jointly be more effective. The main goals of the network are to promote innovative resource mobilization and strengthen country capacity for implementation of the global NCD action plan.

Objective 6. Monitoring

Accurate data on CVD risk factors and mortality are not available in a significant number of LMIC. Reliable information on NCD mortality and risk factors are required to measure trends in risk factors and diseases and also as a yardstick for evaluating the impact of national NCD/CVD programs. Country capacity is being strengthened to collect information on a few reliable indicators that can be accurately measured over time through institutionalization of monitoring and evaluation programs. This is essential for accountability of all stakeholders.

Primary prevention of coronary heart disease and cerebrovascular disease

Prevention is the most sustainable solution for CVD, particularly in LMIC. However, most countries invest very little on prevention as the results of prevention are not immediately visible.

Primary prevention should receive the highest priority, because of the high case fatality and debilitating outcomes of heart disease and stroke [8]. There are two complimentary approaches for primary prevention of CVD which have synergistic effects: a) Population-wide approaches to reduce risk factors (tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol). These public health programs will have the best chances of success if they are part of a coordinated prevention effort to address major NCDs, under the stewardship of the Ministry of Health. b) Approaches for early detection and management of those at high cardiovascular (stroke) risk. Population-wide primary prevention has been shown to be very cost-effective. Early detection and care of those at high risk of heart disease and stroke is also cost-effective and affordable to LMIC when a total risk approach is used for treatment decisions [3,8]. This calls for a paradigm shift from vertical programs targeting single risk factors which are not cost-ef-

fective, to a total risk approach. Risk stratification can be based on risk factors that are measurable in low resources settings e.g. age, gender, tobacco use, blood pressure, blood glucose and blood cholesterol [18]. WHO has developed WHO/ISH risk prediction charts to enable this approach to be implemented worldwide.

Population-wide interventions alluded to above are highly cost-effective and include tobacco control and actions to promote a healthy diet and physical activity [3,8,9]. WHO's Framework Convention on Tobacco Control [11] and the Global Strategy for diet, physical activity and health [12] provide guidance to countries on tobacco control and life course action related to diet and physical activity. These prevention activities also prevent other major NCDs; cancer, diabetes and respiratory disease and need to be implemented in a coherent and coordinated manner within and overarching national NCD policy [19].

Primary prevention interventions targeting individuals include pharmacological and nonpharmacological interventions to lower cardiovascular risk through tobacco cessation, blood pressure, blood sugar and cholesterol lowering agents [8]. These evidence-based interventions are cost-effective particularly when targeted at high risk groups. Even in primary care settings in LMIC risk prediction charts with simple variables can be used for risk stratification and provision of treatment based on the degree of risk [5].

Acute care and secondary prevention of CVD

Evidence-based interventions are available for reducing complications and mortality from transient ischemic attack, unstable angina, acute myocardial infarction and stroke. These interventions are not accessible to many in LMIC due to limitations in the health systems.

Same is true for secondary prevention measures which are effective in reducing recurrent heart attacks and strokes [9]. All people with suspected TIA or unstable angina need referral for specialist care.

Challenges to prevention and management of CVD in LMIC

What should be done to address the CVD epidemic is clear, based on available research evidence and lessons learned in developed countries. However, more work is required to have clarity on *how* it should be done in order to overcome multiple challenges that are the reality in LMICs. There are many causes for these complex challenges. They include resource constraints, competing public health priorities (communicable diseases, maternal and child health, HIV/AIDS, disasters and emergencies, and violence and injuries) and limited capacity of the health workforce and the health

systems. In this context-innovative and context-specific approaches are required for application of *what is known*. As there are no short-term solutions to CVD, long-term sustainability and affordability of programs should be prime concerns in establishing CVD programs in LMIC. Sustainability could be best achieved through domestic capacity strengthening, domestic investment, integration of CVD programs within overarching NCD frameworks and institutionalization.

Health workforce need to trained to develop skills and competence to deliver quality health care. In addition the capacity of Ministries of Health need strengthening. In many developing countries there is only one focal person to address NCDs, whereas Ministries require a multidisciplinary team for this purpose. The composition of the team needs to be such that there is a skill-mix for a range of functions required for NCD prevention and control including policy formulation, implementation, intersectoral collaboration, regulation, legislation, advocacy, partnerships and monitoring and evaluation.

The majority of people in LMIC have no health insurance and spend out of pocket for health [14]. In such settings strokes and heart attacks result in loss of employment as well as catastrophic spending on health care. Acute care of cardiovascular events requires early identification of eligible patients by health care workers and their urgent transfer to expert treatment centers. Thrombolysis, if indicated, and aggressive supportive care need to be provided in emergency care units. These centers also need to offer imaging, admission to a cardiac or stroke care unit, and access to a specialist. Many LMIC are ill-equipped to provide such care. Further, many people die before they ever get to a hospital due to difficulties of access and lack of organized ambulance and paramedical services. Thrombolytic therapy is costly and is unaffordable to the majority who are uninsured. Even if thrombolytic therapy and acute coronary and stroke care is made available at public costs, most patients seen in emergency departments in LMIC are unlikely to be eligible for thrombolysis because of delay in seeking care due to lack of awareness or lack of access [20]. In addition, lack of trained staff, poor access to imaging facilities and shortage of public health sector funds make it difficult to provide these services on a national scale in LMIC [21].

Feasible approaches for prevention and management of CVD in LMIC

The realities alluded to above that prevail in LMIC reiterate the urgent need for affordable prevention and control of heart attacks and stroke. Emphasis needs to be given to upstream public policy measures for prevention, population (school, community and worksite) based prevention programs,

intersectoral collaboration to create conducive policy and environment for behaviour change, ensuring consumer access to information, early diagnosis at first contact level, improving clinical practice patterns in primary care, strengthening provider and patient communication and promoting self-care.

The public need education on how to reduce the risk of CVD and on the importance of seeking prompt medical attention for CVD events and on self-care. Medical and health worker curricula need to be modified so that doctors and other health workers are trained and made aware of the importance of correct diagnosis, timely referral and evidence based-primary and secondary prevention of CVD.

Acute coronary and stroke care delivered by trained multidisciplinary teams in dedicated units may be too costly for wide implementation in LMIC. Other models need to be explored including 'mobile cardiac and stroke services' with multidisciplinary teams that manage heart attack and stroke patients in different wards in hospitals, provision of 'care' in medical wards by general physicians and their teams and telemedicine approaches.

Prevention and treatment of strokes and heart attacks require integrated programs in primary care. The metabolic risk factors, raised blood pressure, raised blood sugar and raised blood cholesterol are common to vascular disease of different vascular territories; stroke, coronary heart disease and peripheral vascular disease. Programs for primary and secondary prevention of these diseases can therefore be integrated into primary care [5]. Risk stratification, primary prevention and prevention of recurrences, are feasible, in primary care, even in LMIC [5,22]. Primary care workers can also be trained to detect and diagnose acute coronary syndromes, transient ischemic attacks and strokes, provide urgent treatment and refer for specialist assessment.

The use of multidisciplinary teams to implement a chronic care model as is done in some developed countries, is beyond the resources of most low income countries. Context specific service delivery models need to be developed to engage communities and to prioritize actions to suit local needs.

Given the social gradient of CVD, special attention is required to identify and rectify factors that increase vulnerability, exposure to risk and poor cardiovascular outcomes of disadvantaged segments of the population [23]. Explicit action is needed to address social inequalities in behavioural risk factors and access to and utilization of health services.

Conclusion

Programs for prevention and control of CVD in LMIC need to be integrated with the national NCD program and linked to the national health plan and strategy.

The key components of a national CVD program include:

1. A national CVD program within an overarching national NCD policy framework;
2. Survey of cardiovascular risk factors and a risk factor surveillance system institutionalised within the national health surveillance system;
3. A CVD prevention service integrated with NCD prevention focusing on implementation of the FCTC and initiatives for reduction of salt and elimination of *transfat* in processed foods;
4. School, worksite and community health programs to reduce risk factor levels by making structural changes and establishing incentives to promote physical activity and a healthy diet (e.g. intake of fruits and vegetables and reduction of salt and saturated fat);
5. Integrate evidence-based and cost-effective primary and secondary prevention interventions into primary care as part of a core set of NCD interventions
6. Early detection of high risk people in worksites and communities using easily measurable risk factors and risk stratification systems;
7. Public education campaigns to create awareness of risk factors of heart attacks and stroke and symptoms of acute coronary events, TIA and stroke;
8. Evidence-based clinical practice for management of people with high cardiovascular risk, acute coronary syndromes, angina, TIA, acute stroke and cardiac and stroke rehabilitation;
9. Strengthened capacity in acute coronary and stroke care and stroke rehabilitation services;
10. Assessment (and modification) of the impact of government policies on CVD and NCDs, e.g. policies related to transport, trade, finance, education and sports, agriculture and food.

Finally, health including cardiovascular health is a right of every human being and not a commodity to be bought, sold or provided merely on a charitable basis. In this context human rights implications of health and non-health sector policies require scrutiny. Government policies of all sectors need to be health promoting and not damaging to health, particularly to population groups considered most vulnerable in society, e.g. children, elderly and the poor.

The ingredients of a right-based approach to health are well recognized. Yet, in the area of CVD/NCDs human rights are violated on a daily basis, e.g. health damaging products are sold to minors and the illiterate while multinational companies make unethical profits and sick people are left to

die because they do not have access to essential CVD interventions and medicines [24]. Governments, development agencies, international organizations, religious establishments, the private sector and commercial entities have an obligation to act to alleviate this situation.

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DIABETES AND OBESITY

THE IMPORTANCE OF DIET, OBESITY AND TYPE II DIABETES FOR VASCULAR DISEASE¹

■ ARNE ASTRUP

Summary

Obesity, the metabolic syndrome, pre-diabetes and type 2 diabetes are important risk factors for the development of coronary artery disease and stroke (cardiovascular disease, CVD). Obesity, physical inactivity, diet composition, short sleep duration and smoking are the most important risk factors for type 2 diabetes; moderate alcohol and coffee consumption exert a weak protective effect. Excessive body weight together with inactivity can account for almost 90% of all new cases of type 2 diabetes. So prevention and treatment of weight gain, excessive body weight, and the metabolic syndrome, are the cornerstones of prevention of type 2 diabetes.

The major risk factors for weight gain and obesity are a sedentary lifestyle with little physical activity, impaired or short sleep duration, and an inappropriate diet. The dietary risk factors are large portion sizes, sugar-rich soft drinks, and high intakes of energy-dense foods poor in fibre and whole grain, including low intakes of fruit and vegetables. The optimal diet for prevention of weight gain provides 20-25% of energy from protein (low-fat meat, game, dairy products, fish, shellfish, and plant protein from peas, beans etc.), 25-30% of energy from fat (high ratio of polyunsaturated to saturated), and 45-55% from fibre-rich, whole-grain carbohydrates characterised by a low glycemic index. Moderate amounts of alcohol from beer and wine contribute to the prevention of type 2 diabetes and CVD, but should be recognised as contributors to total energy intake. The diet recommended for the prevention of obesity and type 2 diabetes is fortunately the same as that considered optimal for the prevention of CVD.

Introduction

On a population level, epidemiological studies suggest that a healthy lifestyle with no tobacco smoking, avoidance of excessive alcohol consumption, adequate sleep, regular physical activity, an ideal body weight, and a

¹ Essential parts of the manuscript are based on a modification of a book chapter: Astrup A. A healthy lifestyle and cardiovascular risk reduction. In *Metabolic Risk for Cardiovascular Disease*. Ed. R.H. Eckel. American Heart Association 2010.

healthy diet, can reduce the risk of cardiovascular disease by up to 85–95%. Figure 1 (see p. 179) depicts the environmental factors that influences the risk of weight gain, obesity & type 2 diabetes.

Adequate treatment of risk factors would add ~221 million life-years and 244 million quality-adjusted life-years to the US adult population, or an average of 1.3 years of life expectancy for all adults. To achieve this, an intensive management is required, targeting the individual, as well as major changes in the toxic environment that tends to maintain unhealthy habits.

The present paper will focus on diet, smoking, impaired sleep and physical activity as risk factors for obesity and type 2 diabetes, which are major causes of CVD in this millennium. There is robust evidence that a large proportion of the cardiovascular disease seen today can be prevented by a generally healthier lifestyle in the population as a whole, and by targeting lifestyle change and medical management of cardiovascular risk factors in high-risk individuals (1). The high prevalence of obesity in most Westernized countries has important health consequences, and particularly abdominal obesity, increases the risk of several co-morbidities (Figure 2, see p. 179).

Prevention does not mean that CVD and death can be avoided, but rather that the onset of disease can be postponed and life expectancy prolonged. With the exception of smoking cessation, preventive lifestyle intervention will probably not save money on a societal level, as people will live longer and require medical care for other illnesses and extended social support. Effective prevention in the USA population could potentially reduce the incidence of MI by >60%, the incidence of stroke by ~30%, and increase life expectancy by an average of 1.3 years [1]. European studies have found that population-wide, best-practice interventions have the potential to reduce coronary heart disease mortality by 57%, and for primary prevention the corresponding reductions would be 75–85% [2]. This analysis did not, however, include the effect of weight reduction in the overweight section of the population, and prevention of weight gain by changed diet and exercise habits.

The potential impact of a healthy lifestyle on CVD

The most effective way to prevent CVD is to maintain a healthy lifestyle. Stampfer *et al.* defined low risk among adult women as those who were non-smokers, had a BMI below 25, consumed an average of half a unit of alcohol per day, engaged in moderate-to-vigorous physical activity for at least 30 min per day, and had a diet moderately high in cereal fiber, marine n-3 fatty acids, and folate, with a high ratio of polyunsaturated to saturated fat, and low in trans fat and glycemic load [3]. They found that only 3% of

the US population complied with this lifestyle, but that this 3% had a relative risk of coronary events of only 0.17 as compared to all the other women, and that 82% of coronary events could be attributed to lack of adherence to this healthy lifestyle.

General advice for the prevention of CVD and obesity

The diet for the prevention of CVD

A reduction of CVD can be achieved by modifying the diet to affect risk factors such as body weight and the components of the metabolic syndrome (LDL-cholesterol, postprandial triglycerides, blood pressure etc.). Diet plays an important role in achieving this goal. Previous analyses of the importance of saturated fat (SFA) for the development of CVD have overestimated its importance, and failed to compare foods rich in SFA with other relevant foods. From a recent consensus conference the following conclusions were reached [4]. Newer meta-analyses of observational studies have found that substituting polyunsaturated fat (PUFA) for SFA is associated with lower CHD risk, whilst substituting carbohydrate for SFA is associated with a moderately increased risk of CHD. Few studies have addressed the quality of carbohydrates. There is no evidence that monounsaturated fat (MUFA) is associated with CHD risk. Also the individual saturated fatty acids and the food matrix are important for cardiovascular risk. Despite having high contents of saturated fat, both dark chocolate and cheese have no negative impact on cardiovascular risk factors and can be part of a heart-healthy diet.

Industrially produced trans fat (TFA) is consistently associated with increased risk of CHD. On a gram for gram basis, TFA is associated with stronger risk than SFA, but the lowest risk is found for diets high in PUFA and low in TFA.

It is generally assumed that cheese, due to the high content of saturated fat, should be reduced in a diet that reduces cardiovascular risk. However, scientific evidence shows that the content of protein, calcium and other nutrients in the food matrix modifies the effect of saturated fat so the overall effect of cheese rather is cardioprotective [4] (Figure 3, see p. 180).

The evidence from epidemiological, clinical and mechanistic studies is consistent in finding that risk of CHD is reduced when PUFA replaces SFA. In countries following a 'western' diet, replacing 1% kJ of SFA with PUFA is likely to produce a 2-3% reduction in the incidence of CHD. Cohort studies find no evidence of lower risk of CHD when CHO replaces SFA. In fact, the evidence suggests a higher risk. The type of CHO is important. For ex-

ample, replacing SFA with CHO from wholegrain foods may lower the risk of CHD. The amount and type of carbohydrate are likely to have less effect on CHD risk in normally healthy and physically active individuals.

So what should we eat and drink to maintain a healthy body weight, and to prevent T2D & CVD? (Figure 4, see p. 180). The habitual diet should be low in industrially produced trans fat and saturated fats, sugar and salt, and contain plenty of fruit and vegetables (at least five portions a day), whole grain products and fish. Fish such as herrings, kippers, mackerel, pilchards, salmon, sardines and trout contain oils that can reduce the risk of thrombosis. Other foods that have a beneficial impact on CVD risk are beans, peas, lentils and oats, because they contain soluble fiber.

Regular aerobic (cardiovascular) exercise, for at least 30 minutes a day at least 3–4 times a week, has a beneficial impact on several CVD risk factors, and also helps to maintain a healthy body weight.

Diet for the prevention of obesity

Overweight and obesity, and in particular abdominal fat distribution, adversely affect several risk factors of CVD, and generate numerous other comorbidities (Figure 2, see p. 179), and weight reduction has been shown to decrease incidence and cardiovascular mortality in severely obese subjects. Obese individuals are known to be capable of losing weight, but weight maintenance is more problematic, so prevention of weight gain is a primary focus. The major risk factors for weight gain and obesity are a sedentary lifestyle with little physical activity, impaired or short sleep duration, and an inappropriate diet. The dietary risk factors are large portion sizes, sugar-rich soft drinks, high intakes of energy-dense foods poor in fibre and whole grain, and low intakes of fruit and vegetables (Figure 4, see p. 180). The optimal diet for prevention of weight gain provides 20–25% of energy from protein (low-fat meat, dairy, fish, shellfish, game, protein from plants; peas, beans etc.), 25–30% of energy from fat (high ratio of polyunsaturated to saturated), and 45–55% from fibre-rich, whole-grain carbohydrates characterised by a low glycemic index [5]. Moderate amounts of alcohol from beer and wine contribute to the prevention of type 2 diabetes and CVD, but should be recognised as contributing to total energy intake. The diet recommended for the prevention of obesity and type 2 diabetes is fortunately the same as that considered optimal for the prevention of CVD.

Smoking and alcohol

For smokers, giving up will reduce the risk of developing coronary heart disease by 50%. Smoking causes the majority of cases of coronary throm-

basis in people under the age of 50. Small amounts of alcohol may help to reduce CVD. However, excessive alcohol consumption increases blood pressure and risk of stroke, as well as several other health risks, and it is therefore advisable that individuals abide by public health recommendations regarding alcohol consumption. Health guidelines in the UK recommend that men consume no more than three to four units of alcohol a day, and that women do not exceed two to three units. Binge drinking should be avoided.

Blood pressure can be controlled by eating a healthy diet that is low in saturated fat, and high in fruit, vegetables, and low-fat dairy products, and by exercising regularly. In addition, avoiding smoking and excessive alcohol consumption assists in maintaining a normal blood pressure. Diabetics have a greater risk of developing CVD. The risk of developing type 2 diabetes can be reduced dramatically by maintaining a healthy body weight, being physically active, and by eating a healthy diet.

Multifactor interventions

For clinicians and their patients, studies addressing the total reduction in risk of CVD that can be achieved by a healthy lifestyle are more relevant than addressing each of the lifestyle components individually. However, the flip side of the coin is that these studies leave the contribution of each of the components uncertain. Regarding the primary prevention of CVD, larger intervention studies are obviously required to demonstrate a risk reduction, but observational epidemiological studies have suggested that dramatic health gains can be achieved. An analysis by Asaria *et al.* [6] found that 13.8 million deaths could be prevented over 10 years if measures to reduce tobacco and salt exposure were implemented. About three out of four deaths averted would be from cardiovascular diseases [6]. Hu *et al.* found that the incidence of coronary disease declined by 31% from 1981 to 1992, while the proportion of smokers declined by 41%, the proportion of postmenopausal women using HRT increased by 175%, and the prevalence of overweight increased by 38%. These factors could explain a 21% decline in the incidence of coronary disease, representing 68% of the overall decline. The reduction in smoking could account for a 13% decline in the incidence, improved diet could account for a 16% decline; and increase in HRT could explain a further 9% decline. However, the increase in overweight could account for an 8% increase in incidence in coronary disease [7].

Major benefits could also be achieved from secondary prevention of CVD. Ornish *et al.* [8] showed that intensive lifestyle changes (fat-reduced diet, aerobic exercise, stress management training, smoking cessation, group psychosocial support) for 5 years produced greater regression of coronary

atherosclerosis and fewer cardiac events than in a control group. An effect of comprehensive cardiac rehabilitation sessions was recently assessed in the randomized controlled GOSPEL trial in post-MI patients, comparing a long-term, reinforced, multi-factorial educational and behavioral intervention with usual care, including supervised aerobic exercise and lifestyle modification consisting of risk factor counseling about a Mediterranean diet, smoking cessation, and stress management [9]. The targets of the intervention strategy were smoking cessation, adoption of a healthy Mediterranean diet, increase in physical activity up to at least 3 h/wk at 60% to 75% of the mean maximum heart rate, and maintenance of BMI at <25 kg/m and blood pressure of <140/85 mmHg. After 3 years of observation there were only small improvements in most of the lifestyle variables, and these did not significantly reduce the primary end-point [9], though several secondary end-points were decreased: CV mortality plus nonfatal MI and stroke (3.2% vs 4.8%; HR, 0.67), cardiac death plus nonfatal myocardial infarction (2.5% vs 4.0%; HR, 0.64), and nonfatal MI (1.4% vs 2.7%; HR, 0.52). The intervention group still had plenty of room for further improvement in lifestyle, such as smoking cessation and weight gain prevention, and this emphasizes the potential for health benefits that can be achieved even in patients with established CVD.

Smoking

A smoke free environment is an important part of a healthy lifestyle. The first major epidemiological study showing a strong correlation between smoking and cardiovascular disease was published around 1960, and although observational studies could not provide definitive evidence that tobacco smoke is responsible for increased coronary risk, it prompted the first anti-smoking measures by the US Surgeon General in his 1964 report. Smoking is a highly addictive habit, and despite major reductions in smoking prevalence in most Western countries over the last 50 years, tobacco use continues to grow in global importance as a leading preventable cause of cardiovascular disease. Tobacco smoking exerts both prothrombotic and atherogenic effects, and it increases the risk of acute myocardial infarction, sudden cardiac death, stroke, aortic aneurysm and peripheral vascular disease [10]. It has been found that even low-level exposure (e.g. passive smoking) increases the risk of acute myocardial infarction. Figure 5 (see p. 181) shows the number of years of life lost being obese at age 40 ~ the effects of smoking [11].

Fortunately, smoking cessation and avoidance of passive smoking rapidly reduces this risk. A major problem with smoking cessation is that the majority of smokers experience a weight gain when they stop smoking which,

in many cases, leads to taking up the habit again. It has been estimated that more people in the USA die from obesity-related complications than from tobacco. Only a small proportion of the weight gain observed in the population can be attributed to smoking cessation [12], but the observation emphasizes the need to include advice on prevention of weight gain in the package of smoking cessation tools.

Physical inactivity

Regular physical activity is an important part of a healthy lifestyle, and sedentary behavior can account for a substantial risk of CVD. Individuals who regularly undertake physical activity have a decreased risk of obesity, heart disease, hypertension, diabetes, and premature mortality. Systematic reviews and meta-analyses have consistently found that physical activity is associated with a marked decrease in cardiovascular and all-cause mortality in both men and women, even after adjusting for other relevant risk factors.

Nocon *et al.* recently reported a meta-analysis including 33 studies with 883,372 participants, with follow-up ranging from 4 years to over 20 years [13]. Physical activity was associated with a risk reduction of 35% in cardiovascular mortality (95% CI: 30–40%). All-cause mortality was reduced by 33% (28–37%). Oguma *et al.* examined the dose-response relationship in women based on a meta-analysis of 30 studies and found, when studies were combined according to relative levels of physical activity, that the risk reduction showed a dose-response relationship for CHD (RR=1 [reference], 0.78, 0.53, 0.61, respectively) for studies with four PA levels, $n = 5$); for stroke (RR=1 [reference], 0.73, 0.68) (14). For overall CVD the reduction was also substantial (RR=1 [reference], 0.82, 0.78). When studies were combined by absolute walking amount, even 1 hour/week walk was associated with reduced risk of CVD outcome.

Analyses from the Health Professionals' Follow-up Study of the importance of levels of leisure-time physical activity for incidence of CHD found that total physical activity, running, weight training, and rowing were each inversely associated with risk of CHD. Men who ran for an hour or more per week had a 42% risk reduction (RR, 0.58; 95% CI, 0.44–0.77) compared with men who did not run (16). Men who trained with weights for 30 minutes or more per week had a 23% risk reduction and those who rowed for 1 hour or more per week had an 18% risk reduction compared to those who did not undertake these activities. Average exercise intensity was also associated with reduced CHD risk, independent of the total volume of physical activity. Half an hour or more of brisk walking per day was associated with an 18% risk reduction, but walking pace was associated with

reduced CHD risk independent of the number of walking hours. These results show that various activities can be used, and that exercise intensity and fitness should be considered, as well as the amount of time spent on exercise activities, when calculating the health benefits of physical activity.

Is “fat but fit” a sufficient goal?

With an increasing proportion of the population being either overweight or obese, the question has been raised whether physical activity can eliminate the adverse health effect of obesity. In a recent meta-analysis of observational studies Blair and Brodney concluded that: 1) regular physical activity clearly attenuates many of the health risks associated with overweight or obesity; 2) physical activity appears to not only attenuate the health risks of overweight and obesity, but active obese individuals actually have lower morbidity and mortality than normal weight individuals who are sedentary; and 3) inactivity and low cardio-respiratory fitness are as important as overweight and obesity as mortality predictors [17]. Notably, their findings were entirely based on observational studies, and randomized clinical trials addressing these questions should be undertaken. Patients with established CVD will benefit from more exercise and increasing fitness, and the risk of sudden death induced by exercise is negligible compared with the benefits.

In order to reduce the ill health caused by physical inactivity the CDC and the American College of Sports Medicine recommend that adults engage in at least 30 minutes of moderate physical activity on most days, and preferably on all days [18]. Recently, the CDC analyzed data from the Behavioural Risk Factor Surveillance System (BRFSS) and found that from 2001 to 2005 the prevalence of regular physical activity increased 8.6% among women overall (from 43.0% to 46.7%) and 3.5% among men (from 48.0% to 49.7%) [18]. These figures may be due to over-reporting bias, but they suggest that efforts to increase the proportion of individuals complying with the recommendations is increasing. However, they also demonstrate that the majority of the adult population does not meet the recommendations for physical activity, and there is obviously potential for further reductions in the incidence of CVD by activating the sedentary section of the population. State and local public health agencies, and other public health stakeholders, should continue to implement evidence-based, culturally appropriate initiatives to further increase physical activity and fitness levels in all adults.

Sleep

Sleep of sufficient duration and quality is inherent as part of a healthy lifestyle, and too little high-quality sleep promotes CVD through a dis-

rupted appetite control, and through effects on metabolism that increase the risk of type 2 diabetes. Too little sleep has become a common health problem in western societies. The average duration of sleep has decreased by approximately one hour compared to 30 years ago [19], with more severely impaired sleep seen in certain individuals and/or groups. Sleep loss, widespread in modern societies, is an under-recognized public health problem that has a cumulative effect on physical and mental health. Epidemiological studies support the hypothesis that there are links between impaired sleep and overweight, especially in the young [20–22]. A number of intervention studies also imply that disturbed sleep has an impact on numerous physiological functions, such as appetite regulating hormones, substrate metabolism, and blood pressure [22–26]. In addition, numerous reports have found too little or impaired sleep to be a risk factor for mental distress, depression, anxiety, obesity, hypertension, diabetes, high cholesterol levels, and premature CVD death [27,28]. Though confounding by other adverse health behaviors such as cigarette smoking, physical inactivity, and heavy drinking may be important, there is accumulating evidence that too little and impaired sleep per se increase risk of CVD, partly directly and partly through weight gain and insulin resistance. Recently, King *et al.* [27] found a robust association between objectively measured sleep duration and 5-year incidence of coronary artery calcification, a subclinical predictor of future coronary heart disease events. They found that one more hour of sleep decreased the estimated odds of calcification incidence by 33%. The magnitude of the observed effect was similar to that of other important CVD risk factors (e.g. one additional hour of sleep reduced risk similarly to a reduction of 16.5 mmHg in systolic blood pressure) [27].

Recent intervention studies have provided a mechanistic explanation for the deleterious effects of sleep deprivation on health. These physiological data suggest that short-term partial sleep restriction leads to striking alterations in metabolic and endocrine functions, such as insulin resistance, increased sympathetic tone, elevated levels of cortisol and pro-inflammatory cytokines, and decreased leptin and increased ghrelin levels [22]. Furthermore, abnormal sleep-wake patterns probably alter intracellular circadian clocks, which may potentiate disrupted metabolism [28]. Chronic lack of sleep is stressful and biologically demanding and must be avoided if good health is a goal.

There seems to be good reason to question patients about sleep duration and sleep quality, and to recommend efforts to ensure that they get sufficient amounts of high quality sleep. The optimal sleep duration for adults appears to be 7–8 hours. Sleep of longer duration is a strong risk factor for increased mortality [29], but it is unclear whether the association is confounded by

other adverse health behaviors. More than 7.5 hours of sleep may increase the risk of cerebrovascular deaths, both in women and men [230]. It is not clear why sleep exceeding 7.5 hours should be associated with excess mortality, and the observation has not been confirmed by all studies. Long sleep duration may not be a causal factor for the increased mortality in itself, and sleep apnea may be an underlying confounding factor.

It should be kept in mind that there are still research questions to be answered, and there is obviously a need for RCTs to demonstrate that improved sleep duration and quality can reduce CVD risk. However, there is no risk in taking a pragmatic approach and encouraging a good night's sleep as an adjunct to other health measures. Sleep is a modifiable risk factor and the benefit of increasing sleep duration in at-risk individuals outweighs the harms.

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▶ HYPERTENSION

HYPERTENSION: WHY IS IT POORLY DETECTED AND POORLY TREATED?

■ CONRADO J. ESTOL

Is hypertension a significant vascular risk factor?

Hypertension is a highly prevalent disease. There are more than one billion hypertensive people worldwide [1]. The lifetime risk of developing hypertension is 90% at age 50. The age adjusted mortality from hypertension has increased 53% over the last decade and high blood pressure accounts for 54% of strokes and almost 50% of coronary cardiac events [1]. This compares to cholesterol accounting for approximately 15% of strokes and a similar proportion for smoking. Hypertension is especially concerning in women because one out of two become hypertensive at age 55, yet, most are unaware of this fact and concerned about hypotension which is a common problem among young women. This diagnosis delay results in missing valuable years of treatment. Recent studies from Canada show that only 16% of treated patients were controlled [2]. Different studies from other world regions including low and high-income countries show the same proportion of poorly controlled patients under treatment. Hypertension results in a six fold increase in stroke risk, which is only comparable to that caused by atrial fibrillation, and is only lower to have suffered a previous stroke. Hypertension results in 7 million deaths annually, which imply 13% of all deaths worldwide [3-7]. Importantly the Framingham study has shown that treatment of moderately increased high blood pressure significantly reduces the risk of cardiovascular events. This is consistent with the notion that most vascular events occur in people with few risk factors.

The preceding data strongly supports the notion that hypertension is the most important modifiable risk factor. However, only 2 out of 3 patients are diagnosed and 1 out of 3 patients diagnosed and treated are controlled. Only 25 to 50% of hypertensive patients receive treatment in North America and Europe, 50% of patients admit not taking medications properly, and 50% of patients adjust the medication based on self-measured blood pressure [8-10].

An important issue that contributes to poor compliance is the 'poison pill' effect in which the patient will not only tend to stop a medication causing side effects but also medications prescribed for other pathologies [11]. Although different studies have shown similar effectiveness for all anti-hypertensive drug classes, there is a different side effect profile for each of

these drug groups. Therefore, the appropriate drug selection to minimize the incidence of side effects is crucial. As an example, diuretics cause more frequent side effects than angiotensin receptor blockers (ARB). Thus, if a diuretic is the only hypertension treatment, side effects could result in the so-called 'poison pill' effect.

A different approach to show the effectiveness of hypertension treatment is the NNT (number needed to treat) (Figure 1, see p. 182). In the case of secondary prevention where a larger therapeutic effect is expected, in symptomatic carotid stenosis 8 patients have to be operated over 2 years to prevent 1 stroke. With aspirin, 55 patients have to be treated for 2 years to prevent an MI or 200 patients will have to receive aspirin for 2 years to prevent 1 stroke. In primary prevention, the numbers have lower power and in asymptomatic carotid stenosis, 83 patients have to be operated over 2 years to prevent 1 stroke. Numbers are more conspicuous for scenarios such as atrial fibrillation where 66 patients have to be treated with anticoagulants for 1 year to prevent 1 death. Focusing on hypertension, 30 patients (average BP 140/90 mmHg) have to be treated for 5 years to prevent 1 death and for people older than 80 years, only 40 patients have to be treated for 2 years to prevent 1 death. The aforementioned numbers clearly reflect the significant benefit of treating even slightly hypertensive patients.

What is normal blood pressure?

The VII Joint Commission (2003) has defined 130/80 mmHg as 'normal' blood pressure [1]. However, this value as a definition of normal has changed in the past and is likely to change in the future. Moreover, the lower threshold at which the relationship between cardiovascular mortality and blood pressure no longer applies has not been identified. The concept of 'pre-hypertension' adds confusion in the non-expert medical and general population. Many interpret this concept as encompassing the still-not-hypertensive but data shows that 16% of hypertension-related deaths occur in 'pre-hypertensives' [12]. In fact, blood pressure is a continuous risk variable and as such the relative risk for cardiovascular events progresses with increasing values starting at a systolic pressure close to 110 mmHg [13,14]. The lowest blood pressure value at which cardiovascular risk disappears has yet to be defined. Data from various studies have suggested that in diabetes mellitus the blood pressure threshold considered normal is probably lower than the value for the general population. The ACCORD study recently analyzed a subgroup of approximately 5000 patients randomized to an intensive blood pressure treatment group with a target systolic value of less than 120 mmHg versus a standard treatment group (BP less than 140

mmHg) [15]. The BP differential achieved was 14 mmHg. However, the study failed to show a significant difference favoring the primary endpoint of stroke MI, and death. A caveat is that the control group had a 50% lower rate of events than expected. This widened the confidence intervals and thus the statistical power of the study significantly dropped below the initially calculated value. This methodological shortcoming questions the validity of the study results. Interestingly, stroke was reduced (although not statistically significantly) in the intensive treatment group. Moreover, a limited treatment time and the fact that both groups had BPs close to 'normal' may have contributed to the negative study results.

In 2009, Law *et al.* published a meta-analysis of anti-hypertension treatment that evaluated 464,000 patients in 147 studies [16]. One of the important observations in the analysis was that 119 of the studies included patients with pre-treatment values lower than 140/90 mmHg. Despite this large number of patients with normal BP, the authors reported a 50% cardiovascular risk reduction for each 5 mmHg reduction in diastolic blood pressure. Based on this benefit, they concluded that BP reduction should not be limited to people with high blood pressure. Most important, the percentage reduction in coronary heart disease and stroke was similar regardless of blood pressure before treatment and down to a BP of 110/70 mmHg.

Another meta-analysis including 1 million patients from 61 cohorts and no previous cardiovascular disease showed that death rates doubled for each 20/10mmHg systolic and diastolic pressure increments [17]. The risk of cardiovascular death associated with BP was observed down to a pressure of 115/75 mmHg. A valuable observation from both meta-analyses is that it is not that risk was not observed below the 110/70 value, but rather that there were not enough patients in that group to make any conclusions. Nor was there suggestion of a 'J' shaped curve revealing increased risk below the lowest blood pressure associated with cardiovascular morbidity. In a study by Verdecchia, 1000 patients were randomized to a group with BP below 130 mmHg systolic or to another with BP below 140 mmHg [18]. The primary endpoint of left ventricular hypertrophy was significantly lower in the tight control group and secondary endpoints (all cause mortality, fatal or non fatal MI, fatal or non fatal stroke, TIA, CHF, AF, CABG) also favored tightly controlled BP. Another finding that is important to underscore is that there were no significant differences in side effects between groups. The NIH has planned the SPRINT study on 7500 patients older than 55 years with no stroke (SPS 3 is including these patients) or diabetes (included in ACCORD) [19]. One group will be randomized to a systolic of 120 mmHg or less with an average of 4 anti-hypertensive drugs versus another

group with BP under 140 mmHg using an average of 2 drugs. The study is expected to last 9 years and will cost approximately US\$ 100 million. Assessment of cognitive function will be included in the analysis.

In summary, the above data supports the axiom that the lower the blood pressure the better. However, we should be concerned to define how many vascular events are occurring in people that have their BP between that to be defined as 'ideal' in ongoing and future studies and the current 130/80 mmHg presently considered normal.

Are hypertension effects proven and understood?

The etiology of hypertension is related to multiple genes and environmental factors. Despite this, the available treatment is highly effective. A wealth of studies over the last 20 years has shown a major decrease in stroke and MI in treated patients [20-27]. A decision to terminate some of the studies was due to the large beneficial effect in the treatment versus the placebo groups. HYVET was a landmark study done on almost 4000 patients older than 80 years of age with a sustained systolic BP of 160 or more [28]. Patients were randomized to the diuretic indapamide with or without perindopril versus placebo to achieve a BP of 150/80 mmHg. Although without the support of scientific evidence, the usual recommendation has been to limit hypertension treatment in this age group to avoid medication side effects and other complications attributed to lowering BP (cognitive dysfunction, precipitating stroke or MI). The primary endpoint of HYVET was positive for a significant reduction in cardiovascular death, stroke, and CHF. There was also an unexpected reduction in death from any cause. Unexpectedly, and challenging current dogma, fewer side effects occurred in treated patients.

The previously mentioned meta-analysis by Law also adds to the knowledge on hypertension treatment effects. In this meta-analysis there were 22,000 coronary events and 12,000 strokes [16]. There was a 22% reduction in coronary heart disease and a 41% stroke reduction with each 10/5 mmHg decrease in systolic and diastolic BP respectively. The analysis also showed that all 5 drug classes had similar effects. There was an additional 25% reduction in CHF. Patients receiving 3 drugs at 50% the standard dose had a 46% decrease in coronary heart disease and a 62% reduction in stroke compared to one drug given at the usual standard dose, which had 50% of the aforementioned effects. This means that it would be preferable to use multiple drugs at a lower than maximum dosage since this is likely to cause a greater therapeutic effect with a lower incidence of side effects and therefore of drug discontinuation. The meta-analysis also showed that the percentage reduction in coronary heart disease and stroke was similar in

patients with and without history of cardiovascular disease. This has the important implication that there was an equal effect for primary and secondary vascular prevention. Comparing the results of this meta-analysis and that of individual trials in BP lowering it becomes clear, observing the causal relation between blood pressure reduction and benefit, that the effect of these medications in reducing vascular risk is almost entirely due to their BP lowering properties. This is in contrast to statins and other medications that, in addition to their expected effect, have indirect pleiotropic action. Data accumulated in recent years suggests a significant interaction between hypertension and cognitive dysfunction beyond that associated to the presence of cerebral infarcts and dubbed 'vascular dementia'. Dai *et al.* from the University of Pittsburgh studied 40 patients with normal cognitive status who had their cerebral blood flow measured with CASL-MRI (continued arterial spin labeled MRI) [29]. Twenty had hypertension under treatment and 20 were normotensive. Results showed a statistically significant decrease in cerebral blood flow in the hypertensive patients but no change in blood flow in the normotensive patients. Most interestingly, the decrease in blood flow was noted in areas related to Alzheimer's disease: limbic and paralimbic structures and other frontal and sub cortical cerebral regions. The authors concluded that hypertension could lead to a vulnerable brain state to develop degenerative dementia.

Despite all the information available on the significant reduction of cardiovascular events secondary to high blood pressure treatment, hypertension is usually not detected or is detected but not controlled.

Hypertension is not detected

Physicians, patients and equipments for BP evaluation encompass all the players in BP assessment that may lead to measurement errors. A statement by the American Heart Association published in 2005 evaluated in detail all BP measurement devices [30]. Sphygmomanometers with mercury are being abandoned or banned and the use of aneroid machines is associated with different operator-related measurement errors (visual, auditory, terminal digit preference) [31-33]. Electronic devices are probably the most reliable equipments. We have also found that it is helpful to show the patients the BP numbers in the screen to increase awareness of the implications of these values. These automated oscillometric devices allow an increase in the number of readings and decrease observer-related errors. Patients may also have responsibility in the inaccuracies of BP measurement. One German study entitled 'Manipulation of BP self-monitoring values' randomized 48 patients to a group that was aware that the electronic device given by the

investigators to the patients had a storing capacity and another group unaware of this machine's capability [34]. The investigators asked the patients to take their BP twice in the morning and in the evening and to make a written log of the measurements, which they analyzed after a few weeks. The agreement rate between stored and reported values was significantly lower in the 'unaware' group. The reasons were due both to the use of fictional data in which patients simply invented numbers without measuring their BP and to inadequate reports in which patients would measure their BP enough times until they obtained a normal result, which was the one they wrote down in the BP log.

However, the deadliest myth about BP measurements lies on the medical side and is the so-called 'white coat' or 'office' hypertension. Mancia in 1983 described this phenomenon in patients that showed increase BP values when measured in the office by a physician compared to the same patient's values measured at home [35]. Most physicians consider that these increased values at the office are 'harmless' and take no specific action or treatment to correct them. Different studies have shown that measurements at home and with a 24 hr Holter provide similar results and are both lower than office recordings [36]. The problem of this indifferent medical behavior with high office recordings is its conflict with a myriad of studies showing that isolated hypertension in the office is as harmful as sustained office- or home- hypertension. Different studies show similarly increased carotid artery intimal-media thickness (IMT) in isolated office hypertension and sustained hypertension; a study on 1200 patients with a 20-year follow up showed increased stroke risk in those with isolated systolic hypertension; arterial stiffness and left ventricular size increase similarly in patients with 'white coat' and sustained hypertension; microalbuminuria, retinopathy, IMT and LVH were seen in similar proportions in patients with 'white coat' and sustained hypertension; and 'white coat' hypertension occurring during mental stress and mathematics was a stronger predictor of atherosclerosis progression than smoking and cholesterol levels [37-43]. A recent meta-analysis on 11 studies confirmed the higher risk of coronary heart disease, stroke and death in patients with 'white coat' hypertension compared to the normotensive population [44]. The risk of developing sustained hypertension is significantly higher in patients with 'white coat' hypertension [45]. A recent study from Australia followed almost 9,000 patients in 11 centers with the aim of identifying which were the ambulatory BP equivalents to clinic BP thresholds for the diagnosis of hypertension [46]. The authors found that when patients had a BP of 150/100 mmHg at the clinic, they had 8/4 mmHg less in systolic and diastolic BP respectively during

ambulatory measurement. When clinic BP was 140/90 mmHg, the ambulatory BP was 4/3 mmHg less and when BP was 130/80 mmHg (i.e. normal) at the clinic, ambulatory BP was 2/2 mmHg less. These findings showed that there was no significant difference between ambulatory and clinic BP measurements and, importantly, that the closer to normal the BP, the greater the agreement in ambulatory and clinic BP. This implies that a patient who has a BP of 150/95 mmHg measured at the office should not be expected to have a large difference such as 120/70 mmHg at home or during ambulation as a reliable measurement. Thus, patients may have a higher BP at the clinic when measured by a physician (BP measured by a nurse compared to MD recordings was usually slightly lower) but these expected differences do not justify the large gaps consistently obtained when clinic BP is compared to that reported by patients. Interestingly, all the evidence showing that hypertension damages different organs is based in studies done using BP measurements made by medical staff at the office or clinics. In addition, most of the evidence proving that treatment of hypertension is beneficial is based on measurements done mostly at the office or at clinics by physicians. The practice to tell patients that high BP obtained at the clinic does not require treatment because it is a benign phenomenon reflecting a 'nervous' reaction to the measurement is a fallacy. The data available suggest that office or 'white coat' hypertension is hypertension.

On following the question about reliability of patient self-BP measurements, we performed a study in 200 patients in Argentina measuring BP at the clinic in 4 different visits over 6 months [47]. BP rates above 140/90 (used as limit for normal BP) were close to 80% in all visits despite adjustment of treatment. At first visit measurements, 60% of the patients had BP values above 160/100 mmHg. The study included another BP measurement self-reported by the patients, 1 week after visit 1 at the clinic and 3 weeks before visit 2. For this measurement, patients were asked to have their BP taken at home or any other place and call the office with the result obtained. Not surprisingly, only 38% of the self-reported values were above 140/90 mmHg, there were no measurements equal to or above 160/100 and 44% of the reported values were equal to or lower than 120/80 mmHg.

As a follow up of this report, we selected a large group of 20,000 patients randomized in the PRoFESS study (C. Estol personal communication). In this analysis, BP at visit 1A (self-reported by the patient) was statistically significantly lower than BPs measured at visit 1, 2, 3 and 4 at the clinic (by physicians) similarly to what we found in the smaller Argentine study. There was a significantly higher report of falsely 'normal' BPs measured outside the clinic.

Hypertension is detected but not controlled

In 2005 we reported a study made at a Neurology Clinic on 670 patients with an average BP of 142/86 mmHg measured at visit 1 [48]. Of all patients evaluated, 59% were hypertensive at the 1st visit (23% had a BP higher than 160/95 and 12% had a BP greater than 180/105). Among those that did not have a previous diagnosis of hypertension, 54% were hypertensive and of the 37% of patients with a previous diagnosis of hypertension, 83% were hypertensive implying that BP was treated but not controlled. We referred most patients to their MDs for treatment of hypertension but at our neurology clinic follow up 95% had no change in their BP treatment. We designed a new study starting in 2005 but this time we treated hypertensive patients at the neurology clinic. Neurological diagnosis of the patients included: 16% stroke, 14% headache, 14% dementia, 13% movement disorders, 10% spine problems and other neurological diagnosis [49]. We found that of the 1,464 patients included in the study, 500 had a prior diagnosis of hypertension yet their average BP was 160/93 mmHg with only 76 patients (15%) under control. These results reproduce the same rates of hypertensive population that achieve normal BP values under treatment in other world regions. Among the 1,000 patients that did not have a prior diagnosis of hypertension, 577 (60%) had an average BP of 151/93 and only 382 were truly normotensive. In total, 70% of the patients were found hypertensive during the 1st visit at the neurology clinic. They all had their treatment adjusted by a vascular neurologist or a cardiologist. Of the 544 that returned for follow up, the BP decreased in average from 155/93 mmHg to 143/86 mmHg and in 222 the BP reached an average of 123/78 mmHg. The average decrease in BP was 12 mmHg systolic and 7 mmHg diastolic and the difference in BP achieved at the Neurology Clinic was significantly better compared to BP control outside the Neurology Clinic.

Conclusions

Several factors limit implementation of available knowledge on effective hypertension treatment. These barriers should be identified to define strategies that could overcome them. Difficulties to treat hypertension effectively similarly affect high and low income countries. Although better economies possibly contribute to improving BP management, they do not necessarily address the various social and cultural factors that play a role on poor BP control. A feasible initial approach is to favor the creation of 'Vascular Clinics' with the active participation of stroke, cardiology, diabetes, lipid and other vascular specialists over individual 'Stroke Clinics'. In addition, the population in general (physicians and patients) is not taking 'seriously' the

results of BP measurements. The adequate behavior should be to treat BP values every time they are found elevated and avoid a watchful-waiting attitude. Since two meta-analyses including 1.5 million patients have shown benefit with BP reduction even in normotensive patients, BP should be readily treated even when slight hypertension is diagnosed. BP measurements should be done at clinics by adequately trained medical personnel and, ideally, patients should not be asked to control their BP due to the significant issues that result in inaccurately reported values. An alternative is to change BP measuring systems since present methods, even electronic devices, use numerical scales that confuse the result interpretation by patients. A medical statement against the 'white coat hypertension' concept should be published explaining that high blood pressure measured at a clinic corresponds to a slightly lower pressure measured at home but when the BP is equal or above 140/90 mmHg at the clinic the evidence supports pharmacologic treatment. Current studies are addressing the issue of 'normal blood pressure' to define the lowest value that is not associated with an elevated cardiovascular risk. Most physicians can and should treat hypertension. The high prevalence worldwide of patients with abnormally elevated BP is unacceptable and reveals a concerning degree of neglect in which the medical community has most of the responsibility.

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▶ LIPIDS

LIPIDS: HDL, LDL, ROLE IN PRIMARY PREVENTION, THE MESSAGE FROM TRIALS?

■ TERJE R. PEDERSEN

Lipid changes: What have we learned?

Blood lipids and lipoproteins are the strongest determinants of risk of cardiovascular disease [1]. Cholesterol levels are associated with ischemic heart disease in both middle and old age [2]. There are approximately log-linear associations between total and non-HDL-cholesterol levels regardless of smoking status, and at different levels of blood pressure or body-mass index (BMI). In populations with very low levels of non-HDL cholesterol like rural China before 1990 coronary heart disease was extremely rare [3]. In contrast, ischemic heart disease was extremely prevalent in countries with very high cholesterol levels like Finland in the 1970s and 1980s and since then mortality from coronary heart disease has fallen by approximately 80% as the population level of blood cholesterol has declined [4]. Recently a mutation in the gene encoding for the enzyme PCSK9 was found to be associated with 20–40% lower LDL-cholesterol levels than the population mean [5]. Since this condition is lifelong, such individuals have approximately 90% lower risk of suffering a coronary heart disease event. While such individuals have no other specific characteristics and live in an environment with usual exposure to modifiable risk factors, they can be regarded as participants in ‘nature’s own randomized trial’ (so-called Mendelian randomization) of cholesterol lowering [6].

The epidemiological evidence for a protecting role of high blood levels of HDL-cholesterol is also impressive. The Prospective Studies Collaboration found a log-linear inverse relationship between HDL-cholesterol and mortality from coronary heart disease, regardless of presence of other risk factors [2]. People with exceptional longevity have been shown to have significantly higher blood levels of HDL-cholesterol, larger HDL, and also LDL particle sizes [7].

Randomized clinical trials have provided overwhelming and conclusive evidence that reduction in LDL-cholesterol blood levels reduce the risk of cardiovascular disease. Already in the 1960s and 1970s trials in patients with documented coronary heart disease as well as in healthy individuals with moderate hypercholesterolemia showed that lowering cholesterol with diet or drugs reduced the risk of coronary events [8–11]. The lack of significant effect on

all-cause mortality however, left the medical community mostly skeptical about the over-all benefit of such treatment. Also the favorable results of treatment with partial ileal bypass surgery to reduce the reabsorption of cholesterol and thus the plasma level of LDL-cholesterol [12] or with the new drug gemfibrozil to modify lipid composition in plasma [13] left most physicians unimpressed because of lack of impact on all-cause mortality in the trials.

It was only in 1994 that the first large-scale randomized trial provided evidence that effective lowering of LDL-cholesterol using a statin in patients with established coronary heart disease prolonged life [14]. The trial called 4S used simvastatin to lower LDL-cholesterol a mean of 35% compared to placebo and showed a relative reduction of all-cause mortality of 30% with no excess mortality from non-coronary disease. The trial was followed by a very large number of randomized studies in a variety of patient populations using several different statins at both moderate and high doses. The results of these trials have been summarized in two prospective meta-analyses, the first comprising 14 trials with over 90,000 participants [15] and the second with additional 12 trials comprising a total of 170,000 participants [16]. These analyses demonstrate that the long-term effect per 1 mmol/L (38.6 mg/dl) lowering of LDL-cholesterol is a relative risk reduction of 22% of suffering any major vascular event (myocardial infarction, stroke or coronary revascularization procedure). In trials comparing moderate and high doses of statins the improvement in risk reductions per unit reduction of LDL-cholesterol was similar to the results of trials comparing active statin treatment with placebo. There was no difference in effects of statins between trials performed in secondary or primary prevention populations. The explanation for this is most likely that statins act through retardation of the atherosclerotic process, or even in some instances stabilization or regression of atheroma plaques [17]. The development of the atherosclerotic lesions that ultimately leads to the athero-thrombotic events starts early in life in populations with relatively high blood cholesterol levels [18].

An excess number of LDL particles undergo oxidation and at hemodynamically vulnerable parts of the arterial vessels get trapped in the sub intimal space where they are taken up by monocytes that are transformed into macrophages. Ultimately these cells end up as foam cells in plaques and attract inflammatory molecules that further intensify the pathological process. The main mode of action of statins is most likely that they lead to a marked reduction in the number of LDL-particles, because of the reduced synthesis of mevalonate, the building brick of cholesterol, although several other mechanisms resulting from the reduced availability of mevalonate may contribute to the beneficial result.

In the meta-analyses the trials that included statin-naïve patients at baseline, their weighted mean LDL-cholesterol concentration was 3.70 mmol/L (143 mg/dl) which is very close to the average level found in adults in Western countries. The relative risk reduction was, however, independent of the baseline concentration of LDL-cholesterol, even at levels less than 2.0 mmol/L (77 mg/dl). This may still be exceeding the usual levels of LDL-cholesterol in populations where coronary heart disease is rare such as rural China, where mean population levels in many communities could be less than 1 mmol/L [19].

In the JUPITER study the 17,802 participants were selected, based on age (men >50 years, women >60 years), LDL-cholesterol levels less than 3.4 mmol/L (130 mg/dl) and C-reactive protein [20]. This trial was stopped before the planned duration of 60 months because the 50% reduction in LDL-cholesterol provided by rosuvastatin 20 mg daily resulted in a highly significant 44% relative risk reduction in the primary end point, a composite of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes. Prior to this trial, primary prevention of cardiovascular disease with statins had been demonstrated in populations selected based on modest or mild hypercholesterolemia [21,22], with type 2 diabetes [23], or hypertension [24]. In the very large Heart Protection Study (n>20,000) that mainly comprised patients with prior cardiovascular disease, there were statistically significant benefits of statin therapy also in subgroups selected based on high risk because of diabetes, hypertension and advanced age [25].

While the beneficial effects of LDL-cholesterol reduction have been established without any doubt, the benefit of raising blood HDL-cholesterol has been far more difficult to determine, mainly because until recently there have been few methods to effectively provide such change. Non-pharmacological methods that raise HDL-cholesterol modestly are smoking cessation, physical aerobic exercise, weight loss, increased intake of food rich in n-3 polyunsaturated fatty acids and soy protein and alcohol consumption [26]. Statins may increase HDL-cholesterol modestly; fibrates and niacin are somewhat more effective. The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) compared the effect of the fibrate gemfibrozil with placebo in a long-term trial [27]. In this study gemfibrozil did not change LDL-cholesterol levels but increased HDL-cholesterol levels by 6% (ref.VA-HIT). This led to a significant decrease in the primary end-point of non-fatal acute myocardial infarction or coronary death compared to placebo. It is, however, uncertain what mechanisms were responsible for this since gemfibrozil reduces serum triglyceride levels substantially, which

might lead to an increase in LDL particle size, that make them less atherogenic [28]. Niacin is a drug developed in the 1950s and at full dose of 2 or more grams per day might increase HDL-cholesterol levels 15-30% [29]. In the Coronary Drug project niacin provided a significant reduction in the rate of myocardial infarction in patients with previous coronary heart disease, but the main mechanism behind this effect is subject to discussion [30,31]. Recently a new class of drugs has been developed that inhibit the enzyme cholesterol-ester transfer protein (CETP) that facilitates the transfer of lipids between lipoprotein particles. One of these drugs (torcetrapib) increased the plasma level of HDL-cholesterol by 80% or more and decreased LDL-cholesterol by 30% or more but a controlled clinical trial was stopped prematurely because of excess mortality and morbidity in the actively treated group [32]. This was ascribed the adverse effects that torcetrapib had on the renin-angiotensin system, leading to increase in systemic blood pressure and other adverse effect. Two other controlled trials also failed to demonstrate any beneficial developments of atherosclerosis as shown with various ultrasound techniques [33,34]. At present two other CETP-inhibitors, dalcetrapib and anacetrapib are being developed, capable of raising HDL-cholesterol levels by 30-100%, and testing has so far not unveiled any adverse effects [35,36].

HDL-particles have been shown to exert several properties that theoretically might have favorable effects on the atherosclerotic process [37]. Apart from being able to transport cholesterol from the plaque to the liver, mainly through passing cholesterol over to other lipoprotein particles such as LDL that are taken up by the LDL-receptors, the HDL particle has anti-inflammatory and anti-oxidative properties and may provide improvement in endothelial function and endothelial repair [38].

Future use of lipid-lowering

Few preventive measures have been studied as extensively as lipid-lowering drugs, in particular statins. Still, several questions remain unanswered. Since statins are among the safest classes of drugs used long-term, should we start using them more extensively and start earlier in life? While the typical recipients of statins in Western societies are middle-aged or elderly people with established atherosclerosis, we know that this condition starts in childhood and develops mostly slowly over several decades before causing symptoms. If starting statin use earlier in life, on what criteria should we select the candidates for treatment? This might be a family history, presence of other high-risk conditions, like diabetes, metabolic syndrome or frank obesity, but also lipoprotein levels or imaging techniques. Use of traditional

risk factors such as age, gender, smoking, blood pressure and cholesterol levels may be insufficient since we know that the majority of patients coming to the coronary care unit with acute myocardial infarction are neither particularly hypercholesterolemic nor do they have clusters of such risk factors [39,40]. Against a more widespread use of statins at younger ages have been the cost, the branding of healthy people as patients and the fear of adverse effects. Today, however, the cost is relatively minimal since statins have become off patent, a vast proportion of healthy people consume a large variety of medications such as vitamin pills or 'natural health products' without necessarily identifying themselves as patients. Tens of thousands of participants in double-blind placebo-controlled trials have demonstrated that adverse effects occur equally frequently in placebo groups, so there is a strong reason to suspect the many alleged adverse effects of statins as a nocebo-effect. Many reject the idea of consuming 'artificial' or 'synthetic' drugs over long periods because of fear of corrupting their body. It is less well known that statins have 'always' been around in nature. The first statin drugs were produced from fermentation broths using various soil dwelling molds. The source of lovastatin is a fermentation broth using *aspergillus terreus* [41]. A more widespread source is oyster mushrooms (*pleurotus ostreatus*) that have been part of the diet for generations in South Asia and are also increasingly being grown in sawdust cultures in kitchens in Western countries. Oyster mushrooms may contain as much as 6 mg lovastatin per gram of the fruiting bodies [42]. Even more frequently is the lovastatin-containing *Monascus purpureus* used in daily food consumption, better known as 'red yeast rice', having been in use in traditional Chinese cooking for at least 1000 years [43]. In controlled clinical trials of red yeast rice products in China, typical reductions in LDL-cholesterol was 20-30 mg/dl (0.5-0.75 mmol/L) [44].

Are there then no real risks of long-term adverse effects of statins? We know that statins might cause a dose-dependent rise in liver enzymes in the blood in 1-2% of users but serious liver damage has not been observed. The combination of statins with other drugs that are eliminated via the same metabolic pathway as statins may lead to blood concentrations of statins that may cause myopathies and rhabdomyolysis. This is particularly true for people of East Asian origin and when using high doses of certain statins, e.g. simvastatin. In the SEARCH study that compared moderate (20 mg/day) and high doses (80 mg/day) of simvastatin there were 4.2 cases of myopathy per 1000 patients treated the first year with 80 mg/day compared to only 0.2 cases per 1000 patients treated with 20 mg/day [45]. Combination of simvastatin should be avoided with drugs such as erythromycin, cyclosporin, gemfibrozil, ketokonazol, itrakonazol, HIV-protease inhibitors

and nefazodon, amiodarone and verapamil, but also other drugs used less frequently and consumption of grapefruit juice in more than small quantities should be avoided [46]. Meta-analyses of statin drugs have indicated that there is a small risk of developing diabetes and that this risk may be dose-dependent [47,48]. It is, however, uncertain whether this risk has any long-term consequences as a large proportion of participants in the trials have had metabolic syndrome with borderline serum levels of Hemoglobin A1c or serum glucose and only minimal increases in such levels might have changed the patient's status to frank diabetes.

Despite these caveats statins are today safely in daily use by hundreds of millions of people and will remain an important tool to limit the adverse consequences of adopting a diet and lifestyle that promotes atherosclerosis. Whether other modifications of blood lipids will add to the favorable effects of statins remains to be proven in the next decade.

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RESEARCH NIH

VASCULAR DISEASE: ONGOING NATIONAL INSTITUTE OF HEALTH RESEARCH & RESOURCES

■ WALTER J. KOROSHETZ

Vascular disease is the leading cause of death around the world. A growing epidemic of cardio- and cerebrovascular disease is now projected to kill many more millions and create further disability due to stroke, heart and renal failure, peripheral vascular disease and the other consequences of atherosclerosis and hypertension. This epidemic threatens the economic health of developed and developing countries as well as the health of its peoples. The situation is not at all hopeless because the largest component of the burden of illness due to vascular disease is preventable. However, lack of action will lead to irreversible consequences. The United States National Institutes of Health (NIH) is the major funding body for medical research and is committed to developing the knowledge to combat this global health problem.

The toll in life and quality of life in the United States due to atherosclerotic-hypertensive vascular disease is enormous. Heart disease is the second leading cause of death, and 8% of the total health expenditures is devoted to treatment of established heart disease. Stroke is the third leading cause of death and has been associated with 2% of the total health expenditure. Stroke is also the leading cause of adult long-term disability. Peripheral arterial disease affects over 8 million Americans and leads to over 50,000 amputations per year. Hypertension and hyperlipidemia account for 5% of US health spending and with atherosclerosis are also the major causes of 24% of cases of renal failure. Lastly recent evidence suggests that cerebrovascular disease combines with Alzheimer's disease to cause dementia in the elderly. Those risk factors associated with future development of ischemic complications are now being identified as significantly associated with development of dementia. The major risk factors are hypertension, elevated blood lipids, overweight, tobacco smoking and sedentary life style.

The rising US health care costs are considered unsustainable. A major component of these costs are due to the treatment of hypertensive and atherosclerotic vascular disease once it has become manifest as myocardial infarction, stroke, claudication, or hypertensive kidney disease. A comparison with disease and disability rates of other Western countries suggest that the enormous investment in US health technology does diminish disability and

prolong life in affected individuals. However, diagnostic vascular testing and surgical or endovascular revascularization procedures for coronary, carotid, intracranial, aortic, renal and peripheral arterial disease are costly and associated with substantial procedural risk. The treatment of persons with chronic heart failure, debilitating stroke, and end stage renal failure are substantial. Advances in treatment likely contribute to the decreases in the annual risk of mortality due to stroke and heart disease but these medical interventions are incurring more and more cost. Figures from the Centers for Disease Control (CDC) indicate that the deaths due to cardiovascular disease, stroke and peripheral vascular disease decreased between 2000 and 2005 by 8, 10, 12% respectively. However the prevalence of persons living with coronary artery disease, heart failure and stroke has increased much more, 24, 8 and 23% respectively.

Three major shifts in the epidemiology of vascular disease if unchecked will contribute to a 'perfect storm' in US health care. First is the fact that vascular disease is appearing at an earlier age in the US population as compared to other Western countries. This is consistent with a less effective preventative effort and is met by tremendous expenditure in vascular care and disability. The prevalence of hypertension in the US increased by 50%, from 50 million in 2000 to 73 million in 2005. The second threat is the rising prevalence of obesity which all data predicts will lead to a surge in premature hypertensive-atherosclerotic disease. The prevalence of obesity in persons over 20 years old increased 11% from 61 million in 2000 to 67 million in 2005. The third is a direct consequence of our success in treating disease and extending the lifespan. Vascular disease continues to worsen with age. Stroke risk doubles for each decade after 60 years. The prevalence of atrial fibrillation, a cardiac arrhythmia that carries risk of major stroke, also increases with age. It currently affects 2.3 million Americans but will increase to 5.6 million in the year 2050. These three factors call for continued discovery research to develop more effective interventions to prevent the progression of atherosclerotic hypertensive disease and treat its complications. However, the paradigm shift that can save lives as well as a health care system is a more effective prevention strategy. Prevention will eliminate considerable suffering and death but also substantially decrease the resources needed to treat millions of newly affected individuals. Vascular disease prevention not only makes sense from a pure health perspective but it may be the best means to curb the unsustainable growth of health care costs.

The NIH is a component of the US Department of Health and Human Services. It consists of 27 Institutes and Centers with varying related health missions. Almost all have 'intramural' research units in laboratories and the 240-bed research hospital in the Washington D.C. area. The intramural re-

search endeavor is generally assigned 10% of the NIH budget. Each of the Institutes aggressively supports training of research investigators that will contribute to the Institute's mission.

The National Heart Lung and Blood Institute (NHLBI) is the major funder of basic research on atherosclerosis, hypertension, myocardial ischemia, and heart failure. Within NHLBI is the Division of cardiovascular disease with branches in atherosclerosis and coronary heart disease, vascular biology and hypertension. The NHLBI Division of Prevention and Population Sciences also carry out large population and epidemiology studies that uncover important risk factors. The Framingham Heart Study has led to establishment of the major vascular risk factors as well as the Framingham Risk Index which has been validated for its ability to integrate various risk factors into a predictive scale. The Atherosclerotic Risk in Communities Study (ARIC) intensively studied middle aged individuals and tracked them over time to determine those characteristic that are predictive of heart disease and cognitive decline (references). Treatment trials in myocardial infarction and heart failure have led to major advances that reduced death and disability. Current investigation and trials of stem cell replacement therapy and gene therapy are focused on improving heart function in persons with heart failure. Primary and secondary prevention trials from NHLBI have had a major impact on health care in the US. Most recently there has been concerted effort to determine whether there is increased benefit in lowering blood pressure below the currently recommended limits. The recent NHLBI/NIDDK study called ACCORD showed no improvement in cardiovascular outcomes from aggressive lowering in patients with diabetes. However there was reduction in stroke. The NINDS SPS3 study will examine aggressive blood pressure lowering to prevent subsequent stroke in persons with small vessel disease. A new NHLBI/NIDDK/NINDS/NIA funded study, called SPRINT, will examine aggressive blood pressure lowering in persons with renal failure or vascular risk. NHLBI Public information programs based at NHLBI work to inform the US population on how to best prevent heart and vascular disease. The 'Red Dress Campaign' has raised awareness of the great danger of undiagnosed and untreated vascular disease in US women.

The National Institute of Neurological Disorders and Stroke (NINDS) is the major funder of stroke research. NINDS research covers the landscape of cerebrovascular disease and includes basic research on the interconnection of brain metabolism and blood flow, integration of function at the tissue level, i.e. how the cell types (neurons, glia, endothelial cells and inflammatory cells) integrate their function, the brain response to ischemia and hemorrhage, and

how the brain recovers after injury. NINDS often collaborates with NHLBI on the large epidemiologic, genetic, or treatment studies with stroke and/or cognitive endpoints, i.e. ARIC, SPRINT. NINDS clinical trials have established the substantial effectiveness of warfarin in preventing stroke in persons with atrial fibrillation and defined the risk/benefit ration of carotid endarterectomy and endovascular stents in persons with carotid artery stenosis.

The demonstration of the timely infusion of tissue plasminogen activator has led to decrease in disability due to acute ischemic stroke. The Brain Attack Coalition, a partnership between professional societies, non-profit stroke associations and government, based at the NIH, has also led to a revolution in the care of acute stroke patients into organized stroke centers. Substantial benefit in stroke outcome is likely and is also derived from the benefit of an organized stroke unit. Treatment trials are now underway studying acute reduction of blood pressure in persons with intracerebral hemorrhage, removal of blood from patients with hemorrhage into the ventricles, and intra-arterial clot removal/dissolution after intravenous tPA treatment. Basic research in 'neuroplasticity' and 'neurodevelopment' are now being integrated into basic and translational studies on how the brain recovers after stroke. Given the explosion of basic science of neuroplasticity and neurodevelopment, future breakthroughs in promoting stroke recovery seem quite possible. Like the variability in global rates of stroke and heart disease, the United States also has great regional variability. The southeastern US is a 'stroke belt' with extremely high stroke mortality. The Reasons for Geographic and Racial Differences in Stroke study (ReGARDS) is ongoing to determine the underpinnings of these disparities. Secondary stroke prevention studies for persons with small subcortical strokes (lacunar stroke), cardioembolic stroke in persons with heart failure, intracranial stenosis and TIA/non disabling strokes are underway. NINDS's 'Know Stroke Campaign' focuses on raising awareness about the warning signs of stroke and transient brain ischemia, which should be triggers to seek emergency attention. A few research studies focus on developing best practices in stroke prevention, emergency access to stroke treatment some of which are targeted at specific racial-ethnic groups.

The National Institute of Diabetes, Digestive and Kidney Disorders (NIDDK) has been a lead in research on obesity and the complications of diabetes. Obesity and lack of physical activity are causally related to the development of type 2 diabetes with its complication of dyslipidemia and hypertension. The long-term consequence is atherosclerosis and its disease manifestations. Unfortunately obesity is becoming more prevalent in both developed and developing countries. CDC figures indicate that the preva-

lence of diagnosed diabetes increased from 0.9% in 1958 to 6.9% in 2009. This underlies much of the coming epidemic in heart disease and stroke. The NIH responded to the growing epidemic of obesity by creating a multi-institute task force on obesity. Although most NIH research is initiated by investigators, the Obesity Task Force is an example of how the NIH stimulates the research community to focus on high priority health or scientific problems. They have issued a number of program announcements calling for grant applications in topics such as school nutrition and physical activity policies, obesogenic behaviors, and weight outcomes. Home and Family Based Approaches for the Prevention or Management of Overweight or Obesity in Early Childhood, Geographic and Contextual Influences on Energy Balance-Related Health Behaviors (R01), Identifying and Reducing Diabetes and Obesity Related Health Disparities within Healthcare Systems (R01). In addition to these three institutes, others such as the National Institute of Aging (NIA) for issues related to cognitive decline, National Institute of Nursing Research (NINR), the National Institute of Bioimaging and Bioengineering, have programs in vascular related research.

Many aspects of the problem have been defined by NIH funded research. Biological events that begin early in life lead to the development of lipid deposition in the wall of aorta. Over time this process occurs in most large- and middle-sized arteries in the body. Uncovering the genetic causes of atherosclerosis, knowledge of lipid metabolism, vascular biology, and the role of inflammation have given scientists a strong but still incomplete understanding of atherosclerosis. Similarly changes in vascular tone, volume and sodium regulation, hormonal and neural circuits, are known to contribute to cause hypertension. The interaction between the clotting system and the vascular wall is the third major piece to the puzzle. Many ischemic manifestations, especially stroke, heart attack and peripheral embolism occur when thrombus forms on the diseased vessel wall. In the case of acute coronary syndrome the thrombus occludes flow to the heart muscle. In stroke and hypertension the thrombus breaks free to travel in the arterial system till it enters a vessel that is too small to allow it to pass. Hemorrhage into the brain occurs when a vessel damaged from chronic hypertension leaks blood into the brain substance. From the biological discoveries have come medications that reduce blood pressure and create a partial block in decreasing lipid deposition, and tolerable reduction in thrombus formation. These medical interventions have been extensively studied and show definite benefit in reducing important endpoints like death, myocardial infarction and stroke.

There is every reason to expect that further scientific research will lead to more effective medications that can control hypertension, prevent pro-

gression of atherosclerosis or prevent the acute thrombotic consequences such as stroke, myocardial infarction and embolism. NIH has recently placed greater emphasis in developing translational programs that aim to bring promising new therapies to patients. The NINDS office of translational research funds cooperative agreements which focus on developing compounds as drugs to the point of application to the Food and Drug Administration (FDA) for an Investigational New Drug application. New agents are surely to be more expensive than the older effective therapies which have come off patent. The new agents generally have a side effect or effectiveness profile that is an advance over older, less expensive medications. However the incremental value is often small. Many effective medications are now inexpensive. In both developed and underdeveloped countries the lack of medical treatment of persons who need it is often a logistical or systems problem and not related to the expense of medications. Major research questions in the future will focus around who should receive preventative medications. Age is one of the most important risk factors and many with atherosclerosis-related MI stroke have few risk factors. An argument has been made in the literature to treat all persons above a certain age with combined lipid lowering agent, antiplatelet agent, and an anti-hypertensive polypill. A major question will become how early to begin medical treatment in persons who are asymptomatic and how aggressive to lower blood pressure, and blood lipids, in addition to the risk/cost/benefit relationship for treating patients with few risk factors.

Guidelines for the prevention of vascular disease focus around control of the evidence-based risk factors of hypertension, blood glucose and blood lipids. Weight loss and increased physical activity are recommended first, with medications to follow if this has not led to normalization. The paradigm shift that is necessary to stave off the epidemic of vascular disease is a culture change that emphasizes exercise and maintenance of healthy body weight from an early age. The latter is even more important given that the lack of physical activity and obesity in children has been identified as causes of Type 2 diabetes in children. Such a strategy would be expected to decrease the proportion of the population with Type 2 diabetes, hypertension and dyslipidemia. Tobacco smoke is an extremely important preventable risk for cardiovascular disease and public health has profited from reductions in smoking. However there has been less reach in specific groups especially young people and those of low socioeconomic strata where smoking rates are still high.

Reduction, or at least significant delay, in the development of atherosclerotic complications could be expected if physical activity increases and obesity and smoking decline. Without the discovery of an agent that pow-

erfully prevents atherosclerosis, our country's shift toward an 'unhealthy lifestyle' will eventually be met by an explosion in the burden of vascular disease. Attacking this cultural issue is not fixable with medication. We know that atherosclerosis begins at young age. The health decision to begin medication at young age is fraught with concerns for safety and cost. However a healthy lifestyle has no downside and is likely to be more effective, more sustainable if started young. A concerted education effort must be made to educate at every level. But only disseminating information is not likely to have the needed impact. NINDS and NHLBI recently held a workshop on the Science of Behavior change focusing on the vascular risk factors. The workshop pointed to lessons from the behavioral and communication sciences, with a focus on health related behavioral economics, to enable the development of healthy habits. Communication tools are now far advanced over the print media of most health campaigns. Harnessing the power of social networks is now possible to promote healthy behavior if properly targeted at specific segments of society. The new technologies: YouTube, Facebook, Twitter, the global penetration of cell phones and the internet offer both more personalized and greater regional reach. Indeed, the feasibility of widely accessible global communication also enables the consideration of international cooperative programs aimed at segments of populations with the optimized 'message'. Technology also allows the design of personalized 'coaches', methods can be developed that interact with the individual's decision-making environment; i.e., automated calorie counters, food classifiers, pedometers, cell phone reminders, even systems that capture real-time data from individuals followed by analysis and feedback.

An individual effort to rearrange one's environment to increase the probability of a healthy behavior is possible on the individual level but population effects likely require an integration of policy with healthy behaviors. Those who make decisions that affect the work or school environment, 'planners', can contribute over years to health. Most do not have any realization of their potential to affect health. Because caloric intake and physical activity have not come into the decision-making by 'planners' their decisions have had random effects, sometimes positive, sometimes negative or neutral. It's easy to understand that the absence of healthy food choices in a work or school cafeteria will predispose to an unhealthy outcome. However less obvious is that the arrangement by which foods are presented, or offering choice with regards to portion sizes can increase the probability of health choices. Planning of communities and the workplace can have major effects on the amounts of physical activity of those who live and work in the environment. Placing stairs but not elevators at the entrance to the

building encourages walking. Safe bike lanes and bike racks encourage biking to work or school. Realization that cardiovascular disease is actually a cost to companies has even led to active programs focused on healthy lifestyle among employees. Because so little has been done to increase the probability of healthy choices there may be considerable population level gains to be made from a concerted cultural change toward healthy lifestyle. In most cases the goal should not be to restrict choice but instead to engineer the environment to make healthy choices more likely.

A proportion of the NIH's effort focuses on global health. The Fogarty International Center (FIC) coordinates international programs. Joint programs with the other Institutes fund research training and joint research grants with international investigators. Relevant to vascular diseases are the FIC's *International Tobacco and Health Research and Capacity Building Program*, *Millennium Promise Awards: Non-communicable Chronic Diseases Research Training Program* and *Brain Disorders in the Developing World*. Recently, Dr. Francis Collins, the NIH Director, has called for NIH to redouble its impact on global health. NHLBI has developed 11 Centers of excellence around the globe. In 2009 NHLBI joined as one of the founding members of the Global Alliance for Chronic disease. The Global Alliance is composed of national health research institutions and intends to coordinate and support research activities that address, on a global scale, the prevention and treatment of chronic non-communicable diseases. The alliance's focus is on the needs of low- and middle-income countries – where 80% of deaths from chronic diseases occur – and on those of low-income populations of more developed countries. NHLBI is also involved in a partnership with World Health Organization and the Pan American Health Organization. A variety of Institutes execute clinical research with sites distributed around the world.

The research supported by the NIH holds the potential to inform individuals, health care providers, payers, and policy makers on how best to combat the epidemic of vascular disease. Though it studies how best to disseminate information to improve health it does not provide healthcare or set policy. In truth a great deal is currently known about how to prevent vascular disease and its consequences. There is a gap between the knowledge base and translation into the culture and fabric of society. Coordinated action on the part of governmental and educational agencies, church, community and industry leaders is required to turn what is known about decreasing disability, mortality and health care costs into a reality.

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HEART DISEASE

ACUTE MYOCARDIAL INFARCTION: A CENTURY OF PROGRESS

■ EUGENE BRAUNWALD

The year 2010 marks the centenary of the first description of acute myocardial infarction (AMI). In 1910, Obratsov and Strazhesko from Kiev in the Ukraine presented their landmark observation in five patients. Remarkably, in the very first paper on the subject, they described correctly the key clinical findings of this important condition. To quote them (translated from Ukrainian):

All patients noted an acute, sudden onset of the disease. Direct events often precipitated the disease; the infarct began in one case on climbing a high staircase, in another during an unpleasant conversation and in a third during emotional distress associated with a heated card game.

They stated that the symptoms were of three types:

1. Substernal pain with radiation to the neck, head and left hand
2. Shortness of breath, reaching such a severe degree that it did not permit the patients to lie or sleep
3. Heaviness and severe pressure in the epigastrium

Just three years later, Anitschkow and Chalutow (1913) produced atherosclerotic lesions in the arteries of healthy rabbits who were fed a diet containing large quantities of fat, thereby raising the cholesterol concentration in the circulating blood to approximately 1000 mg/dl.

From these two landmark observations – one clinical and the other experimental – the mechanism of obstruction of coronary arteries secondary to atherosclerotic changes, and the serious clinical consequences of such obstruction, were firmly established.

The pathophysiology of acute myocardial ischemia was studied experimentally by Tennant and Wiggers (1935). They occluded a coronary artery in anesthetized open chest dogs and observed that contraction of the myocardium in the distribution of the occluded vessel ceased immediately. If the occlusion was relieved rapidly (within 23 minutes) contractions returned. With longer occlusions contraction did not return. Several years later Blumgart and colleagues showed, also in dogs, that prolonged, although temporary, coronary artery occlusion caused myocardial necrosis (infarction). They stated that their observations afford evidence that temporary ischemia, if of sufficient duration, may cause myocardial infarction of the

same character and degree as that which occurs after permanent and complete occlusion of a [coronary] artery'. (Blumgart H.L. *et al.*, 1941)

During the first half of the twentieth century the number of patients in North America and Europe in whom the diagnosis of AMI was made increased rapidly and the short-term (30 day) mortality was prohibitive – approximately 30%. Indeed, by mid-century, AMI was identified as the most frequent cause of death in adults. In 1961 Desmond Julian, a trainee in cardiology in Edinburgh, published a landmark paper describing what would become the coronary care unit. (Julian, 1961) He recommended the creation of a specific area in the hospital for patients with AMI, an area that contained all of the equipment necessary for these patients (catheters, drugs, solutions, pacemakers, defibrillators, etc.) and where specially trained physicians and nurses were available at a moment's notice. Coronary care units sprang up almost immediately around the world and resulted in a reduction by half of the short-term mortality to approximately 15%. The coronary care unit was made possible by the four distinct advances shown in Table 1.

Myocardial oxygen consumption

Approaching the problem from a different perspective, my colleagues and I, beginning in 1955, in Stanley Sarnoff's laboratory at the National Heart Institute in Bethesda Maryland in the US, began to dissect out the determinants of myocardial oxygen consumption (Sarnoff *et al.*, 1958) (Figure 1). We found that there were at least eight separate functions of the heart which required oxygen (Braunwald *et al.*, 1969) (Table 2). The most important of these were myocardial tension development, myocardial contractility, as reflected in the velocity of myocardial shortening (V_{\max}) and the frequency of contraction.

After moving from the NIH to the University of California, San Diego, my colleagues and I developed and tested the hypothesis that following coronary artery occlusion the fate of the ischemic myocardium in the distribution of the occluded artery was dependent on its balance of oxygen supply and demand. We found that early reperfusion of the ischemic muscle (increase in oxygen supply) and beta adrenergic blockade (lowering of oxygen demand) reduced the quantity of myocardium which became necrotic, i.e. reduced infarct size, while hypotension (reduction of coronary perfusion through collateral vessels), decreased oxygen supply and the administration of positive inotropic agents such as isoproterenol (augmentation of oxygen demand), increased infarct size. We speculated: 'In patients with myocardial ischemic injury resulting from coronary occlusion, measures designed for reduction of myocardial oxygen demands and improvement of coronary perfusion when effected promptly after a patient has

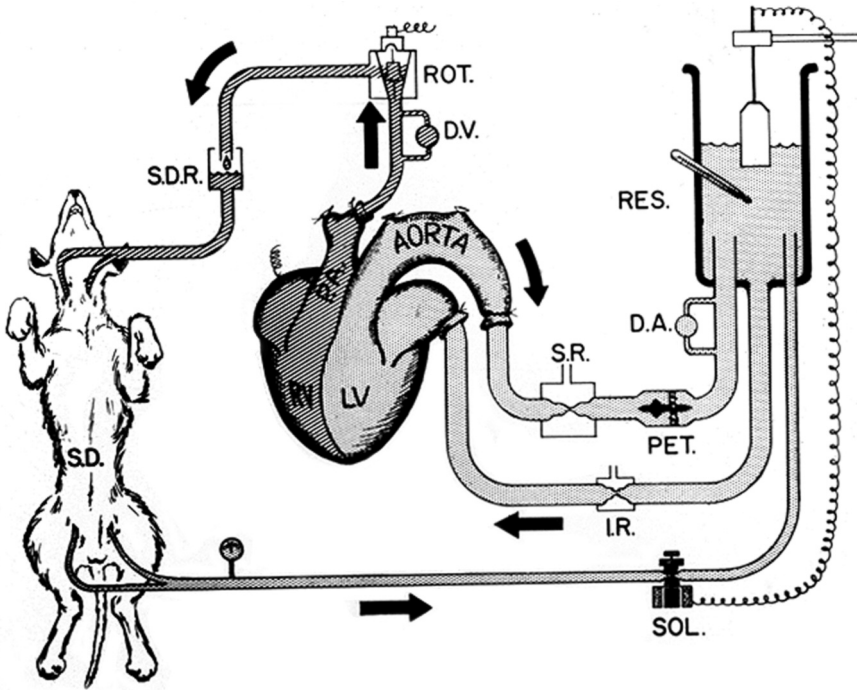


Figure 1 Schematic diagram of the isolated support heart (ISH) preparation. SR = air-filled Starling resistance. PET = Potter electroturbidometer. DA = arterial densitometer. RES = reservoir. LR = water-filled inflow Starling resistance. DV = venous densitometer. ROT = rotameter. SDR = support dog reservoir. SD = support dog. SOL = solenoid valve electrically operated by microswitch at top of reservoir float. From: Sarnoff, S.J., Braunwald, E., Welch, G.H., Jr., Case, R.B., Stainsby, W.N., Macruz, R. (1958) Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 192:148-56.

<i>Technical</i>	Continuous ECG monitoring with alarms
<i>Clinical</i>	Closed chest CPR
<i>Administrative</i>	Clustering of AMI patients
<i>Social</i>	Empowerment of nurses

CPR = cardiopulmonary resuscitation; AMI = acute myocardial infarction

Table 1. Advances Leading to the Development of the Coronary Care Unit

- Tension development
 - Contractility
 - Heart rate
- } 92%

-
- Basal
 - Depolarization
 - Activation
 - Maintenance of active state
 - Shortening against a load – Fenn effect

Table 2. Determinants of myocardial O_2 consumption. From Braunwald E. 13th Bowditch Lecture. The determinants of myocardial oxygen consumption. *The Physiologist* 1969;12:65-93.

been brought to a hospital, might reduce the ultimate size of the infarct' (Maroko *et al.*, 1971).

Successful reperfusion of patients with AMI using the fibrinolytic agent streptokinase injected into the occluded artery was first performed by Chazov and his collaborators in Moscow. Their work was published in a Soviet journal in 1976 (Chazov E.I. *et al.*, 1976) and was not adequately known or appreciated in the West for a number of years.

Percutaneous coronary intervention

In 1978 Gruntzig described percutaneous transluminal coronary angioplasty (PTCA) (Gruntzig *et al.*, 1978), which provided the foundation for rapid, complete reperfusion of ischemic myocardium. Indeed, several years later, Meyer and colleagues (Meyer J *et al.*, 1982) successfully treated a patient with AMI who was in cardiogenic shock with what later became known as 'pharmacoinvasive therapy'. This consisted of intracoronary streptokinase, which provided partial flow through the occluded artery, followed immediately by PTCA which resulted in full reperfusion.

In 1985, after development of the powerful fibrinolytic agent tissue recombinant plasminogen activator (rt-PA), the National Institutes of Health in the US established the Thrombolysis in Myocardial Infarction (TIMI) Study Group, which still remains active after 25 years and completing 50 trials. In our first trial, we compared the abilities of streptokinase and rt-PA

to open occluded coronary arteries in patients with AMI and found that the latter was superior (The TIMI Study Group, 1985) (Figure 2, see p. 183). We also observed that patients who achieved patency of the occluded artery had a considerably lower one year mortality rate than did those in whom the vessel remained occluded (Dalen JE *et al.*, 1988) (Figure 3, see p. 184). This provided support for the 'open artery hypothesis' in which we called attention to the concept that early opening of an occluded coronary artery in a patient with ischemic myocardium was highly desirable. We also observed that intravenously administered beta adrenergic receptor blockers in concert with fibrinolytic reperfusion were associated with reduction of re-infarction and of recurrent myocardial ischemia (Roberts *et al.*, 1971). An important step was taken by the ISIS Study Group which showed in 1988 that both streptokinase and the antiplatelet agent, aspirin, each independently reduced mortality. These benefits were additive when the two drugs were combined (ISIS-2 Collaborative Group, 1988) (Figure 4, see p. 185).

It was well known, before the development of the coronary care unit, that of the 70% of patients with AMI who survived the first month, an additional 20% died because of heart failure, thus leading to a 1 year survival of only about 50%. The development of angiotensin-converting enzyme inhibitors (ACE-i) made it possible to determine whether enlargement of the left ventricle and subsequent death in the increasing number of patients who were now surviving AMI could be reduced by the administration of these agents. Drs. Marc and Janice Pfeffer showed in rats in which the coronary arteries had been occluded that left ventricular remodeling and death could be reduced by the administration of an angiotensin converting enzyme inhibitor (Pfeffer *et al.*, 1985). We then extended this observation to patients in the Survival and Ventricular Enlargement (SAVE) trial (Figure 5, see p. 186), and showed that in patients with AMI the administration of an ACE-i begun at discharge from the hospital showed improved long-term survival benefit (Pfeffer MA *et al.*, 1992).

It had been demonstrated in the fibrinolytic trials that the reduction of mortality from reperfusion was greatly dependent on the duration of ischemia. As had been shown by both Tennant and Wiggers (1935) and by Blumgart *et al.* (1941), the earlier the reperfusion, the smaller the ensuing infarction. In 1993, the European Myocardial Infarction Project Group shortened the time from the onset of symptoms to reperfusion by administering the fibrinolytic agent in the ambulance rather than waiting until the patient reached the hospital. They concluded: 'Prehospital thrombolytic therapy for patients with suspected AMI is both feasible and safe when administered by well-equipped, well-trained mobile emergency medical staff.

Such therapy reduces mortality from cardiac causes' (The European Myocardial Infarction Project Group, 1993).

Reocclusion is reduced by the addition of heparin to the fibrinolytic agent. In the TIMI- 25 trial, Antman *et al.* demonstrated the superiority of the subcutaneous administration of a low molecular weight heparin when compared to intravenous administration of unfractionated heparin. (Figure 6, see p. 187) (Antman *et al.*, 2006). Building on the benefit of adding aspirin to streptokinase in the above-mentioned ISIS 2 trial (ISIS-2 Collaborative Group, 1988), Sabatine *et al.* showed, in the CLARITY-TIMI 28 trial, that the addition of a second anti-platelet agent, clopidogrel, to aspirin in patients with AMI treated with a fibrinolytic-heparin combination greatly increased myocardial perfusion and reduced death or recurrent myocardial infarction (Sabatine *et al.*, 2006) (Figure 7, see p. 188). Going a step further, the TRITON-TIMI 38 trial showed that prasugrel, a more powerful antiplatelet agent than clopidogrel, in patients with ST-segment elevation myocardial infarction (STEMI) treated by reperfusion reduced the incidence of cardiovascular death, recurrent MI and stroke (Figure 8, see p. 189) (Montalescot *et al.*, 2009). This more powerful antiplatelet agent also reduced by half the incidence of stent thrombosis, a serious complication of stent placement, although it did increase the severity of bleeding.

There are currently two methods of reperfusion of AMI – pharmacologic and mechanical, i.e. the percutaneous coronary intervention (PCI). (Antman *et al.*, 2008) (Figure 9, see p. 190). Each has advantages and disadvantages. Overall, PCI, when conducted early after the onset of AMI, is more effective than fibrinolysis in salvaging ischemic myocardium and has become the treatment of choice in Western Europe and North America and in selected populations elsewhere. However, immediate PCI is not yet widely available in much of the developing world, where fibrinolysis using the relatively inexpensive fibrinolytic streptokinase is still employed. These two techniques, i.e. PCI and fibrinolysis, can be used together in a technique known as 'rescue PCI'. A 2008 update of the American College of Cardiology/American Heart Association guidelines for the management of patients with ST-elevation myocardial infarction statement states: 'A strategy of coronary angiography with intent to perform rescue PCI is reasonable for patients in whom fibrinolytic therapy has failed (ST-segment elevation less than 50% resolved after 90 min following initiation of fibrinolytic therapy) and a moderate or large area of myocardium is at risk [anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression]' (Antman *et al.*, 2008).

An approach to using these two techniques together was tested in the TRANSFER AMI trial (Figure 10, see p. 191). This was a study of a phar-

macoinvasive strategy in 1059 high-risk patients with STEMI presenting to non-PCI-capable hospitals within 12 hrs of symptom onset. All patients were treated with a fibrinolytic agent and then randomized to a pharmacoinvasive strategy (fibrinolytic therapy followed by immediate transfer for PCI) or to standard treatment after fibrinolytic therapy (rescue PCI only for patients with ongoing chest pain and less than 50% resolution of ST-elevation hemodynamic instability at 60–90 minutes). The results indicated that when high risk STEMI patients present to hospitals without PCI-capability following treatment with a fibrinolytic agent, transfer to a PCI center to undergo coronary angiography and PCI should be initiated immediately, without waiting to determine whether reperfusion has occurred (Cantor WJ *et al.*, 2009).

Sudden cardiac death remains a most serious complication of AMI. Patients with impaired left ventricular function are at particular risk and should be treated with an implanted cardioverter defibrillator (ICD). The approach to preventing this complication is shown in Figure 11, p. 192 (Antman EM *et al.*, 2008).

Future directions

Cell therapy, most commonly intracoronary administration of autologous bone marrow cells, is a recent development in the treatment of AMI. A five year followup in one trial is shown in Figure 12, p. 193 (Yousef M, 2009). A second trial using mononuclear autologous bone marrow cells with favorable long term outcomes was also published recently. (Cao *et al.*, 2009) Efforts are now underway to use gene therapy in AMI (Hammond and Tang, 2009) (Figure 13, see p. 194). In addition, left ventricular assist devices are becoming smaller and much more reliable than heretofore and have become suitable for the heart failure that follows large STEMIs.

One can now foresee a five step approach to patients with AMI and cardiogenic shock, which remains a complication associated with a very high mortality. 1) Attempt immediate reperfusion by PCI; 2) Insert percutaneous left ventricular assist device; 3) harvest the patient's own bone marrow cells; 4) treat these cells and reinject them into the damaged myocardium; and 5) when these cells become functional, wean the patient from the left ventricular assist device and remove the device. An alternative, in place of, or in addition to, autologous bone marrow cells, i.e. steps 3 and 4 above, is to insert genes into cells which are viable but not contracting.

From a public health perspective, the next major goal is to prevent, rather than merely treat, AMI. A number of risk factors are associated with the development of AMI. These include elevations of blood pressure and low-density lipoprotein cholesterol, cigarette smoking, and the presence of diabetes mellitus.

Both primary and secondary prevention of MI can be accomplished by improving lifestyle (discontinuation of cigarette smoking, exercise and weight loss in overweight and obese subjects) and pharmacologic control of diabetes mellitus, hypertension and hypercholesterolemia. The recent discovery of genetic risk factors for the development of AMI now allows greater precision in the assessment of risk (Figure 14, see p. 195) (Kathiresan *et al.*, 2009).

Summary

It has been an extraordinary century in the history of AMI. The condition was described in 1910 and by the middle of the twentieth century it was recognized to be the most common cause of adult death in the industrialized world. Intensive research into the causes and the management of AMI has reduced the one year mortality from about 50% to 10%. The number of patients with AMI has declined markedly during the past two decades. However, AMI remains a serious condition, especially in the developing world. There has been progress both in identifying subjects at high risk of developing AMI and of lowering this risk in order to reduce its incidence. At the same time, high technology approaches to the management of patients who develop serious complications are being pursued actively. A major challenge now is to apply what has been learned about AMI – both its prevention and treatment – to the developing world, and to do so at costs that are realistic in their economies.

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GENETIC AND ENVIRONMENTAL FACTORS FOR ISCHAEMIC HEART DISEASE

Towards more cost-effective and personalized preventive strategies

■ ATTILIO MASERI

As indicated by H.E. Msgr. Marcelo Sánchez Sorondo in his introductory remarks to this conference, the major, most ambitious challenge nowadays in this field is primary prevention worldwide.

In my presentation I will discuss the potential contributions to more cost-effective preventive strategies that could derive from a more precise understanding of the varied genetic and environmental components of Ischaemic Heart Disease (IHD).

Achievements of primary prevention

Conclusive evidence indicates that the average statistical probability of developing cardiac ischaemic events in population subgroups can be identified on the basis of the presence of traditional predisposing risk factors and that such average probability can be reduced by over 50% by their correction.

These remarkable achievements indicate the opportunity for the immediate implementation of the strategies for risk reduction proven successful and cost-effective.

However the current statistical preventive approach presents limitations. These limitations could be overcome by a better understanding of the mechanism responsible for the actual development of acute ischaemic cardiac events, which could allow a more cost-effective, personalized prevention.

Limitation of statistical preventive approaches

The possibility of stratifying individuals into prognostic categories of risk, has led to focus the attention on the percentage reduction of the number of individuals who develop an event, paying insufficient attention to investigate:

1. Why the large majority, in spite of the same burden of global predisposing factors, doesn't develop events;
2. A substantial percentage develops events in spite of correction of risk, or in the absence of any known risk factor.

Indeed, if in a given group, for example, on average, 30% of individuals are estimated to be at risk of an event, this implies that the remaining 70% with the same risk level will not have an event!

At present there is no way, nor any interest, to try and identify, within the same level of risk, the 30% who are vulnerable from the 70% who are protected. Thus 100% are treated and worried (with the inherent discomfort, risk of side effects and costs) and it may be that one half of those treated will have events in spite of treatment, and in addition a substantial fraction will have events although they do not have known risk factors [1] (Figure 1, p. 196).

The overall final conclusion of the Pooling Project was that ‘coronary atherosclerosis is very common but acute cardiac events are very rare!’

Striving to implement available preventive strategies, these issues are usually neglected.

An innovative approach to these issues should start from the reconsideration of the universal validity of the traditionally established paradigm that risk factors, acting over a period of years and decades, cause the progressive accumulation of coronary atherosclerosis which, in turn, when it reaches a critical threshold, causes ischaemic cardiac events. Such paradigm is so prevalent that often the terms *coronary atherosclerosis* and *IHD* are used interchangeably.

Yet, this reductionist paradigm is true only as a crude first approximation because it does not account for many clinical observations, which are systematically disregarded, confirming Carl Popper’s statement that ‘The dogmatic way of thinking is due to a natural need of regularities and to the inherent mechanisms of discovery. Mechanisms that induce to search for regularities’.

Risk factors atherosclerosis and IHD

The universal validity of this traditionally accepted paradigm is challenged by 4 major clinical observations which demand a more precise understanding of the relationship among risk factors, atherosclerosis and ischaemic events.

1. In a recent meta-analysis of 122,450 patients with coronary disease, 15% of females and 20% of males had none of the known risk factors. About 40% had only one, about 30% had 2 and only about 10% had 3 risk factors [2]. This is in agreement with many previous findings and with the observation of the Italian registry by ANMCO, just completed (but not yet published) which reveals that, of over 10,000 consecutive patients admitted to 168 Italian coronary care units over a 6-month period, about 30% had none of the 4 major risk factors.

Thus established predisposing risk factors do not appear a necessary pathogenetic component of IHD.

2. In a metanalysis of 350,000 individuals, among those with a ≥ 2 risk factors, during an average 30-year follow up, 70% died of non cardiac causes [3].

Thus established predisposing risk factors do not appear to be a sufficient pathogenetic component of IHD.

3. Intracoronary IVUS shows a weak correlation between atherosclerotic burden and risk factors [4].

This observation is totally consistent with the findings of the Pooling Project which failed to find any correlation between coronary atherosclerotic burden, estimated at postmortem, and hypertension or smoking and only a very weak correlation with total cholesterol [5]. Indeed the same study demonstrated a very wide overlap in the extension of coronary atherosclerotic raised fibrous plaque in postmortem studies of patients who died of ischaemic heart disease and of controls who died of non cardiac causes as illustrated in Figure 2 (see p. 177).

Thus the extension of coronary atherosclerosis is on average greater in patients who died of IHD, but with a very wide overlap with controls, particularly above the age of 60, and is only weakly correlated with total cholesterol levels, but not with the other risk factors.

4. Following an acute myocardial infarction, many patients remain totally symptom-free for years and decades (also in the pre-statin era). Moreover patients who present with chronic stable effort angina, on average, have a much greater extension and severity of coronary atherosclerosis than those presenting with their first myocardial infarction [6], who often have single vessel coronary disease and only a mild or moderate stenosis in the infarction-related artery in about 70% of the cases.

Thus the paradigm of a critical threshold of coronary atherosclerosis which, once reached, causes an acute ischaemic event, appears too simplistic and not easily compatible with these observations. In many cases severe coronary atherosclerosis may remain stable, or may return quiescent for years or decades (did the atherosclerotic burden decrease?), conversely some patients may develop infarction also with a mild atherosclerotic burden.

Environmental and genetic risk factors for acute myocardial infarction

We just completed a multiethnic study in which we obtained a blood sample within a maximum of 6 hours from the onset of symptoms in patients with their first ST segment elevation myocardial infarction (FAMI project) admitted for emergency coronary recanalization belonging to

three ethnic groups from metropolitan areas: Italian, Scottish and Chinese and in matched controls (Tables 1, 2 and 3). They had no previous evidence of IHD and, given their very early assessment, their risk factors should closely reflect those immediately before the development of symptoms.

The initial analysis of the data demonstrated a very large dispersion of all individual risk factor values about the medians, similar in the three ethnic groups, and overlapping very widely with those of controls.

Thus the similarity of risk factor levels in very carefully selected patients, with an unequivocal diagnosis of acute infarction, from metropolitan areas of three distinct ethnic groups, suggests a large prevalence of 'western' lifestyle predisposing risk factors compared to genetic mechanisms, which may play a modulatory role in some individuals.

This observation is consistent with the discouraging results obtained by the candidate gene approach and by the limited quantitative success obtained so far by genomic wide screen in the search for single common genetic correlates in a broad clinical syndrome such as myocardial infarction [7]. These findings are not a surprise for haematologists who followed a pathogenetic rather than a statistical preventive approach for anemia!

Future development of cardiovascular prevention

The immediate goal is undoubtedly the promotion of the preventive strategies which are already proven to be, on average, cost-effective. In countries which had great excess of cardiovascular mortality such as Norway and Finland, control of risk factors, produced by extensive lifestyle changes, reduced risk to the level of Mediterranean countries.

Similar results can also be achieved in countries which did not have such a high baseline risk to start but certainly will require massive coordinate campaigns by physicians, mass-media and departments of health and education.

However, preventive strategies should not rely only on what we already learned. The promotion of healthier lifestyles and the timely correction of elevated risk factors should be associated to novel research strategies which should complement the information collected by focusing the attention on 'average' prognosis and 'average' response to intervention, during the last century.

The time has come to focus research on the two extreme group of patients who deviate most from the average prediction: those who do not develop events in spite of a large risk factor burden (in order to discover their protective factors) and in those who develop events in the absence of risk factors (in order to discover their novel risk factors).

Finally known predisposing factors only indicate the statistical probability of an event, but cannot tell in whom and cannot tell whether the event will develop in one month, in one year or in ten years. Thus it would be essential

to concentrate research also on the actual triggers of acute myocardial ischaemic events, responsible for the transition from stability to instability of coronary atherosclerosis (which appears to be largely independent from total coronary atherosclerotic burden!).

FAMI STUDY	
•	First STEMI
•	No previous history of CAD
•	Within 6 hours of onset of symptoms
•	Matched Controls

Table 1.

Patients Enrolment	
	FAMI
Italy	370
Scotland	234
China	443
<i>Total</i>	1047

Table 2.

FAMI BioBank	
•	WHOLE BLOOD: 10 ml
•	SERUM: 10 ml divided in 0.5 ml cryovials
•	PLASMA (NA-Citrate): 6-8 ml stored in 0.5 ml Cryovials
•	PLASMA (Li-Heparin): 6-8 ml in 0.5 ml cryovials
Stored at -80°C	

Table 3.

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SURGICAL OPTIONS IN MYOCARDIAL INSUFFICIENCY

■ FELIX UNGER

Myocardial Insufficiency is becoming a big challenge in cardiology. Over 10% of all people aged over 65 years suffer from myocardial insufficiency in various degrees. The incidence will increase with aging. Overall the outcome is more or less equal to malignancies, the prognosis is poor.

The causes of myocardial insufficiency are manifold, due to coronary artery diseases, cardiomyopathy and rhythm disorders.

In 1985 WHO in Salzburg recommended establishing that the need for cardiac surgery was of 1,000 cardiac operations per million population, whereby the volume of coronary artery surgery is 70%, valve surgery 20%, congenital cases 6%, aortic dissections 2% and replacement by means of transplantation 1%, a statement which is still valid today.

The surgical options for treating myocardial insufficiency are:

- Coronary revascularization
- Valve correction
- Volume reduction in enlarged left ventricles
- Correction of the rhythm and finally
- Assisted circulation and replacement of the heart by means of transplantation and artificial heart.

Bypass surgery

Coronary revascularization bypass surgery is one of the best evaluated procedures in medicine. Bypass surgery has been routinely performed since 1967 and was introduced by Favaloro. The Golden Standard for revascularization is the use of the left internal mammary artery in combination with a saphenous vein. It is evident that arterial graft in form of the left internal mammary has the best patency and should be used in any case to revascularize the left anterior descending artery of the heart. The veins are quite good, but the patency is inferior to the arteries. There are still cases in which the grafts are still open after 20 years. The occlusion depends on the flow and uptake of blood by the myocardium and on the quality of the veins. As an alternative to the LIMA there are the *Arteria radialis* and the *Arteria gastroepiploica*.

A risk with bypass surgery is the age of the patient, which is increasing constantly in the population. The multimorbidity of the patients, due to diabetes,

previous stroke and concomitant diseases such as kidney failure, lung diseases and a low ejection fraction are also risks. During the operation myocardial infarction can occur as well as stroke and postoperative kidney and lung failure.

In 1985 the mean age was 64 years, the patients received 2.1 grafts, in elective cases mortality was 0.69%. Twenty-five years later the mean age is 78, the patients get 4.2 anastomosis, the mortality has increased up to 3%.

An alternative to bypass surgery is PCI (stenting). Stenting is also limited due to in-stent stenosis. A multicenter study (ARTS-Study) clearly demonstrated in the long term that bypass surgery in multivessel disease is superior to stenting. Repeat PCI increases with diabetes up to 30%.

Valve surgery

Valve surgery has a long history. It started with mitral stenosis without heart lung machine in the 1930s. Since 1962 a routine replacement of the valves has been performed. As prosthesis there are mechanical and biological valves in use. With a mechanical valve the problem is thromboembolism, in the biological valve it is calcification. The valves have to be properly selected per indication for every patient individually. In many cases mitral valve reconstruction is possible, especially when the valve is degenerated, has an enlarged ring or rupture of the chordae and the papillary muscles. Today 30% of aortic valve replacements require an additional revascularization, mainly in elderly patients.

The number of left ventricular aneurysmectomies after myocardial infarction is decreasing. This technique is for volume reduction by plication of the scar of the left ventricle or removing the scar and inserting a patch. The reduction of the quantity mirrors the positive effect of modern cardiology. Early revascularization – early re-opening of a vessel. Thirty years ago we saw 30–40 patients per year, today only 1 or 2 patients per year.

Assisted circulation

The eldest routine form of assisted circulation is intra aortic balloon pumping, a technique introduced in 1968, where 25% of the cardiac output can be overtaken by the balloon pump. A balloon is inserted in the descending aorta and driven according to the ECG. In the early 70s cardiopulmonary bypass was a risk in itself. Many patients could not be weaned from bypass. This was the incentive to develop a Left Ventricular Assist Device which is implanted transatrial to the ascending aorta. 100% of the left ventricular work can be overtaken. Now such Left Ventricular Assist Devices are used as a bridge to transplantation. The original idea of a Left ventricular Assist Device was to unload the heart until it could recover. In the last

decade many patients with cardiomyopathy caused by viral infections recovered, so that the device could be removed.

The total artificial heart with its first European clinical use in Salzburg 1986 is not the choice anymore. The driving systems are still too complicated. There are 3 areas of hazards: the valves, the biomaterial and the driving system. The first clinical cases of total artificial heart showed the feasibility but it is not desirable as an alternative to transplantation. An alternative could be Left Ventricular Assist Devices. There are some long-term experiences over five years now available. The limitation is still the driving system.

The transplantation introduced by Barnard in 1967 is a standard procedure in replacing a failing heart. The limits are still rejection and donor availability. These limits are not seen in artificial ventricles.

Conclusion

Overall modern cardiac surgery is an important tool for fighting myocardial insufficiency in the whole context of interventional cardiology. With an aging population the indications for assisted circulation are increasing. These small devices will be available to unload a failing heart.

The incidence of cardiac operations is constant with 1,000 operations per million/population in developed countries. In an aging population, even with all the multimorbidities, thanks to the improved techniques that give optimal results most patients can return to their normal lives.

CARDIOVASCULAR DISEASE: FROM TREATMENT TO PROMOTING HEALTH; A CHALLENGE FOR THE NEXT DECADE

■ JASON C. KOVACIC AND VALENTÍN FUSTER¹

Cardiovascular disease (CVD) is the most prevalent cause of mortality across the globe [1-2]. Of every 10 deaths worldwide, 6 are due to non-communicable conditions; 3 to communicable, reproductive or nutritional conditions; and 1 to injuries. Of the noncommunicable conditions CVD is by far the most prevalent cause of death, accounting for at least 30-40% of mortality attributable to noncommunicable conditions [2]. Importantly, CVD can manifest in many ways, including as coronary artery disease (CAD) and myocardial infarction, stroke, renal failure, aortic aneurysm and degenerative brain disease (DBD). This massive burden of disease consumes a significant share of the world's fiscal and health care resources, and has a major, adverse influence on the physical and mental wellbeing of patients and their families.

Added to this, in many nations the looming 'aging epidemic' will soon compound this problem. Framed by the aging 'baby-boomer' cohort, the number of persons at risk for CAD and CVD is predicted to increase dramatically in the coming decade [1], which will place significant additional demands on health care resources. Meeting the challenges of the 'aging epidemic' is something that will assume increasing importance in the coming decade. Moreover, as can already be seen from this complex matrix of factors, attempts at reducing the morbidity and mortality attributable to CVD will require a multi-pronged approach spanning biology, treatment modalities, societal attitudes and health care resource utilization [3].

Primary cardiovascular disease prevention

Primary prevention must be the core of our efforts to promote cardiovascular health. Lifestyle modification is central to primary prevention, and one

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of the most powerful ways of illustrating the need for lifestyle change is by defining to a patient their risk for CVD-related morbidity and mortality. Current guidelines place great emphasis on CVD risk evaluation, recommending that global risk scores incorporating multiple traditional cardiovascular risk factors should be calculated for risk assessment in all asymptomatic adults without a clinical history of CAD/CVD [4]. While there are several risk assessment algorithms, perhaps the best known is the Framingham Risk Score, with simple online tools available to calculate 10-year risk of CAD-related adverse events. Physicians and patients should be encouraged to make use of these resources, and to take action to mitigate high-risk aspects of their CVD risk profile or to initiate therapy as appropriate [3].

Contemporary treatment of coronary artery disease

For those already afflicted with CAD, a treatment strategy based on medical management, rather than invasive revascularization, may be an increasingly viable option. A major turning point was the recent COURAGE trial (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation). COURAGE compared a strategy of percutaneous coronary intervention (PCI) plus optimal medical therapy (OMT) versus OMT alone in stable patients, showing no difference in the rate of the primary endpoint (death or myocardial infarction) during a follow-up period of 4.6 years [5]. Supported by other studies such as BARI-2D in diabetic patients [6], the advent of COURAGE has seen increasing scrutiny with respect to the appropriateness of performing PCI and other revascularization procedures. In effect, COURAGE has opened the door for the use of OMT as a primary treatment for CAD, particularly in select low-risk patients. We foresee that with the increasing movement toward cost-effective, evidence-based medical practice, the next decade will see a rise in the use of OMT as a primary strategy for the treatment of patients with CAD and CVD. Furthermore, even in patients undergoing invasive revascularization, the use of OMT will be increasingly emphasized as a critical aspect of routine post-procedural care that reduces the likelihood of further cardiovascular events [7]. COURAGE also suggests that for the majority of patients who are unable to readily access or afford invasive revascularization, medical therapy is an appropriate long-term treatment option.

At the same time as COURAGE was being conducted, physicians were becoming more aware of the fact that for patients suffering from complex multivessel CAD, any consideration of a potential revascularization strategy must be made with very close attention to coronary anatomical and physiological factors. Regarding CAD anatomy, several studies have shown the

value of the SYNTAX risk score for triaging patients to either PCI or coronary artery bypass graft (CABG) surgery [8-10]. The SYNTAX score assesses coronary anatomy complexity from the perspective of potential PCI or CABG surgery, and has been shown to relate to improved outcomes when patients with especially complex disease (SYNTAX score ≥ 33) undergo CABG surgery rather than PCI [8]. In addition, if the anatomy is not overly complex (SYNTAX score < 33) and the patient is an appropriate PCI candidate, then the physiological assessment of lesions proposed for PCI by fractional flow reserve (FFR) is now advocated. FFR is a technique used in the catheterization laboratory to measure pressure differences across a coronary stenosis, and determine if a lesion is likely to be functionally significant and associated with myocardial ischemia. This drive towards FFR-based physiological lesion assessment is as a result of the FAME study, which showed that measuring FFR in patients with complex multivessel CAD who are undergoing PCI reduces death, nonfatal myocardial infarction and repeat revascularization at 1 year [11].

While these studies remain important new guides in how to best manage complex CAD patients, lingering questions remain. One of these continues to be the role of PCI versus CABG surgery in diabetic patients. The ongoing FREEDOM trial is poised to answer this question (FREEDOM, Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease) [12]. The study population comprises 2,400 patients with diabetes mellitus and multivessel CAD amenable to either PCI or CABG surgery, with indication for revascularization based upon chest pain symptoms or other evidence of myocardial ischemia. This study is expected to report initial findings in the near future.

A final group of patients that we know very little about is those with asymptomatic CAD/CVD who are at risk for near-term events. Aggressive primary prevention in these patients is vital to avoiding morbidity and mortality and a window of opportunity exists for averting CAD/CVD events if these at risk patients can be identified. However, most cardiovascular events occur in persons who would be classified as low or intermediate risk by a risk factor-based approach. Thus, although attention to risk factors is of critical importance, it has been estimated that $> 75\%$ of all coronary events may occur in persons classified at low or intermediate risk [13]. In an attempt to discover novel and efficacious approaches to identify and treat these at risk persons, the High Risk Plaque (HRP) Bioimage study was recently initiated [13]. A total of 7,687 patients without evidence of atherothrombotic disease but presumed to be at risk for near-term CVD events were enrolled. The majority then underwent comprehensive baseline

assessment, including determination of CVD risk factors, quantification of coronary artery calcification and assessment of numerous other measures of CVD burden. Participants with one or more abnormal screening test then underwent additional multi-modality imaging and other testing to further evaluate their vascular disease burden. The trial is now in an active follow-up phase and will provide a wealth of information about these at risk individuals. The results of the HRP Bioimage study will provide novel directions in the drive to promoting cardiovascular health in the next decade and epitomizes the goal of maximizing primary prevention efforts to avert CAD/CVD. Most importantly, this study will facilitate the aggressive treatment of at risk patients to avert CVD events.

Optimal medical therapy for CAD and medication adherence

Regardless of whether a patient is to be managed by PCI, CABG surgery or OMT alone, risk factor modification in terms of comprehensive medical therapy (aspirin, lipid lowering therapy, anti-hypertensive medication) and lifestyle modification (healthy diet, regular exercise, weight loss, smoking cessation) is the cornerstone of secondary prevention. Indeed, even in the very elderly (nonagenarians and centenarians) with unstable CAD, adherence to guideline-recommended therapies is associated with decreased mortality [14]. However, what has emerged from studies such as COURAGE [5] and BARI-2D [6], is that only approximately 50% of patients are achieving treatment goals for blood pressure, cholesterol and glycemic control. Medication non-adherence is thought to be a large part of this problem, and across all health-care categories non-adherence is believed to account for \$290 billion dollars of annual health care expenditure in the USA [15]. Multiple socio-economic factors play into the equation of why patients stop taking their medications and a major initiative to combat this problem is the increasing drive towards the polypill. The idea of combining numerous medications into a single tablet that targets risk factors associated with CVD was first proposed almost a decade ago [16]. Most cardiovascular polypill formulations address several CVD risk factors at once (hypertension, lipid levels, platelet adhesiveness). Not only does this increase patient convenience, but by combining several compounds in a single tablet, out-of-pocket costs to patients and insurers are reduced. Estimates suggest that the across-the-board use of the polypill by US adults aged ≥ 55 years may prevent 3.2 million CAD events and 1.7 million strokes over 10 years, while among those with a history of CVD, the potential to prevent 0.9 million CAD events and 0.5 million strokes is projected [17]. With this huge potential to benefit such a large number of persons, several randomized clinical

trials have now been initiated to study the potential effects of polypills on CVD risk factors and clinical outcomes [17].

Cardiovascular disease, degenerative brain disease and reverse cholesterol transport

Promoting cardiovascular health in the coming years will see redoubled efforts to improve our understanding of the biologic nature of HRP and CAD/CVD. While significant strides have recently been made in this direction, particularly major advances in our understanding of the interactions of cellular senescence, inflammation, aging and CVD have served to underscore the systemic nature of the atherothrombotic disease process [1,18]. As an example and as we have recently reviewed elsewhere [1,3,18], not only is atherosclerosis and HRP responsible for strokes, but it is now clearly implicated in Alzheimer's and other degenerative brain diseases (DBDs); conditions previously thought to be solely due to degenerative neurologic processes [18-19]. This 'HRP-DBD axis' of disease highlights the systemic inflammatory nature of atherosclerosis, and emphasizes the fact that the local opening of an isolated coronary artery obstruction does not treat the entire patient. Again, the burden of this disease is enormous. Alzheimer's disease is the most common form of dementia, accounting for 50 to 56% of cases [20]. More than 35 million people worldwide – 5.5 million in the United States – suffer from this condition. The principal risk factor for Alzheimer's disease is age. However, vascular disease affecting the brain is thought to affect 60-90% of patients with Alzheimer's disease, and contributes to a worsened clinical outlook [20]. As the aging of the population increases, the prevalence will approach 13.2 to 16.0 million cases in the USA by mid-century. Our current understanding of the mechanisms whereby HRP and CVD contribute to DBD is rudimentary, but aging, hypertension, the deposition of certain proteins and inflammation likely act in concert with vascular mechanisms to induce neuronal and brain dysfunction. It is at this intersection point that the interactions between atherosclerosis, aging and DBD can be readily appreciated, and the pathways forward from risk to health are most sharply brought into focus (Figure 1).

Of all the potential pathways whereby CVD and atherosclerosis may give rise to DBD, increased inflammation is likely to be a critical mechanism. An exciting mode of decreasing vascular inflammation is to reduce the amount of cholesterol in atherosclerotic plaques. This concept of 'reverse cholesterol transport' – the removal of cholesterol from plaque – is evolving rapidly. The prototypical family of drugs which promote reverse cholesterol transport is the cholesteryl ester transfer protein (CETP) inhibitors. CETP

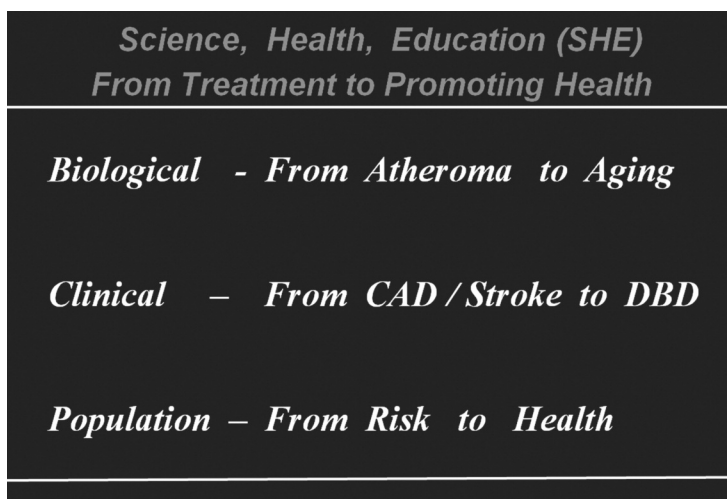


Figure 1. Overview of the interactions between atherosclerosis, aging, CVD and DBD, and the proposed therapeutic transitions from CVD risk to global cardiovascular health.

is a protein which facilitates the shuttling of different cholesterol-related particles in the body, in particular the reverse transport of cholesterol from the tissues back to the liver. Recently, treatment with anacetrapib, a CETP inhibitor, was found to lower low-density lipoprotein (LDL) ('bad') cholesterol and dramatically raise HDL ('good') cholesterol by 138%, with an acceptable side-effect and adverse event rate [21]. Our group will soon embark on the study of another CETP inhibitor, dalcetrapib, with the specific aim of investigating its effect on reducing the size of atherosclerotic vascular lesions.

Promoting global cardiovascular health

With the rapid 'Westernization' of many low- and middle-income countries (LMICs), rates of smoking, obesity, physical inactivity and other adverse factors associated with CVD are rising dramatically in these regions. A veritable explosion of global CVD appears certain if high-level action is not taken [3]. The Institute of Medicine (IOM; the health arm of the US National Academy of Sciences) has undertaken an extensive review of the problems faced in LMICs and has produced a report titled *Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health* [22–23]. The document lays out a strategic path forwards for how

we might form broad partnerships and strategic alliances which allow a multipronged attack on CVD in LMICs. A summary of these recommendations is provided in Figure 2, and provides a comprehensive framework for addressing the global threat of CVD.

Equally as important, in May 2010 a resolution was passed by the United Nations to move forward with a high-level meeting on noncommunicable diseases. This meeting, scheduled for September 2011, is a clear signal that CVD is now seen as a critical factor in worldwide health. Areas where inroads can most readily be made have already been identified: raising public awareness; avoidance of risk-taking behavior (e.g. smoking, physical inactivity); and improved access to effective and affordable CVD medicines by generic availability, removal of legal restrictions, enhanced bulk procurement and the elimination of mark-up and tariffs [24]. The development of a polypill may play a major role in expediting a number of these objectives.

Now that the global problem of CVD has been defined and an initial path forward laid out, the greatest challenge ahead will be translate these plans into actions. Moving from IOM recommendations and United Nations meetings to global cardiovascular health will require an iterative approach grounded in science, health and education (Figure 1).

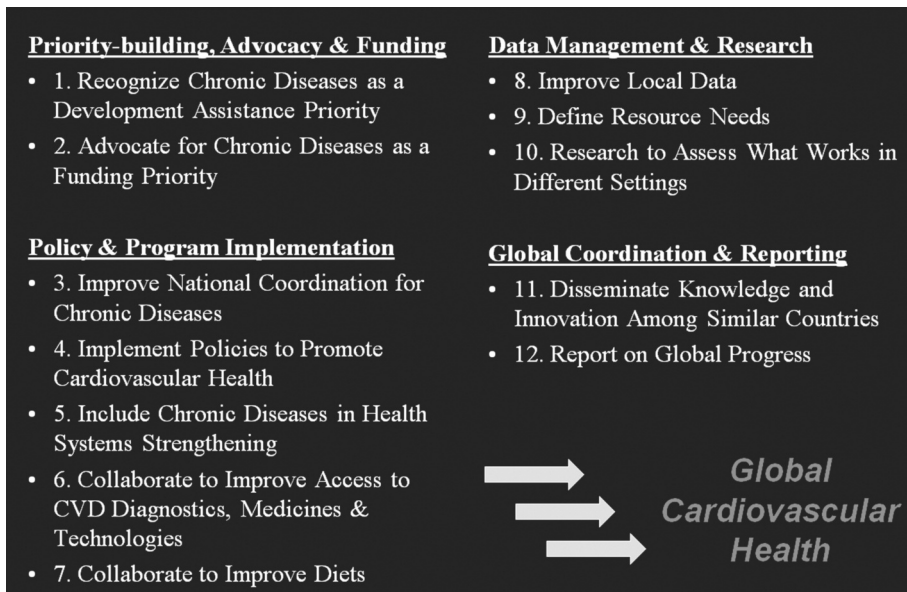


Figure 2. Recommendations for improving global cardiovascular health from the IOM document *Promoting Cardiovascular Health in the Developing World: A Critical Challenge to Achieve Global Health* [22-23].

Conclusions

We are facing an epidemic of CVD. However, there are many potential advances and strategies that might be implemented to address this problem. At all levels, from the scientific laboratory, subsistence-level LMICs and to the highest international political platforms, maintaining a comprehensive and energized (but yet achievable) outlook toward this problem will be paramount. Maximizing the use of current knowledge, infrastructure and resources while minimizing factors such as political gain and corporate agendas will be key. Motivating ourselves, our families and our societies to take the required steps towards cardiovascular health is something we must all strive towards.

Conflicts of interest/Disclosures and acknowledgements

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► CEREBROVASCULAR DISEASE

ACUTE STROKE TREATMENT: A WINDOW OF OPPORTUNITY¹

■ WERNER HACKE

Introduction

Stroke is a medical and occasionally also a surgical emergency. Stroke rates are on the rise all over the world and stroke has become the number one cause of mortality in several parts of the world including China, Russia and India. We may expect a doubling of strokes in the next 3 decades with the increase of life expectancy.

The success of care of the acute stroke victim begins with the recognition both by the public and the health professionals [Wang, 2001] that stroke is an emergency, like acute myocardial infarction or trauma. Care of the acute stroke victim as an emergency depends on a four-step chain:

1. Rapid recognition and reaction to stroke warning signs,
2. Immediate EMS contact and priority EMS dispatch,
3. Priority transport with notification of the receiving hospital,
4. Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, therapeutic decision and administration of appropriate treatments at the receiving hospital.

Referral

Applying the 'time is brain' concept means that medical attention and treatment of stroke should be considered as an emergency. Thus, avoiding time delays should be the major aim in the prehospital phase of acute stroke care. This has far-reaching implications for recognition of signs and symptoms of stroke by the patient himself or his relatives or bystanders, the means of first medical contact, and transportation to hospital. In several studies, delays have been identified at three different levels of acute stroke management [Kwan, 2004]:

1. Delays at the population level attributed to a failure to recognise the symptoms of stroke and contact emergency services.

¹This manuscript is based on the ESO-Guidelines for ischemic stroke management. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008 – Hacke W for The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. *Cerebrovascular Diseases* 25, 5:457-507.

2. Delays at the level of the emergency services and emergency physicians due to failure to prioritise stroke transport.
3. Delays at the hospital level due to delays in neuroimaging and inefficient in-hospital acute stroke care.

A large amount of time is lost outside the hospital [Evenson, 2001]; for stroke patients of a Portuguese university hospital this accounted for 82% of time [Ferro, 1994]. Studies that identify demographic, social, cultural, behavioural and clinical factors associated with longer prehospital time may provide targets for educational campaigns [Moser, 2006; Gil Nunez, 2004]

To improve the accuracy of stroke identification and speed up transfer to the hospital education should also be directed to paramedics and ED staff [Kwan, 2004]. Education of paramedics increased stroke knowledge, clinical and communication skills [Gordon, 2005 #336] and decreased pre-hospital delay [Behrens, 2002 #298].

Recommendations

- *Immediate emergency medical system (EMS) contact and priority EMS dispatch are recommended (Class II, Level B).*
- *Priority transport with advance notification of the receiving hospital (outside and inside hospital) is recommended (Class III, Level B).*
- *Suspected stroke victims should be transported without delay to the nearest medical centre with a stroke unit that can provide ultra-early treatment (Class III, Level B).*
- *Dispatchers and ambulance personnel should be trained to recognise stroke using simple instruments such as the Face Arm Speech Test (Class IV, Level GCP).*
- *Immediate emergency room triage, clinical, laboratory and imaging evaluation, accurate diagnosis, therapeutic decision and administration of appropriate treatments at the receiving hospital is recommended (Class III, Level B).*
- *In remote or rural areas helicopter transfer should be considered to improve access to treatment (Class III, Level C).*
- *In remote or rural areas telemedicine should be considered to improve access to treatment (Class II, Level B).*

In-hospital treatment

In-hospital delay may account for 16% of total time lost from stroke onset to CT [Ferro, 1994]: Reasons for in-hospital delays are a lack of identifying stroke as emergency, inefficient in-hospital transport, delayed medical assessment, delay in imaging or an uncertainty in administering rt-PA [Kwan, 2004; Evenson, 2001; Gil Nunez, 2004]. Stroke care pathways have the potential to organize care more effectively, although a recent meta-

analysis identified insufficient good quality evidence and so could not support their routine implementation. Pathways may reduce in-hospital delays in door to medical department time, door to imaging time [Suzuki, 2004; Mehdiratta, 2006], door to needle time [Mehdiratta, 2006] and, in case of endovascular treatment, in door to arteriography time.

Stroke patients should be medically assessed as a priority. While only a minority present in an immediately life-threatening condition, many have significant physiological abnormalities or comorbidities. Symptoms and signs which may predict later complications such as space-occupying infarction or bleeding, recurrent stroke, and medical conditions such as hypertensive crisis, co-existing myocardial infarction, aspiration pneumonia, cardiac and renal failure must be recognised early. Stroke severity should be assessed by a targeted neurological examination using the National Institutes of Health Stroke Scale by trained staff [Lyden, 1994].

<i>In all Patients</i>	
1	Brain Imaging: CT or MR
2	ECG
3	<i>Laboratory Tests</i> Complete blood count and platelet count, prothrombin time or INR, PTT Serum electrolytes, blood glucose CRP or sedimentation rate Hepatic and renal chemical analysis
<i>When Indicated</i>	
4	Extracranial and transcranial Duplex/Doppler ultrasound
5	MRA or CTA
6	Diffusion and perfusion MR or Perfusion CT
7	Echocardiography (transthoracic and/or transoesophageal)
8	Chest X-ray
9	Pulse oxymetry & Arterial blood gas analysis
10	Lumbar puncture
11	EEG

Table 1. Emergency diagnostic tests in acute stroke patients.

Stroke units

A stroke unit consists of a discrete area of a hospital ward that exclusively or nearly exclusively takes care of stroke patients [Stroke Unit Trialists' Collaboration, 2007] and is staffed by a specialist multidisciplinary team. The core disciplines of the team are medical, nursing, physiotherapy, occupational therapy, speech and language therapy and social work [Langhorne, 2002]. The multidisciplinary team should have a specialist interest in stroke management and work in a coordinated way through regular meetings to plan patient care. Programmes of regular staff education and training should be provided [Langhorne, 2002].

All stroke patients require specialist multidisciplinary care delivered in a stroke unit. Selected acute patients will require additional higher technology interventions, in particular thrombolysis and neurointensivist care. Health services need to establish the infrastructure to deliver these interventions to all patients who require them. This has been the subject of recent consensus documents [Alberts, 2005; Leys, 2007] which have defined the component parts of primary and comprehensive stroke centers.

Primary stroke centers (PSC) are defined as centers with necessary staffing, infrastructure, expertise and programs to provide appropriate diagnosis and treatment for most stroke patients. At the same time, some patients with rare disorders, complex stroke and multi-organ diseases may need more specialized care and resources that are not available in PSC.

Comprehensive stroke centers (CSC) are defined as centers with not only necessary staffing, infrastructure, expertise and programs to provide appropriate diagnosis and treatment for most stroke patients, but also with high technology medical and surgical care (new diagnostic and rehabilitation methods, specialized tests, automatic monitoring significant number of physiological parameters, interventional radiology, vascular surgery, neurosurgery).

General stroke treatment

The term 'general treatment' refers to treatment strategies aimed at stabilising the critically ill patient in order to control systemic problems that may impair stroke recovery. There is a consensus that the management of such problems is a central part of stroke treatment [The European Stroke Initiative Executive Committee and the EUSI Writing Committee, 2003; Leys, 2007] and includes respiratory and cardiac care, fluid and metabolic management, blood pressure control, the prevention and treatment of seizures, deep vein thrombosis, pulmonary embolism, dysphagia, aspiration

pneumonia, other infections, pressure ulceration and occasionally management of elevated intracranial pressure. However many aspects of general stroke treatment have not been adequately assessed in randomised clinical trials.

Recommendations

- *Intermittent monitoring of neurological status, pulse, blood pressure, temperature and oxygen saturation is recommended for 72 hours in patients with significant persisting neurological deficits (Class IV, level GCP).*
- *Continuous monitoring is recommended in medically unstable patients with known cardiac disease or arrhythmia, unstable blood pressure, sepsis, cardiopulmonary disease such as heart failure, cardiac arrhythmias (current or previous history), depressed conscious level or severe stroke and reduced oxygen saturation (Class IV, Level GCP).*
- *Oxygen should be administered if the oxygen saturation falls below 95% (Class IV, level GCP).*
- *Regular monitoring of fluid balance and electrolytes is recommended in patients with severe stroke or swallowing problems (Class IV, Level GCP).*
- *Normal saline (0.9%) is recommended for fluid replacement during the first 24 hours after stroke (Class IV, Level GCP).*
- *Routine blood pressure lowering is not recommended following acute stroke (Class IV, Level GCP).*
- *Cautious blood pressure lowering is recommended with extremely high values (>220/120mm Hg) on repeated measurements (Class IV, Level GCP).*
- *Blood pressure lowering may be required with severe cardiac failure, aortic dissection, hypertensive encephalopathy (Class IV, Level GCP).*
- *Abrupt blood pressure lowering should be avoided (Class II, Level C).*
- *Low blood pressures secondary to hypovolemia or associated with neurological deterioration in acute stroke should be treated with volume expanders (Class IV Level GCP).*
- *Monitoring serum glucose levels is recommended (Class IV, Level GCP)*
- *Treatment of serum glucose levels above 10 mmol/l with insulin titration is recommended (Class IV, Level GCP).*
- *Pyrexia (temperature >37.5°C) should promote a search for concurrent infection (Class IV, Level GCP).*
- *Treatment of pyrexia (temperature >37.5°C) with paracetamol and fanning is recommended (Class III, Level C).*
- *Antibiotic prophylaxis is not recommended in immunocompetent patients (Class II, Level B).*

Diagnosics

Acute stroke is an emergency and stroke victims should have a clear priority for brain imaging compared to other patients, because time limits are so crucial. Rapid, focussed neurological assessment assists considerably in determining which imaging technique is likely to be most helpful and to tailor the individual imaging examination. In patients with stroke, diagnostic brain imaging must be performed immediately on arrival at a hospital so that treatment can be started immediately. Investigation of TIA is equally urgent, because up to 10% of these patients will suffer stroke within the next 48 hours. Immediate access to imaging on arrival at hospital is facilitated by pre-hospital notification and good communication with the imaging facility: stroke services including the ambulances should work closely together with the imaging department to plan best use of resources. Imaging tests should take into account the patient's condition, for example a substantial proportion (up to 45%) of patients with severe stroke may not tolerate MR examination because of their medical condition and contraindications [Schramm, 2004; Barber, 2005; Hand, 2005].

Imaging of the brain and supplying vessels is crucial in the assessment of patients with stroke and transient ischaemic attacks (TIA). Brain imaging distinguishes ischaemic stroke from intracranial haemorrhages and stroke mimics, identifies the type and often also the cause of stroke, may help to differentiate irreversibly damaged tissue from areas that may recover thus guiding emergency and subsequent treatment, and may help to predict outcome. Vascular imaging may identify the site and cause of arterial obstruction, and identifies patients at high risk of stroke recurrence for specific preventions.

Plain CT is widely available, reliably identifies most stroke mimics, and distinguishes acute ischaemic from haemorrhagic stroke within the first five to seven days [Wardlaw, 2003; Kidwell, 2004]. Immediate CT scanning is the most cost-effective strategy for imaging acute hospital-admitted stroke patients [Wardlaw, 2004]. CT is not sensitive for old haemorrhage. Overall, CT is less sensitive, but as specific, for early ischaemic changes as MRI. Two thirds of patients with moderate to severe stroke have visible ischaemic changes within the first few hours of stroke [von Kummer, 2001; Barber, 2000; Wardlaw, 2005; Chalela, 2007], no more than 50% of patients with minor stroke have a visible relevant ischaemic lesion on CT, especially within the first few hours of stroke. Training in identification of early ischaemic changes on CT [Wardlaw, 2005; von Kummer, 1998], and the use of scoring systems [Barber, 2000] improves detection of early ischaemic changes. Some centres prefer to use MRI as first line routine investigation

for acute stroke. It has the advantage that it can identify early ischaemic changes with diffusion weighted sequences (DWI) with higher sensitivity than CT. The higher sensitivity of MRI is particularly useful in diagnosis of posterior circulation stroke and lacunar or small cortical infarctions. It can also detect small and old haemorrhages with T2* (gradient echo) sequences [Dimigen, 2004]. However, DWI can be negative in patients with definite stroke [Ay, 2002].

The degree of restricted water diffusion in the DWI lesion can be quantified by measuring the apparent diffusion coefficient (ADC). Restricted diffusion on DWI is not 100% specific for ischaemic brain damage because hyperintensities may be seen in other conditions, e.g. in epileptic fits, in MS, encephalitis, hypoglycaemia. DWI high signal can be seen in the presence of T2-high signal lesions as 'shine through'. In such cases, examination of ADC maps will show that diffusion is not restricted.

Carotid ultrasound can visualise well the carotid bifurcation and proximal internal carotid artery (ICA) stenosis and can determine the degree of stenosis and plaque characteristics. MRA and CTA can also visualise carotid stenosis well. Systematic reviews and individual patient data meta-analysis indicate that contrast enhanced MRA (CE-MRA) is the most sensitive and specific of the non-invasive imaging modalities for carotid artery stenosis, closely followed by Doppler ultrasound, and then CTA and lastly non-contrast MRA [Wardlaw, 2006]. Transcranial Doppler (TCD) ultrasound allows flow velocity recordings from intracranial vessels and detection of stenosis. A disadvantage is that up to 20% of acute stroke patients do not have an adequate acoustic window particularly in elderly individuals and certain ethnic groups, such as black individuals [Postert, 1997]. The problem can be considerably reduced by using ultrasound contrast agents [Droste, 1999; Droste, 2000]. The combination of ultrasound imaging techniques and MRA reveals excellent results equal to DSA [Niederkoorn, 2003].

All acute stroke and TIA patients should have a 12 channel-ECG. Cardiac monitoring should be conducted routinely after an acute cerebro-vascular event to screen for serious cardiac arrhythmias. For stroke and TIA patients seen after the acute phase, 24 hour Holter ECG monitoring should be performed when arrhythmias are suspected and no other causes of stroke are found.

There is controversy about the indications for, and type of, echocardiography in stroke and TIA patients. TTE is sufficient for patients with ventricular pathology. TEE is superior to TTE in evaluation of the aortic arch, left atrium, and atrial septum. CT and MRI show promise in cardiac evaluation.

Recommendations

1. *In patients with suspected TIA or stroke, urgent cranial CT (Class I) or alternatively MRI (Class II) is recommended (Level A).*
2. *If MRI is used, the inclusion of DWI and a T2*-weighted gradient echo sequences are recommended (Class II, Level A).*
3. *In patients with suspected TIA or stroke, urgent vascular imaging (ultrasound, CTA, or MRA) is recommended (Class I, Level A).*
4. *Patients with TIA, minor stroke, or early spontaneous recovery immediate diagnostic work-up including imaging is recommended (Class I, Level A).*
5. *Perfusion imaging with CT or MRI or the mismatch concept is currently a research tool and cannot be recommended for routine treatment decisions.*
6. *In patients with acute stroke and TIA, early evaluation of physiological parameters, routine blood tests, and ECG is recommended (Class I, Level A).*
7. *Continuous ECG recording is recommended for ischaemic stroke and TIA patients. (Class I, Level A).*
8. *Echocardiography is recommended in selected patients (Class III, Level B).*

Specific stroke treatment

Thrombolytic therapy with recombinant tissue plasminogen activator (tPA; 0.9 mg/kg body weight, max. 90 mg) given within 3 h after stroke onset to patients with acute ischemic stroke significantly improves outcome [The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995], with an NNT of 7 patients to achieve a favorable clinical outcome after 3 months. ECASS and ECASS II tested a 6-hour time window and did not show statistically significant superiority of tPA for the primary endpoints [Hacke, 1998; Hacke, 1995]. A pooled analysis of individual data of the tPA trials showed that even within a three-hour time window the sooner the treatment is initiated the better the outcome (0–90 min: OR 2.11, 95% CI 1.33–3.55; 90–180 min: OR 1.69, 95% CI 1.09–2.62) [Hacke, 2004]. This analysis suggested a benefit up to 4.5 hours.

Finally, in 2008 the ECASS-3 study has provided new data on systemic thrombolysis with rtPA in a time window of 3 to 4.5 hours after stroke onset (27). This multicenter, randomized, placebo controlled, prospective study enrolled over 800 patients to either systemic treatment with rtPA or placebo within 3 to 4.5 hours after stroke symptom onset. Persons older than 80 years, those with a baseline NIHSS score >25, those taking oral anticoagulants, and those who had the combination of a previous stroke and diabetes mellitus were excluded from participation. Symptomatic intracranial hemorrhage, as defined by the criteria used in the NINDS study, was diagnosed in 7.9% of subjects treated with rtPA and 3.5% when given placebo (OR 2.38, 95% CI

1.25 to 4.52, $P < 0.006$). However, this increased incidence of hemorrhage is consistent with other clinical rtPA-trials (3, 6, 8, 28-29). The frequency of the primary efficacy outcome in ECASS-3 (defined as mRS score of 0 to 1 at 90 days after treatment) was significantly greater with rtPA (52.4%) than with placebo (45.2%; OR 1.34, 95% CI 1.02 to 1.76; risk ratio 1.16, 95% CI 1.01 to 1.34; $P < 0.04$). The number needed to treat to achieve the primary efficacy outcome was 14. Mortality in the two ECASS-3 treatment groups did not differ significantly, although it was nominally higher among the subjects treated with placebo [Hacke *et al.*, 2008].

Thrombolytic therapy appears to be safe and effective across various types of hospitals, if the diagnosis is established by a physician with stroke expertise, and a CT of the brain is assessed by a physician with expertise in reading this imaging study [Hill, 2005][Bateman, 2006][Wahlgren, 2007]. Risks and benefits of tPA should be discussed whenever possible with the patient and family before treatment is initiated.

Blood pressure must be below 185/110 mmHg before, and for the first 24 hours after thrombolysis. High blood pressure management according to the NINDS trial is required [The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995]. Protocol violations are associated with higher mortality rates [Katzan, 2003][Graham, 2003].

The European license for rtPA is restricted to patients between 18 years and 80 years of age. An increasing number of stroke patients are older than 80 years, mainly due to demographic development.

Three-month mortality was higher in patients aged >80 years compared to patients <80 years. Favorable outcome (mRS ≤ 1) and intracranial hemorrhage (asymptomatic, symptomatic, or fatal) were similarly frequent in both groups. Stroke severity, time to thrombolysis, glucose level, and history of coronary heart disease independently predicted outcome, whereas age did not (48).

The overall rate of hemorrhagic complications after rtPA treatment for ischemic stroke in octogenarians was 6.9%, compared to 5.3% in younger patients ($p = 0.61$). Baseline imaging method (CT or MRI) had no significant influence on ICH, mortality or on favourable outcome on the mRS after 3 months (52).

Intraarterial and combined (IV+IA) thrombolysis

Intra-arterial thrombolytic therapy of proximal MCA occlusion using pro-urokinase in a 6-hour time window was significantly associated with better outcome in a RCT (PROACT II) [Furlan, 1999]. Pro-urokinase is not available and the use of intra-arterial tPA or any other thrombolytic agent is not substantiated by RCTs but by some observational data [Nedeltchev, 2006].

Intra-arterial treatment of acute basilar occlusion with urokinase or tPA, although available for more than 20 years with encouraging results from observational studies [Brandt, 1996][Hacke, 1988], has not been tested in a RCT. In acute basilar occlusion one trial included 16 patients but was underpowered. A systematic review including 420 patients with BA occlusion compared intravenous to intra-arterial thrombolysis and found no significant difference between the two treatment options (43).

A prospective registry (Basilar Artery International Cooperation Study, BASICS) investigated 592 patients with acute BA occlusion for differences regarding antithrombotic therapy, intravenous or intra-arterial thrombolysis. However, most patients received intra-arterial thrombolysis. No statistically significant superiority for intra-arterial over intravenous thrombolysis was found. Therefore, unequivocal superiority of intra-arterial over intravenous thrombolysis is not shown.

The so-called ‘bridging concept’ is currently preferred in most centers in case of proven vessel occlusion. Therefore rtPA is given with 60% of the full recommended dosage as first-line treatment and – in case of non-responders – either local application of rtPA at the thrombus site, use of mechanical recanalization devices, mechanical clot disruption, or a combination of the aforementioned techniques is performed. Standard-treatment of patients with BA occlusion in non-specialized centers or where neuroradiological intervention is not available, should be intravenous application of rtPA, since there are no trials to support the superiority of intra-arterial thrombolysis in patients with BA occlusion.

Intra-arterial recanalization devices

In the Mechanical Embolus Removal in Cerebral Embolism (MERCI) trial, vessels were opened with a device that removed the thrombus from an intracranial artery. Recanalization was achieved in 46% (69/151) of patients on intention to treat analysis, and in 48% (68/141) of patients in whom the device was deployed within 8 hours of the onset of stroke symptoms [Smith, 2005 #501]. No RCTs with outcome data are available for any recanalization devices.

A randomized trial of standard intravenous tPA as compared with a combined intravenous and intra-arterial approach has started after encouraging phase II results (IMS3) [IMS investigators, 2007].

Anti-platelet therapy

The results of 2 very large randomized, non-blinded intervention studies indicate that aspirin started within 48 h after stroke (International Stroke

Trial, Chinese Acute Stroke Trial) is safe and effective [International-Stroke-Trial-Collaborative-Group, 1997; CAST-Collaborative-Group, 1997]. In absolute terms, 13 more patients were alive and independent at the end of follow-up for every 1000 patients treated. Furthermore, treatment increased the odds of making a complete recovery from stroke (OR = 1.06; 95% CI 1.01 to 1.11). In absolute terms, 10 more patients made a complete recovery for every 1000 patients treated. Antiplatelet therapy was associated with a small but definite excess of 2 symptomatic intracranial haemorrhages for every 1000 patients treated, but this was more than offset by a reduction of 7 recurrent ischemic strokes and about one pulmonary embolus for every 1000 patients treated.

Brain oedema

Space-occupying brain oedema is a main cause of early deterioration and death in patients with large supratentorial infarcts. Life-threatening brain oedema usually develops between the 2nd and 5th day after stroke onset, but up to a third of patients can have neurological deterioration already within 24 hours after symptom onset [Hacke Qureshi, 2003].

Medical therapy in patients with large space-occupying infarctions and brain oedema is based mostly on observational data. Basic management includes head positioning at an elevation of up to 30°, avoidance of noxious stimuli, pain relief, appropriate oxygenation and normalizing body temperature. If ICP monitoring is available, cerebral perfusion pressure should be kept above 70 mmHg [Unterberg, 1997]. Osmotherapy with glycerol 10% usually given intravenously (4 x 250 ml of 10% glycerol over 30-60 min) or intravenous mannitol 25-50 g every 3-6h is the first medical treatment to be used if clinical or radiological signs of space-occupying oedema occur [Righetti, 2002][Bereczki, 2001]. Hypertonic saline solutions given intravenously are probably similarly effective [Schwarz, 2002]. Hypotonic and glucose-containing solutions should be avoided as replacement fluids. Dexamethasone and corticosteroids are not useful for brain oedema treatment after stroke [Qizilbash, 2002 #143]. Thiopental given as a bolus can quickly and significantly reduce ICP, and be used to treat acute crises. Barbiturate treatment requires ICP and EEG monitoring and careful monitoring of haemodynamic parameters, as a significant blood pressure drop may occur.

Decompressive surgery

Malignant MCA infarction: The pooled analysis of 93 patients included in 3 European RCTs (DECIMAL, DESTINY, HAMLET) showed that more patients in the decompressive-surgery group than in the control group

had a mRS ≤ 4 (75% vs. 24 %; NNT 2), a mRS ≤ 3 (43% vs. 21%, NNT 4), and survived (78% vs. 29%; NNT 2) after one year [Vahedi, 2007]. There was no increase in the proportion of patients who survived surgery in a vegetative stage (mRS 5). Inclusion criteria for this combined analysis were age 18–60 years, NIHSS >15 , decrease in level of consciousness to a score of 1 or greater on item 1a of the NIHSS, infarct signs on CT of 50% or more of the MCA territory or >145 cm³ on dw-MRI, and inclusion <45 hours after onset (surgery <48 hours). Follow-up of survival and functional status beyond 1 year is currently ongoing in the DECIMAL and DESTINY.

Cerebellar Infarction: Ventriculostomy and decompressive surgery are considered treatments of choice of space-occupying cerebellar infarctions, although RCTs are lacking. Like in space-occupying supratentorial infarction, the operation should be performed before signs of herniation are present. The prognosis among survivors can be very good, even in comatose patients prior to operation.

Recommendations

- Intravenous tPA (0.9 mg/kg BW, maximum 90 mg), with 10% of the dose given as a bolus followed by an infusion lasting 60 min, is recommended within 3h of onset of ischemic stroke (Class I, level A).
- Intravenous tPA may be of benefit also for acute ischemic stroke beyond 3 h after onset (Class I, level B) but is not recommended in clinical routine. The use of multimodal imaging criteria may be useful for patient selection (Class III, level C).
- Blood pressure higher than 185/110 mmHg must be lowered before thrombolysis (Class IV, level GCP).
- Intravenous tPA may be used in patients with seizures at stroke onset, if the neurological deficit is related to acute cerebral ischemia (Class IV, level GCP).
- Intravenous tPA may also be administered in selected patients over 80 years of age (Class III, level C) although this is outside the current European label.
- Intra-arterial treatment of acute MCA occlusion in a 6-hour time window is an option (Class II, level B).
- Intra-arterial thrombolysis is recommended for acute basilar occlusion in selected patients (Class III, level B). Intravenous thrombolysis for basilar occlusion is an acceptable alternative even after 3 h (Class III, level B).
- ASA (160–325 mg loading dose) should be given within 48 h after ischemic stroke (Class I, level A).
- If thrombolytic therapy is planned or given ASA or other antithrombotic therapy should not be initiated within 24 h (Class IV Level GCP).
- The use of other antiplatelet agents, single or combined, is not recommended in the setting of acute ischemic stroke (Class III, Level C).

- *The administration of GP IIb-IIIa inhibitors therapy is not recommended (Class I, level A).*
- *Early administration of UFH, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with ischemic stroke (Class I, level A).*
- *Currently, there is no recommendation to treat ischemic stroke patients with neuroprotective substances (Class I, level A).*

Summary

The outcome of patients who suffered an ischemic stroke has massively improved over the last decades. Mortality rates are down and the number of patients who will fully recover has increased. Still there are unfortunate cases who survive in a very poor state, but their number also decreases. This all is due to Stroke Unit Care, rapid referral to expert centers, thrombolysis, expert general therapy, multidisciplinary teams and critical care facilities.

This is the good news. On the other side, the incidence rates of stroke are expected to explode over the next few decades. With all the great advances in acute stroke care and the management networks that are evolving, the number one priority must be education and prevention.

For the extensive list of references please refer to the free access download of the article on the ESO-website (eso-stroke.org).

FRUSTRATIONS IN CEREBROVASCULAR DISEASE

■ ALLAN H. ROPPER

As we have made progress in the treatment of atherosclerotic stroke and related brain diseases, the problem of cerebral hemorrhage has remained largely unaddressed. There has been a modest reduction in the incidence of cerebral hemorrhage in many populations, mainly as a result of the treatment of chronic hypertension. However, most of the treatments and methods of control of risk factors for ischemic cerebrovascular and coronary disease may themselves be the cause of cerebral hemorrhage. The main risk factor for hemorrhage, increasing age, will become a larger issue in the future.

The term *cerebral hemorrhage* is roughly equated with ‘hemorrhagic stroke’. It accounts for approximately 20% of all strokes among individuals of European origin, but closer to 45% of all strokes in those of Asian ethnicity. As a rule, the severity of hemorrhagic stroke is more severe than for ischemic stroke and a residual disability is correspondingly greater. The current conceptualization of the nature of cerebral hemorrhages comes from investigations by French neurologists early in the last century and elaborated by C.M. Fisher, published in 1971 in the *American Journal of Pathology*. Fisher found bulbous outpouchings in the small penetrating lenticulostriate vessels. These ‘Charcot Bouchard aneurysms’ are situated in the same small blood vessels that are subject to the effects of chronic hypertension and hyperlipidemia. In the latter circumstances, the pathology occludes a vessel and causes a lacunar stroke.

While cerebral hemorrhage shares many risk factors with ischemic stroke, several appear to have an influence in the opposite direction. For example, greatly reduced LDL concentrations in the blood have been associated with an increased risk of cerebral hemorrhage in several studies of the widespread use of statins. It is also apparent that the increasing use of anticoagulants and t-PA for ischemic stroke have contributed to a resurgence in the incidence of cerebral hemorrhage.

With regard to the risk of cerebral hemorrhage with statins, the recent SPARCL trial (High Dose Atorvastatin After Stroke or Transient Ischemic Attack, NEJM 2006) is representative of many others. Several similar primary and secondary analyses of the effects of cholesterol-lowering drugs on cerebral hemorrhage have generally shown odds ratios of increased risk

for cerebral hemorrhage between two and four but with confidence intervals that barely cross one. Nonetheless, even if the risk is small, if a substantial population is exposed to drugs and severe reduction of LDL, preventative treatment for atherosclerosis may contribute to and to a increased incidence of cerebral hemorrhage.

The risk of cerebral hemorrhage has long been known to increase with the incidence hypertension but there are major covariates including smoking, low LDL, alcohol intake, and BMI. There has indeed been a reduction in the standardized mortality ratio from cerebral hemorrhage over the past several years in numerous populations, but there has been an even more impressive shift in the underlying causes of hemorrhage. Moreover, the reduction in hemorrhage rate that can be attributed to treatment of hypertension has varied widely between ethnic populations.

The Oxfordshire series by Lovelock *et al.* in *Lancet Neurology* 2007 has the advantage of studying a stable population over two well-defined epochs (Figure 1, see p. 198). In the appended figure, 'OCSP' refers to the population from 1981 to 1986 and OVASC refers to it from 2002 to 2006. It is evident that the incidence of cerebral hemorrhage has not changed appreciably between these two time periods.

Figure 2 (see p. 199) taken from the same study, shows that the causes of hemorrhage have changed during the last decade, with an increasing number due to anticoagulation.

Another instructive study in this regard is by van Asch colleagues in *Lancet Neurology* 2010 (Figure 3, see p. 200). The persistently high rate of hemorrhage in Asian populations is evident and scrutiny discloses that the incidence per 100,000 person-years stratified by race is as follows: white – 24.2, black – 22.9, Hispanic – 19.6, and Asian – 51.8. Increasing age continues to be the main risk factor for cerebral hemorrhage. From this same study, using ages 45 to 54 as a reference, the proportional incidences are 1.8 for the decade 55 to 64 years old, increasing to 9.6 for those over age 85.

The implication is that these types of strokes will be more frequent in the future in both developing and developed countries.

Several interesting recent findings in the genetics of stroke may shed light on the origin or propensity to have cerebral hemorrhage. First, the genome wide association study (GWAS) of stroke by Ikram and colleagues in *NEJM* 2009 suggests that polymorphisms on chromosome 12 confer a 30% increased risk of stroke in both black and white people. This is the first of several attempts to look at stroke and its risks from a new perspective. It would be hoped that for spontaneous cerebral hemorrhage in particular, which is a somewhat more homogeneous group than ischemic stroke, this

would offer special insights. Furthermore, the findings by Gould *et al.* in NEJM 2008 that link COL4A1 mutations to both small vessel disease and spontaneous hemorrhage are very provocative.

I suggest for your consideration that cerebral hemorrhage has been relatively neglected in comparison to ischemic stroke although it is more disabling and has a higher short-term mortality. There has been little if any successful prevention aside from the global treatment of hypertension and increasing caution with the use of anticoagulants. The aging population will result in an increase in the incidence of cerebral hemorrhage, almost certainly contributed to by amyloid angiography in the aged.

As we make progress in treating and preventing atherosclerosis, we should be aware of the overall management morbidity that may contribute to increased cerebral hemorrhage rates. The recent conceptions of antithrombin and anti-factor Xa drugs should contribute to a future reduction in cerebral hemorrhage.

ANTIPLATELET AGENTS, ANTICOAGULANTS: NEW MEDICAL STRATEGIES

■ GEOFFREY A. DONNAN

The pathogenesis of stroke

Stroke is a heterogeneous condition in which 85% is caused by arterial acute occlusion or ischaemic stroke and 15% blood vessel rupture or cerebral haemorrhage. Of those with ischaemic stroke, further heterogeneity is evident with cerebral ischaemia caused by artery-to-artery emboli, in situ small vessel disease or cardiac emboli. The underlying pathogenesis can usually be determined after considering the clinical phenotype and the results of this series of predominantly image-based investigations. This may result in a classification such as TOAST, whereby about 30% of ischaemic stroke is usually caused by artery-to-artery embolism, 20% by cardiac embolism and about 15% plus more artery disease. Regardless of the underlying cause of vessel occlusion, a common final pathway involves other platelet aggregation and/or stimulation of the coagulation cascade. Hence, preventative strategies are usually focused on these two basic mechanisms.

Secondary stroke prevention

There have been remarkable advances made in secondary stroke prevention beginning with the landmark Canadian co-operatives study in 1978 [1]. Then followed evidence that carotid endarterectomy was beneficial in 1991, anticoagulation in 1993, clopidogrel in 1996, blood pressure lowering in 2001, aspirin plus dipyridamole in 2006 and cholesterol lowering in the same year. For prevention of cardiac embolism strategies have involved anticoagulation, the use of anti-platelet agents or others such as anti-arrhythmics, antihypertensives or statins. We will discuss mainly anticoagulants which may be broadly divided into vitamin K antagonists such as Warfarin, the more recently developed Tecarfarin or the more novel anticoagulants. The latter include direct thrombin inhibitors such as xymelagatran, dabigatran or AZD 0387 or factor X inhibitors. The latter include Apixaban, betrixaban, Edoxaban, Idraparinux, Rivaroxaban and YM 150.

Stroke of arterial origin: as mentioned earlier, the final common pathway in artery-to-artery embolism or small vessel disease is most likely platelet aggregation. This commences with vessel wall injury followed by platelet deposition, platelet activation and recruitment, the development of a throm-

botic plug which in its own right then generates further platelet activation and recruitment. This process may be interrupted by blocking a number of pathways of platelet activation and aggregation which are well described. These include ADP, thrombin, thromboxane A₂, von Willebrand factor receptors or the final common pathway GP IIb/IIIa receptor. There have been numerous trials and of the secondary stroke prevention involving many of these agents. They may be categorised loosely to those involving aspirin versus controls, Trifusal or clopidogrel versus aspirin, clopidogrel versus aspirin, clopidogrel plus aspirin versus clopidogrel, clopidogrel plus aspirin versus aspirin or dipyridamole plus aspirin versus clopidogrel. By indirect comparison, the relative risk reduction versus placebo may reach as high as almost 30%. However, a sobering head-to-head comparison of aspirin plus dipyridamole versus clopidogrel (PROFESS), which showed no real difference between the two, would suggest that the real relative risk reduction for both approaches is only about 20% (see Hanky and Eikelboom, *Lancet Neurology* 2010 for review). Other approaches include the thromboxane A₂ inhibitor Terutroban (ceased 2010), aspirin plus clopidogrel in acute vascular events (POINT, FASTER), stronger ADP and antagonists (Prasugrel), reversible ADP antagonists (Ticagrelor), Factor Xa inhibition (Rivaroxaban, Apixaban), phosphodiesterase inhibition (Cilostazol) or thrombin receptor antagonists such as SCH 530348. In spite of the significant advances that have occurred with antiplatelet and anticoagulant therapy and this category of vascular disease over the last 20 years, the main problems are the sense that a ceiling effect may have been reached with the relative risk reduction of around 20 to 30% of vascular outcomes and the difficulty in balancing any further anticoagulant benefit against the risk of bleeding.

Stroke of cardiac origin

The most common cause of stroke in this category is the presence of atrial fibrillation. This rhythm disturbance sets up a change in flow dynamics with stasis seen in the atrial appendage particularly. This allows the generation of local clot and subsequent embolism to the periphery and brain. Atrial fibrillation is the most common rhythm disturbance and it is estimated that one in four individuals aged 40 years will develop this condition [2]. The prevalence of atrial fibrillation is likely to double within about 30 years [3]. Overall, stroke is increased by approximately 5 fold for those in Atrial fibrillation and this risk is similar for those in either paroxysmal or permanent fibrillation. Stroke due to atrial fibrillation has a 30-day mortality of around 25% and a 12-month mortality of about 50% [4]. There may be up to 3 million people who develop stroke due to atrial fibrillation worldwide each year.

The standard therapy for patients in Atrial fibrillation to prevent embolism has been the use of vitamin K antagonists such as warfarin. These are associated with significant disadvantages, including an unpredictable therapeutic response, a narrow therapeutic range, the need for routine INR monitoring, slow onset and offset of action, the need for frequent dose adjustments, a number of food interactions, numerous drug interactions and the presence in some patients of warfarin resistance. This has meant that the introduction of a more user-friendly therapeutic intervention for patients with atrial fibrillation would be met with some enthusiasm.

There have been a number of trials of vitamin K antagonists in stroke prevention (AFASAK, BAATAF, CAFA, SPAF, SPINAF), the aggregate of which has produced a relative risk reduction against embolism outcomes of around 70%. In spite of the undoubted biological efficacy of these agents, the difficulties of their usage outlined earlier has limited their uptake in a community setting. A number of community-based studies have placed the lack of uptake in the 30 to 50% range. This again emphasises the need for alternative interventions of at least similar efficacy but greater ease of use.

The Factor Xa and thrombin inhibitors appear as they may achieve this goal. These include particularly the Factor Xa inhibitors Rivaroxaban, Apixaban, Idraparinux and the thrombin inhibitor dabigatran [5]. The latter has been the first to show clinical efficacy in the RELY trial published recently [6]. In this study warfarin was compared to dabigatran 110 mg or 150 mg twice daily in patients with atrial fibrillation plus one or more risk factors. The risk factors included a previous vascular event, left ventricular ejection fraction of less than 40%, aged 75 years or more or age of 65 years or more with diabetes, coronary artery disease or hypertension. With a follow-up of a mean of two years and primary endpoints of stroke or systemic embolism, dabigatran 110 mg was not inferior to warfarin while 150 mg was superior. The relative risk reduction of dabigatran 150 mg compared to warfarin was 34%. Somewhat surprisingly, life-threatening bleed-ing was significantly lower in both doses of dabigatran and Warfarin. Haemorrhagic stroke was also significantly lower with dabigatran at 0.12% for 110 mg, 0.10% for 150 mg but 0.38% for warfarin. This was significantly different at the .001 level.

The pharmacokinetic properties of the thrombin and Factor Xa inhibitors have differences in that the bioavailability of dabigatran is only about 6% while those of the Factor 1Xa inhibitors is 50 to 80%. Conversely, renal clearance is about 80% for dabigatran but only 35 to 65% for the Factor Xa inhibitors. Renal clearance issues may limit the use of dabigatran in patients with renal impairment.

There are a number of ongoing trials using novel anticoagulants such as ROCKET AF (Rivaroxaban), ARISTOTLE (Apixaban), AVERROES (Apixaban) and ENGAGE-AF (Edoxaban) in which these agents are being used to prevent embolism in patients, usually against the warfarin as the gold standard. The completion of these studies over the next few years should provide additional data about the use of novel anticoagulants in this clinical setting. Several issues which have been raised, which may also be answered with the entry of many of these compounds into standard clinical practice, include the maintenance of similar compliance rates to warfarin and the identification of asymptomatic patients with AF in the general community. With increased ease of use, presumably a greater number of patients will be able to be treated and with fewer side effects than is currently experienced with warfarin.

Summary

There are two main therapeutic approaches using anticoagulants in the secondary prevention of stroke. The first of these is the use of antiplatelet agents which are more appropriate for patients in whom artery-to-artery embolism is the most likely causal mechanism. Aspirin plus dipyridamole or clopidogrel are superior to aspirin alone. New combinations remained to be tested although a ceiling effect for antiplatelet agents at about 20 to 30% relative risk reduction probably exists. The novel anticoagulants such as thrombin and Factor Xa inhibitors are probably superior to warfarin in the prevention of stroke and systemic embolism due to atrial fibrillation. There may be a need to identify asymptomatic people with atrial fibrillation in the community as a public health initiative.

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VASCULAR COGNITIVE IMPAIRMENT: AN OVERVIEW

■ JOHN T. O'BRIEN

Dementia is a huge and growing global problem, with up to 25 million cases worldwide and a new case developing every seven seconds (Ferri *et al.*, 2005). Numbers are set to double in the next 25 years and double again in the next 25, thus showing an exponential rise. Costs to health and social care are enormous, with a recent UK Alzheimer's Research Trust report estimating that annual costs of dementia care were five times as high as people with other common diseases such as stroke, heart disease or cancer (ART, 2010). Dementia is age-related, with both prevalence and incidence rising with age. Around 5% of the over 65s are affected, rising to 20% of the over 80s and up to 50% of the very old old – in their 90s.

Dementia refers to a global cognitive decline which can have a number of causes. Once several other pathologies or potentially reversible causes (such as space occupying lesions, vitamin deficiencies, or psychiatric disorders) are excluded, the most common causes in late life are Alzheimer's disease, responsible for around 60% of cases, vascular dementia, responsible for 15–20% of cases, and dementia with Lewy bodies, responsible for around 15% of cases. Other causes include late onset frontotemporal dementia, dementia due to Huntington's disease, and a range of other less common degenerative, metabolic and infective causes. The importance of vascular factors is recognised by the presence of significant vascular pathology in a third of dementia cases acquired from community registers (MRC CFAS, 2001). Rates of vascular dementia rise with age, as for Alzheimer's disease, doubling approximately every 5.3 years as opposed to every 4.5 years for dementia (Jorm *et al.*, 1987). Dementia affects around 15–20% of people three months after stroke, and a further 20–25% develop delayed dementia after stroke, which may be vascular, but increasingly a degenerative component to such delayed dementia after stroke is recognised (Pendlebury and Rothwell, 2009).

Historical background to the concept of vascular dementia

Alzheimer described the first case of 'pre-senile dementia' in 1906 (Alzheimer, 1907) and throughout most of the 20th century Alzheimer's disease, as it became known, was thought to only occur in early (under age 65)

life. Later onset or 'senile' dementia was thought to be due to cerebral arteriosclerosis. Seminal studies undertaken in Newcastle upon Tyne, UK, in the 1960s, examined patients during life and correlated findings with neuropathology at autopsy (Blessed *et al.*, 1969). These studies inclusively showed that Alzheimer's disease, rather than cerebral arteriosclerosis, was the main determinant of dementia in later life. Vascular dementia was therefore thought to occur when there were multiple infarcts in the brain and Hachinski (1974) coined the term 'multi infarct dementia'. Subsequent classification systems such as the ICD and DSM were based on this. Subsequently it became clear that though multi infarct dementia was an important type of dementia, vascular dementia was a more heterogeneous concept and, for example, subcortical ischaemic vascular dementia was as common, if not more common, than multi infarct dementia (O'Brien *et al.*, 2003).

Problems with definition and overlap between pathological causes of dementia

The field of dementia has always struggled with difficulties over terminology and definitions. One of these relates to the term dementia, particularly in relation to non-Alzheimer dementias. This is because most definitions of dementia include memory impairment as a central and prominent component. This is appropriate when the cause is Alzheimer's disease, because 90% of people with Alzheimer's disease have significant memory impairment as an early and predominant feature. However, in non-Alzheimer dementia such as vascular dementia, frontotemporal dementia or dementia with Lewy bodies, memory impairment is variable and may not occur until relatively late in the disease process. This can sometimes lead to some circularity in definition, in that a subject can be quite significantly cognitively impaired in a number of domains, but be classified as 'not demented' because memory may still be largely intact. To recognise the heterogeneity of cognitive features associated with vascular disease, as well as the problems inherent in the 'memory' dominant definition of dementia, a broader term of Vascular Cognitive Impairment has recently been proposed.

The concept of Vascular Cognitive Impairment also recognises the fact that there is no strict cut-off between cognitive impairment and dementia, more a graduation and also that vascular factors are important in dementias apart from vascular dementia. For example, an important interaction between vascular pathology and Alzheimer's disease has been shown (Snowdon *et al.*, 1997). People with Alzheimer's disease who have additional vascular pathology exhibit a greater cognitive impairment during life than those with a similar degree of Alzheimer change but without vascular

pathology. This important interaction between vascular and Alzheimer's disease, already recognised as very common by the MRC CFAS study (MRC/CFAS, 2001), was further developed in the 1990s, when it was recognised that several vascular risk factors were also risk factors for Alzheimer's disease. These included hypertension, smoking, possession of the ApoE protein E4 allele, ischaemic heart disease, hypercholesterolemia, raised homocysteine, diabetes, obesity and atrial fibrillation (O'Brien *et al.*, 2003). Imaging evidence of subcortical vascular change in the form of white matter lesions was also demonstrated to be more common in people with degenerative dementia than similarly aged controls (Barber *et al.*, 1999). More recently, additional genetic factors for late onset Alzheimer's disease have been described beyond possession of the ApoE4 protein allele (see www.alzforum.org for updated list of genetic risk factors) including possession of the angiotensin-converting enzyme gene and factors along the inflammatory and vascular pathways (see Table 1). It is, therefore, increasingly recognised that vascular factors play an important role in primary degenerative dementias such as Alzheimer's disease and their modification may therefore be of relevance for slowing or preventing non vascular types of dementia as well as vascular causes.

Genetic Factors in AD	
• Early onset AD	
– APP	
– PS1	
– PS2	
• Late onset AD	
– ApoE4 (Cholesterol transport)	3.68
– ACE (angiotensin/blood pressure)	0.83
– IL1beta (inflammation)	1.18
– TFAM (mitochondrial transcription factor)	0.82
– CLU (clusterin, A processing)	0.86
– PICALM (vesicle protein trafficking)	0.86
– TNK1 (kinase signalling)	0.86

Table 1. www.alzforum.org, 2010.

Post stroke cognitive impairment

In hospital-based studies rates of dementia three months after stroke approach 30% of which around 10% is pre-stroke dementia (Pendlebury and Rothwell, 2009). Post stroke cognitive impairment and dementia is an important clinical syndrome which slows recovery, increases length of stay, increases the risk of subsequent institutionalisations and increases the risk of recurrent stroke as well as increasing mortality. The rates of dementia after stroke continue to rise in a relatively linear fashion (Pendlebury and Rothwell, 2009), illustrating that stroke, or risk factors associated with it, continue to place the brain at increased risk of vulnerability to dementia in the longer term. Risk factors for post stroke dementia include vascular risk factors, the presence of atrophy and white matter lesions on imaging as well as features of stroke itself, such as large lesion size, bilaterality. Correlates of dementia after stroke remain to be fully determined, but it seems likely that both vascular and, especially in older people, Alzheimer-type changes both play a role, especially in delayed dementia after stroke (Firbank *et al.*, 2007a).

Imaging findings of white matter lesions have been consistently associated with the presence of executive and attentional disturbances, including after stroke (Burton *et al.*, 2004). Lesions are also more common in those with dementia than cognitively intact controls but the prognostic significance of lesions in those without symptoms has been unclear. However, recent findings from a large European study, the Leukoaraiosis and Disability (LADIS) study, which followed 639 subjects with mild, moderate or severe white matter lesions over three years, found that in this non disabled population, increasing burden of white matter lesions (especially those with the more severe confluent lesions) significantly increased the risk of progression to disability or death, with rates of transition to disability or death 30% per year in those with severe lesions compared to 15% of those with moderate, only 11% in those with mild lesions (Inzitari *et al.*, 2009). Although it is not yet clear how such white matter lesions should be treated, their adverse prognostic significance has now been established, opening a way for preventative studies.

Treatment of vascular cognitive impairment

Unfortunately, only a relatively limited amount of research has been done in this area. Studies of aspirin in terms of cognitive benefit are inconclusive. An early study (Meyer *et al.*, 1989) allocated 70 people with multi infarct dementia either to aspirin or no treatment. Subjects were followed annually for three years and those treated with aspirin showed higher cognitive performances compared to those receiving no treatment. However, this study has been criticised because of the small sample size, the high dropout rate, the lack of

placebo and the lack of true randomisation. Other controlled studies in vascular dementia have not been undertaken, but aspirin studies of large community cohorts or those with Alzheimer's disease have consistently failed to demonstrate any clear benefit in terms of cognition of aspirin treatment over placebo. Other putative treatments for vascular dementia including hydergine, propentofylline, nimodipine, pentoxifylline, nicergoline, posatirelin, have largely been negative. Some benefits of nimodipine in subcortical vascular dementia have been described (Pantoni *et al.*, 2005), but effects are modest and primary outcomes are not clearly positive, meaning that it is unlikely nimodipine produces clinically significant benefits. Studies of memantine show a small cognitive benefit but no change in global or functional outcomes (Orgogozo *et al.*, 2002; Wilcock *et al.*, 2002).

Demonstration of a cholinergic deficit in Alzheimer's disease and dementia with Lewy bodies has led to the development of a generation of compounds to boost cholinergic function, the cholinesterase inhibitors (Perry *et al.*, 1978). Licensed treatments in most countries include donepezil, rivastigmine and galantamine, and all produce a modest benefit in people with Alzheimer's disease (O'Brien, 2006). Several studies indicated that a cholinergic deficit may also exist in vascular dementia, though this has recently been questioned (Perry *et al.*, 2005). Early trials of cholinesterase inhibitors in vascular dementia produced mixed benefits, with some suggestions of an improvement (Erkinjuntti *et al.*, 2001). However, several large studies of galantamine, donepezil and rivastigmine have been largely negative. These studies have produced a small cognitive benefit but generally no significant change in terms of global outcome scales, activities of daily living or behavioural features (see Table 2). A study of donepezil in 168 subjects with a rare but relatively pure genetic form of vascular dementia (cerebral autosomal dominant arteriopathy with subcortical ischemic leucoencephalopathy or CADASIL) showed no significant benefit of donepezil treatment on primary outcome, though there were some benefits on secondary endpoints consistent with the fact there may be cholinergic deficits in CADASIL (Dichgans *et al.*, 2008). However, overall meta analyses of cholinesterase therapies for vascular dementia have concluded that, whilst they have produced small benefits in cognition, these are of uncertain clinical significance and the data are insufficient to support widespread use of the drugs (Kavirajan and Schneider, 2007). However, those with mixed Alzheimer and vascular pathology do appear to benefit (Erkinjuntti *et al.*, 2001) and this is consistent with the findings of Perry *et al.* (2005) from autopsy studies who report that cholinergic deficit is as great in those with mixed Alzheimer/vascular pathology as in Alzheimer's disease, but cholinergic function is intact in those with more pure vascular dementia.

RCTs of CHEI in Vascular Dementia				
	Cognition	Global	ADL	Behaviour
Galantamine (Gal-INT-06) (n=121) Erkinjuntti <i>et al.</i> , 2001	No (p=0.06)	No	No	No
Galantamine (Gal-INT-26) (n=788) Auchus <i>et al.</i> , 2007	Yes	No	No	No
Donepezil (307) (n=603) Black <i>et al.</i> , 2003	Yes	No	Yes	n/a
Donepezil (308) (n=616) Wilkinson <i>et al.</i> , 2003	Yes	Yes	No	n/a
Donepezil (319) (n=974) (press release 16.3.06)	Yes	No	No	n/a
Rivastigmine (VantageE) (n=710) Ballard <i>et al.</i> , 2008	Yes (p=0.028)	No	No	No

Table 2.

Prevention of vascular dementia

Clearly this would be the goal of management, either modifying risk factors or using pharmacotherapy. One recent study reported a risk index for developing dementia (Barnes *et al.*, 2009), which is reproduced in Table 3. As can be seen, several of the risk factors including body mass index, MR findings of white matter disease, carotid artery thickening, history of bypass surgery, slow physical performance and lack of alcohol consumption are all potentially vascular risk factors. However, translating such relatively consistent findings from epidemiological studies that vascular risk factors are important risk factors for dementia into preventative studies has not been straightforward. Two well-conducted studies of modification of cholesterol, the PROSPER and the heart protection study (Shepherd *et al.*, 2002; Rea *et al.*, 2005) describe including between 6,000 and 20,000 people with follow-up for five to six years showed no benefits in terms of cognition or prevention of dementia between those allocated to statin therapy and those allocated to placebo. Since the emergence of hypertension as an important risk factor for Alzheimer's disease, there has been great interest in whether treating hypertension will prevent dementia. Findings from the SYST-EUR study showed that nitrendapine treatment significantly reduced the number

Late-Life Dementia Risk Index

(Risk 4% to 56% over 6 years)

- Older age (1–2 points)
- Poor cognitive test performance (2–4 points)
- Body mass index 18.5 kg/m² (2 points)
- 1 Apolipoprotein E ε4 allele (1 point)
- Cerebral MRI findings of white-matter disease (1 point) or ventricular enlargement (1 point)
- Internal carotid artery thickening on ultrasound (1 point)
- History of bypass surgery (1 point)
- Slow physical performance (1 point)
- Lack of alcohol consumption (1 point)

Table 3. CV Health Cognition Study, Barnes *et al.*, 2009.

of cases of dementia compared with placebo, with this effect persisting over the four-year follow-up period (Forette *et al.*, 1998; 2002). Interestingly, and consistent with the finding that hypertension is a risk factor for Alzheimer's disease, the main reduction was in cases of Alzheimer-type dementia. Several other studies have suggested that there is a signal from such therapy, the most recent being the HYVET study (Peters *et al.*, 2008) which examined those over 80 randomising them to indapamide or placebo. There was a non-significant trend for a reduction in dementia cases, but as with many studies of vascular risk the study was halted early because the primary endpoint in terms of reduction in cardiovascular events was found. Overall, meta analyses either just show, or fail to show, a benefit of anti hypertensive treatment and firm conclusions about protective effect of anti hypertensive therapy in cognition cannot yet be made. Of interest, in a sub study of the study on cognition and prognosis in the elderly (SCOPE) which used the angiotensin to inhibit candesartan or placebo and a more detailed neuropsychological battery and repeat neuroimaging assessment, found evidence that a reduction in blood pressure with candesartan treatment was associated with a slowed rate of cognitive decline and a slowing of progres-

sion of white matter change, with a trend to slowed rate of overall brain atrophy (Firbank *et al.*, 2007b). Such studies combined with the known deleterious consequences prognostically of having a significant burden of white matter change (Inzitari *et al.*, 2009) would lend support to further large-scale studies investigating a variety of strategies which may potentially reduce or delay progression of white matter changes. This particular strategy in Alzheimer's disease may also be effective, given that vascular risk factors are common in people with Alzheimer's disease and that vascular pathology is a disparate additive to Alzheimer pathology in the expression of cognitive decline. A naturalistic study of 301 subjects with Alzheimer's disease (Deschaintre *et al.*, 2009) found that only 7% of those with Alzheimer's disease had no vascular risk factors. However, vascular risk factors were fully treated in 32%, partially treated in 43% and not treated at all in 26%. Although a naturalistic study, follow up over two and a half years show that those with treated vascular risk factors had significantly slower rate of cognitive decline compared to those without. However, support that treatment of vascular risk factors would slow cognitive decline in Alzheimer's disease was not provided by a randomised controlled trial by Richard *et al.* (2009) in which 130 subjects with Alzheimer's disease, with evidence of cerebrovascular disease on brain imaging, were randomised to vascular care (aspirin, folate, statin, pyridoxine and blood pressure lowering if BP>140/80) or usual care. At two-year follow-up there was no significant difference in rates of cognitive or functional progression to those allocated to vascular intervention group and placebo. However, although cholesterol was significantly lower in the intervention group compared to placebo, there was no significant difference in blood pressure between the groups (interestingly which dropped to a similar extent 15/5 mm of mercury) in both groups. Therefore, it is not clear whether the vascular package was ineffective as it failed to achieve a difference in blood pressure between groups. Further studies on the effect of intensive blood pressure lowering in preventing future cognitive decline are required.

Conclusions

Dementia is a huge and growing public health problem, with vascular dementia the second commonest cause of dementia and cognitive impairment. However, in addition, vascular factors are also important in Alzheimer's disease, there is still much to learn about the interaction between vascular and degenerative disease. Unfortunately, therapeutic strategies to date have been disappointing and neither the drugs used to treat Alzheimer's disease nor modification of vascular risk factors are clearly effective in preventing future

cognitive decline and dementia. There is a clear need for further mechanistic and therapeutic studies in the area, including preventative studies which should be undertaken in those with early disease, in those with particular vascular subgroups (for example those with post stroke dementia or subcortical ischaemic vascular dementia) and in those with white matter lesions. Because of the close interaction between vascular and Alzheimer pathology and the importance of vascular factors in Alzheimer's disease, successful strategies developed for the treatment or prevention of vascular dementia may also be useful for treating or preventing Alzheimer's disease.

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LESSONS FROM THE PAST FOR THE NEAR FUTURE

■ LOUIS R. CAPLAN

To know where we are and where we are headed in the future, we need to know where we have been in the past. My task is to critically review experience in order to suggest ways to move forward.

I. Diagnosis of acute brain ischemia and intravenous (IV) thrombolytic treatment

A. Clarification of the pathophysiology of acute brain ischemia and modern diagnosis

Myocardial and brain ischemia are dynamic processes that evolve during time. Early studies of the pathology of patients dying of myocardial infarction found a relatively low rate of occlusive coronary thrombi. These studies were performed 12 hours or more after symptom onset. Later studies performed within 4 hours of onset showed that the cause of myocardial infarction in the great majority of patients was acute thrombosis of a coronary artery [1].

Similarly, angiographic and necropsy studies of patients with acute brain ischemia during the last half of the twentieth century showed that most acute brain infarcts were caused by emboli that arose from the heart, aorta, and from atherosclerotic occlusive lesions in the carotid and vertebral arteries in the neck. The process was dynamic and emboli often blocked an intracranial artery and then became dislodged and moved distally. Small emboli were often cleared. Angiography within the first 8 hours after the onset of focal brain ischemia showed a high frequency of embolic occlusion of large intracranial arteries [2,3]. If successive films were taken during angiography emboli often could be shown to move distally [4,5].

Miller Fisher and Raymond Adams extensively studied their necropsy material and defined the pathophysiology and dynamic nature of brain embolism [6,7]. Sudden blockage of a brain-supplying artery caused ischemia to neurons and also resulted in ischemic damage to the small blood vessels within the area of ischemia. When the obstructing embolus moved distally, as it often did, the previously ischemic region was reperfused with blood. The damaged capillaries and arterioles within that region were no longer competent and blood leaked into the surrounding infarcted tissue.

Other studies during the same time described the distribution of atherosclerosis and thrombosis within brain-supplying arteries. In white men, the predominant atherosclerotic disease was at or near the origins of the internal carotid and vertebral arteries in the neck [8,9]. Thrombi that developed within the internal carotid arteries (ICAs) often propagated cranially, and emboli broke off from the top of the clot. Intracranial atherosclerosis was more common in women, African-Americans, and individuals of Asian origin [11,12]. Degenerative changes termed lipohyalinosis often developed in penetrating artery branches of the main intracranial arteries. Occlusive changes in these vessels led to small deep lacunar infarcts [13,14].

During the last decades of the twentieth century there was a dramatic improvement in technology capable of imaging the brain and the blood vessels that supplied the brain. MRI proved superior to CT scan in showing acute infarcts and hemorrhages. Diffusion-weighted images (DWI) showed brain infarcts soon after ischemia onset. CT angiography (CTA) and MR angiography (MRA) could accompany brain imaging with CT and MRI and quickly and relatively accurately showed occlusive arterial and venous lesions. CT and MR perfusion (Perfusion-weighted Images PWI) studies performed concurrently with brain and arterial imaging showed regions of brain tissue that were deprived of their normal blood supply. Duplex ultrasound non-invasively showed occlusive lesions in the neck and transcranial Doppler ultrasound could show and monitor disease in the large intracranial arteries. By the turn of the century clinicians could safely and quickly determine during life the nature and location of occlusive lesions, the extent of brain infarction, and regions of brain that were underperfused but not yet infarcted.

B. Experience with IV thrombolytic treatment

In early thrombolytic studies during the 1980s, acute stroke patients were screened clinically and by CT, and then angiography was performed. If an intracranial arterial occlusion was shown, thrombolytic drugs were given. Follow-up angiography was performed after treatment to assess recanalization. These studies were observational only since controls were not used and patients were not randomized but successive patients meeting protocol requirements were treated [15-18]. Recanalization heavily correlated with outcome. Thrombolytic agents act only by lysing clots. If arteries are not opened the drugs do not facilitate recovery. Knowing the recanalization rate of agents given IV and IA in patients with various occlusive arterial lesions is extremely helpful in choosing appropriate therapy.

In some clinical studies, the vascular lesions were defined by angiography and thrombolytic drugs were given IV [15-18]. Among 370 patients treated

with IV rt-PA, within 6 to 8 hours, one third of the arteries treated showed significant recanalization compared to only 5% of 58 control arteries. MCA branch occlusions recanalized best followed by occlusions of the superior and inferior divisions of the MCA. Mainstem MCA occlusions recanalized less often than branch and division MCA lesions. ICA occlusions rarely recanalized and there were no recanalizations when both the ICA and MCA were occluded. Embolic occlusions recanalized more often than in-situ thrombosis of atherostenotic arteries. Recanalization was better when there was angiographic evidence of good collateral circulation before administration of rt-PA.

These observational studies were followed by randomized trials. None of the IV randomized trials required or reported vascular testing before treatment and all used clinical findings and CT as entry requirements. The first reported large multicenter randomized trial of IV thrombolysis was the European Cooperative Acute Stroke Study (ECASS) which included 620 patients with acute hemispherical strokes among 75 hospitals in 14 European countries [19,20]. 313 patients were randomized to receive rt-PA and 307 to placebo. Treatment was given within 6 hours of the onset of symptoms of brain ischemia. Patients who had major early infarct signs (diffuse hemispherical swelling, parenchymal hypodensity, effacement of cerebral sulci in $> 1/3$ of the MCA territory) and hemorrhage on initial CT scans, which were read at local sites, were excluded. An independent blinded CT scan reading panel later retrospectively reviewed the CT scans and determined protocol violations of the CT scan entry criteria. Many patients had protocol deviations, mostly because local centers failed to recognize CT abnormalities that should have excluded patients. The study was considered negative. More patients treated with rt-PA had good outcomes but more patients did poorly and more patients died [19,20].

The next study was the National Institute of Neurological Diseases and Stroke (NINDS) study [21]. Compared to ECASS I, the NINDS used lower rt-PA dose and had earlier treatment (302 patients were treated within 90 minutes and 322 between 90 and 180 minutes) Ischemia on entry CT scans did not exclude patients. Patients treated with IV rt-PA were at least 30% more likely to have minor or no disability at 3 months. Symptomatic intracerebral hemorrhages were more common in rt-PA treated patients (6.4% vs 0.6%) and patients who had more severe neurological deficits at entry and patients 75 years or older had more hemorrhages. The mortality at 3 months was 17% in the rt-PA group vs 21% in the placebo group [22]. There was no important difference in outcome in stroke subtype groups but quick entry and absence of vascular and cardiac imaging made the clin-

ical diagnosis of stroke mechanism tentative at best. A committee that reviewed the NINDS results reported that the stroke mechanism subtype results were not valid [22].

In the ECASS II trial, investigators treated 800 patients from Europe, Australia, and New Zealand with rt-PA or placebo within 6 hours of stroke onset [23]. They used the rt-PA dose used in the NINDS trial. Patients with major infarcts on CT scan were excluded but vascular imaging was not performed before treatment. Guidelines for control of hypertension were more explicit than in ECASS I or the NINDS trial. In ECASS II, 36.6% of placebo-treated patients had favorable outcomes – a better result than thrombolysed patients in the ECASS I and NINDS trials. Among the rt-PA-treated group, 40.3% had favorable outcomes – not statistically significantly different from the placebo-treated group. Treatment results and hemorrhage frequencies were similar in the 0–3 hour and 3–6 hour treatment groups. In the interval between the 2 ECASS trials, stroke centers had developed widely in Europe and were manned by experienced stroke neurologists, internists, and nurses. The results in the placebo and thrombolysis groups reflect better medical care delivered in dedicated stroke centers. Later a third European study, ECASS III, using a similar protocol to ECASS II, showed that IV rt-PA was more effective than placebo when patients were treated in the 3–4.5 hour window [24].

Concurrent with ECASS III, investigators began to use modern MRI and CT protocols along with clinical data to attempt to better select patients likely to benefit from thrombolysis and those at most risk of hemorrhage and other complications. Trials (EPITHET [25] DIAS [26], and DEFUSE [27]) and extensive experience [29] established the feasibility of using modern brain and vascular imaging to optimally choose patients for thrombolysis.

The Desmoteplase in Acute Ischemic Stroke (DIAS) Trial was a placebo-controlled double-blind randomized dose finding Phase II trial of Desmoteplase [27], a plasminogen activator fibrinolytic enzyme with high fibrin selectivity and a long-terminal half-life derived from vampire bat saliva. Fibrin-selectivity is important since the agent tends to bind at the site of the thrombus and not cause systemic fibrinogenolysis. In DIAS, patients were selected for fibrinolysis if they had a diffusion/perfusion mismatch on MRI and were treated within a 3–9 hour window. The patients treated with desmoteplase had a higher rate of reperfusion and better clinical outcomes than placebo-treated controls [26].

The Diffusion and Perfusion Imaging Evaluation For Understanding Stroke Evolution (DEFUSE) Trial studied whether MRI criteria helped determine responders to IV tPA in patients treated 3 to 6 hours after stroke

symptom onset [27]. A perfusion/diffusion mismatch was found in 54% of patients with interpretable PWI scans and in this group early reperfusion was associated with a favorable response in 56% of patients compared to only 19% of patients with no mismatch. Those patients who had large DWI lesions fared worse with a very low rate of good clinical response and a high rate of hemorrhage when reperfusion occurred [27]. MRA showed that 65% of patients had a symptomatic arterial occlusion before treatment. Complete early recanalization occurred in 27% and partial recanalization in 16% as determined by follow-up MRA. Patients with early recanalization had a 74% reduction in PWI volume compared with 16% with no recanalization [27].

DIAS and DEFUSE showed that MRI and MRA could be used effectively to select patients for thrombolysis even within the 3–9 hour window. Modern CT profiles that included CTA and perfusion CT should also be able to select patients with arterial occlusions with no or small infarcts and larger perfusion defects that would be amenable to thrombolysis irrespective of time.

C. Action responses and guidelines

Release of the results of the NINDS trial stimulated a movement in the USA to quickly (much too quickly in my opinion) introduce IV thrombolysis widely into the community. During the summer of 1996, about one-half year after publication of the NINDS trial, despite the failure of the ECASS I trial, the United States FDA approved the use of rt-PA to treat stroke patients within the first 3 hours. A meeting was called by NINDS shortly after FDA approval to urge immediate institution of IV thrombolysis into every hospital in the USA. The American Heart Association [29] and American Academy of Neurology [30] published treatment guidelines that followed exactly the inclusion and exclusions and the treatment protocols of the NINDS trial. A CT scan done before thrombolysis should not show major infarction, mass effect, edema, or hemorrhage. The guidelines did not require or suggest MRI or vascular tests before treatment. Guidelines updated in 2007 concerning early management of adults with ischemic stroke did not substantially alter the original guidelines concerning IV rt-PA administration [31].

Canadian and European authorities approved the use of rt-PA much later than the USA. The European Medicines Evaluation Agency (EMA) conditionally approved alteplase (rt-PA) in September 2002 to treat ischemic stroke by experienced clinicians within 3 hours of symptom onset. A condition mandated by the European Union regulatory authorities for definitive approval of thrombolytic therapy was that treatment safety would be monitored during a three year period by entering all treated patients in a web register, the SITS

Monitoring Study – SITS-MOST Registry. In this registry, during a 4-year period, data from 6483 patients from 285 centers in 14 countries were entered [32]. At 24 h, 1.7% of patients had symptomatic intracerebral hemorrhages compared with 8.6% in the previously reported pooled randomised controlled trials. The mortality rate at 3 months in SITS-MOST was 11.3% compared with 17.3% in the pooled randomised controlled trials. The investigators concluded that intravenous rt-PA use was safe and effective in routine clinical practice when given within 3 h of stroke onset.

D. Critique and moving forward

If an unbiased committee wrote a report card on the status of IV thrombolysis to date, they would find much good and much to be desired. Finally there was a drug that all agreed was an effective stroke treatment. Before rt-PA therapeutic nihilism prevailed. Approval of rt-PA was a wake-up call. *Stroke can and should be treated.* Stroke patients must be taken quickly to medical centers, and doctors and hospitals must become prepared and able to treat them. Doctors and the media, politicians, and authorities called the attention of the public and of doctors to stroke.

Unfortunately, doctors and medical centers have been slow to heed the call. Only about 1–2% of acute stroke patients are now treated with thrombolytics. About 4–5% of patients who arrive at medical centers in the USA and are eligible for thrombolysis under present guidelines actually receive it. Many hospitals, doctors, ambulance services, and emergency room units are still inadequately prepared to treat acute stroke patients. Some physicians, especially emergency room doctors, remain unconvinced about thrombolysis and are unwilling to give thrombolytic drugs for stroke patients. The guidelines for treatment are hopelessly outdated and do not consider advances made since the randomized NINDS and ECASS Trials. There are not enough doctors sufficiently trained and experienced to handle acute stroke patients. There is still much that is not known about thrombolysis (and is not likely to be learned unless the present guidelines are updated).

When the ECASS and NINDS studies were planned, available technology was limited. Since then there has been a dramatic upgrade in MRI, CT, and ultrasound technology that can safely and quickly yield information about the presence, location, and amount of infarcted brain and arterial and venous occlusions. Thrombolysis can be effective if given within 3 hours following present guidelines, but the present guidelines are not optimal. Patients now excluded such as those who awaken with neurological symptoms, those who have minor deficits or have improved substantially, and those treatable only after 4.5 hours could respond to treatment. Are there also patients now treated

under the guidelines who should not be treated because of little likelihood of success and high risk of hemorrhage or edema?

Knowledge gained from modern brain and vascular imaging can select for treatment some patients now included and excluded under present guidelines. The knowledge used to best choose treatment is listed in Table 1. The present guidelines: use firm time windows, do not suggest or even mention vascular imaging, exclude patients who awaken with deficits, have mild or improving signs, or have seizures.

Patients who awaken with neurological symptoms often have brain and vascular imaging that show treatable vascular occlusion patterns and no or small infarcts and are excellent candidates for thrombolysis [33]. Many patients who enter with slight deficits or improving signs later develop severe strokes. Improving or slight deficits are one of the most common reasons for present exclusion from thrombolysis. A substantial number of patients who later deteriorate have occlusive vascular lesions that are amenable to thrombolytic treatment [34]. Some patients already have large infarcts and little recoverable brain when brain imaging is performed within 3 hours. These patients can be harmed by thrombolysis. Seizures at or near onset do occur in some acute ischemic stroke patients, especially those with embolic strokes [36]. Other reperfusion strategies including initial IA treatment, bridging IV then IA thrombolysis if arteries are not opened, mechanical thrombus removal, primary stenting of occluded arteries are now being used clinically in many advanced stroke centers. Knowing whether there is an arterial occlusion and its location and the extent of infarction already present might lead clinicians to choose no thrombolysis, IV treatment, or to consider IA treatment, or combined IV then IA treatment.

The site of arterial occlusion strongly affects the likelihood of reperfusion after IV and IA thrombolysis. The more one knows about the patient, the more logically the clinician can choose acute and more chronic treatment. The present guidelines desperately need revision to account for information

1. The nature, location and severity of the causative vascular-cardiac-hematological conditions
2. The mechanism of ischemia – hypoperfusion or embolism
3. The cellular and serological components of the blood
4. The state of the brain – normal, “stunned”, or infarcted.

Table 1. Data needed to logically choose treatment for patients with acute brain ischemia.

gained since the NINDS trial was published. The guidelines should build in flexibility according to the technology available and the experience and training of the treating physicians and the desires of the patient.

II. Carotid artery surgery vs angioplasty/stenting

A. Background

Randomized trials clearly showed that carotid endarterectomy was more effective than best available medical therapy used at that time in patients with neurologically symptomatic, severe (70% luminal narrowing) carotid artery stenosis [36–38]. Endarterectomy removed the obstructing lesion dramatically augmenting flow and also removed the source of intra-arterial emboli. Endarterectomy was also shown to be somewhat effective in selected patients with luminal stenosis in the 50–69% range [39–40].

Until recently, endarterectomy was the most common method of unblocking an artery by direct surgery. Capillaries, small arterioles, and neurons were often damaged during ischemia. When flooded with blood under high pressure, these abnormal vessels might bleed. The carotid sinus was also damaged during endarterectomy, leading to failure of the carotid sinus reflex and accelerated hypertension in the hours and days after carotid endarterectomy. Elevated blood pressure and flooding of damaged vessels was a recognized cause of brain edema and ICH after carotid endarterectomy.

The successful use of angioplasty and stenting to treat coronary artery stenosis led to application of stenting for carotid artery and other neck and intracranial arterial stenosis [41,42]. Between 1996–1999, 11 carotid stent series published results in 1,311 patients [42]. The overall reported rate of technical success was >95%; procedure-related mortality rates (including cardiac deaths) were 0.6%–4.5%; major stroke rates were 0%–4.5%; minor stroke rates were 0%–6.5% ; and the 6-month restenosis rate was <5% [42]. Some series that included very high-risk cohorts reported less favorable results.

Clinicians and surgeons asked how carotid endarterectomy and stenting compared. There now have been 5 major trials: Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS) [43], SAPPHERE [44], SPACE [45], EVA-3S [46], and CREST [47]. These trials all had different inclusions and exclusions, different rules for including surgeons and interventionalist, and different use of various protection devices. In the CREST trial stenting was followed by more strokes but endarterectomy was followed by more myocardial infarctions. Younger patients seemed to do better after stenting while older individuals fared better after surgery [47].

During the time that the various surgery and stenting trials were performed, medical therapy improved dramatically especially with the more widespread

use of statins, newer antithrombotic agents, and more available agents for the control of blood pressure and abnormal glucose metabolism. Spence published data derived from aggressive medical therapy of patients with carotid artery disease and posited that now medical therapy might be equal or better than either surgery or stenting in controlling carotid artery disease [48,49].

B. Critique and moving forward

It is rather naïve to posit that one treatment is best for all patients and all situations. One treatment – endarterectomy – may be better in some circumstances and stenting be preferred in others. Table 2 tabulates the factors used to choose one treatment or another. None of the trials considered the nature of the vascular lesions, yet studies show that some lesions might pose more risk for stenting and others for surgery [50].

1. We need further studies of treatment of carotid artery and vertebral artery occlusive disease in the neck
2. Studies should include an arm of optimal modern medical treatment (high dose statins, ACE-inhibitors or ARBs, antiplatelets, and life-style modifications, in addition to surgery and angioplasty/stenting)
3. Studies should include more detailed analysis of the vascular lesions using advanced technology
4. Studies should include analysis of the risk/benefits of distal and other protection devices and strategies.

- | |
|--|
| <ol style="list-style-type: none"> 1. Nature of lesions <ul style="list-style-type: none"> Level of carotid bifurcation Length of lesion especially extent rostrally Severity of the stenosis Distal severe tandem stenosis Smoothness vs irregularity; ulceration 2. Age, sex, and comorbidities 3. Coronary artery disease 4. The benefits vs risks of using needed double antiplatelet use during and after treatment 5. Hypertension and diabetes if poorly controlled 6. The experience and record of the surgeon 7. The experience and record of the interventionalist 8. The benefit vs risk of angioplasty and/or employing protection devices during stenting 9. The patient's and family's preferences. |
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Table 2. Factors used to choose treatment for patients with carotid artery disease

III. Increasing the brain's tolerance and resistance to ischemia ("Neuroprotection")

A. Background

Theoretically, there might be substances or strategies that make the brain relatively resistant, at least for some time, to the deleterious effect of lack of oxygen and energy delivery, that is keeping brain cells alive despite poor perfusion. Trials of putative neuroprotectants, when used alone without adjunctive measures to enhance reperfusion, have all resulted in failure. Agents that were effective in experimental animal models of acute ischemia had no or little benefit in humans with brain ischemia. Many failures are likely due to suboptimal trial design and testing [17].

Armchair ideas and theories abound and far outweigh the data, but this field of investigation still may prove fruitful in the future. Trials in human stroke patients have not always been well designed to show an effect of the various therapies. They have customarily been given to all patients with acute stroke, and in most studies full brain and vascular imaging have not been mandated at entry or follow-up.

Among all patients with acute brain ischemia:

- 1) Many would have already developed large infarcts. These could be identified by DWI MRI scans or full CT protocols. Dead brain cannot respond to neuroprotection.
- 2) In many patients the blood vessels supplying the ischemic brain are occluded. The neuroprotective agents might not reach the ischemic neurons because the entry main road is blocked. Administering the agents to patients who have open arteries or are undergoing thrombolysis or other reperfusion techniques would be most effective.
- 3) White matter infarcts especially lacunes might not respond to neuroprotective agents that are cytoprotective since the white matter consists of tracts and not neurons.

B. Moving forward

If a neuroprotective agent proves effective among patients investigated thoroughly using modern neuroimaging who have small or no brain infarcts, open arteries (or are undergoing reperfusion), and non-lacunar mechanisms, and the agent is safe, it will become widely used. Because cerebral cortex is mostly the aim of protection, cognitive and behavioral testing is needed to show a benefit. The presently pursued strategy of treating all acute stroke patients provides a very difficult barrier for any neuroprotective agent to hurdle. Small studies of fully evaluated patients, after thorough animal

and pharmacokinetic data, might identify suitable neuroprotective agents for larger trials of well evaluated patients.

IV. Randomized therapeutic trials of secondary prevention of stroke and guidelines

The term “evidence-based” has become a sacrosanct icon almost like motherhood. Who could possibly argue against basing medical treatment decisions upon evidence. It is difficult to think of a polite term for decisions based on no evidence. The only evidence now given credence in determining the evidence-base is that garnered from randomized controlled trials (RCTs) especially those that are double blinded. Lectures and reports on treatment are now customarily ended by the authors calling for a new RCT or demanding that future treatment of the condition be evidence-based.

The emphasis on RCTs as a basis for all treatment has been overstated especially in relation to Neurology [51-53]: 1) many, if not most, treatment conundrums, are not suitable for RCTs; 2) RCTs have significant limitations that reduce their applicability to individual patient therapeutic decisions, 3) the quality of the evidence and the context of how the evidence was acquired and the situation in which it will be applied are given insufficient attention, and 4) the evidence does not consider the personal- the complexities of the individuality of each patient.

Marriage of the therapeutic and computer eras has led to the proposition that all treatment should be based on data from therapeutic trials. This is also the managed care era. Some managers warmly embrace evidence-based treatment. Realizing that little that doctors now do is based firmly on trial results, managed care organizations and insurance companies save money if they only pay for scientifically proven treatments. An alarming scenario has evolved. One or more RCTs are performed that show positive results. The treatment is then assigned an “evidence-based” label and organizations promulgate guide-lines based on the results of the RCTs. Managed care organizations and lawyers embrace these guidelines and physicians who deviate from the guidelines in treating individual patients (whether or not the context of the RCTs is relevant to that patient) become potentially culpable. Treatments that are not “evidence-based” are not approved by payers. Medico-legal suits are sometimes pursued against physicians who have not followed “evidence-based” guidelines.

Randomized therapeutic trials placed in clinical perspective

Trials have important limitations. Trials require enormous resources. To provide statistically valid results, randomized trials must contain large num-

bers of patients with enough end points for analysis. Sufficient end points must be reached in a short period of time. The condition studied must either be acute and cause adverse end points or rapid improvement within a short time. Chronic conditions must be severe enough to cause clear end points within 1–5 years of follow up. Many medical and neurological conditions are unsuitable for trials. Patients who are too ill, too old, too young, female and “of childbearing age”, incapable of giving informed consent, too complex, or too full of coexisting illnesses are excluded from trials.

The major limitation of trials is the numbers vs specificity issue. To include large numbers of patients, the condition studied must be common and multiple physicians at multiple centers must be recruited. One center would have too few patients or would take an unacceptably long time to accrue the number of patients needed. Uncommon conditions cannot be studied in RCTs because doctors are unable to acquire enough patients for statistically valid analysis. To achieve numbers, a “lumping” strategy must predominate over “splitting”. The more a study lumps diverse subgroups, the more general are the results and the less they are applicable to specific patients. General answers are useful to introduce subjects, however, for practicing physicians, treatment must be very specific. To be useful, trial results must help physicians treat complex individual patients in given situations. In the free world, no physician is likely to be faced with treating thousands of individuals with the same treatment irrespective of their individual characteristics but that is the situation in trials. RCTs mandate that numbers of patients with a general condition will be given treatment X and the results will be compared with patients given a placebo or treatment Y. The results will be useful to the treating physician only if the general data is applicable to the specific problem.

Brain ischemia and drugs that alter platelet functions

RCTs have shown definite but relatively small benefit for aspirin, aspirin combined with dipyridamole, ticlopidine, cilostazole and clopidogrel in patients lumped together as having TIAs or minor strokes [17]. The patient mix studied and treated with antiplatelet aggregants or placebo was not representative of patients in the community. Classification of the nature and severity of the causative vascular and cardiac lesions was not required for entry in any of these trials. Many trials antedated recent advances in modern vascular imaging. Patients with lesions thought favorable for carotid surgery were often operated on and were ineligible for the trials. Patients with “surgical” lesions deemed unfit for surgery – and patients unfit for angiography were included in medical treatment groups. Some patients with detected

cardiac sources of emboli were not entered. No systematic evaluation for carotid artery or cardiac disease was mandated in any of the studies. Subgroup analysis was only by sex and tempo of ischemia (TIA or minor stroke). The tempo of ischemia does not predict the nature, severity, or locale of causative vascular lesions. Since cardiac studies were not required, the groups also must have included patients with cardiac-origin brain embolism. The studies did not analyze the effect of race on treatment. A meta-analysis of randomized control trials of antiplatelet agents in the secondary prevention of stroke found “for aspirin compared with placebo a nonsignificant reduction in stroke of 15% ... a trend in reduction of stroke for any regimen containing aspirin” ... “It is still conceivable that aspirin alone may decrease the incidence of stroke by as much as 40%, but a sample of >13,000 patients would be needed to confirm the benefit observed in our analysis” [54]. Guidelines use the results of these trials to recommend the use of antiplatelet aggregants for patients with TIAs and minor strokes. However, the results of these studies are difficult for physicians to apply to individual stroke patients with identified stroke mechanisms e.g stenosis of the MCA or cardiogenic embolism. The result is that the trial data, despite enormous expense, is not very useful for physicians treating patients with the conditions studied in the trials. Are platelet antiaggregants useful in patients with microangiopathies (lipohyalinosis and atheromatous branch disease)? Are antiplatelet aggregants more useful than anticoagulants or other drugs in patients with slight or moderate stenosis of the carotid and/or vertebral arteries in the neck or for intracranial artery stenosis?

Critique and moving forward

Future trials of antiplatelet aggregants should contain sufficient subgroup data related to the presence and severity of vascular lesions and various stroke mechanisms to be meaningful to practicing physicians. Guidelines for antithrombotic use need to build in flexibility and context. Medical treatment decisions are often difficult. It takes time to get to know patients and their particular conditions, comorbidities, social-psychological-economic backgrounds, and desires. Table 3 lists the key factors in choosing treatment for an individual patient. Each patient is unique. Comorbidities clearly effective decision-making. So does the social-economic-psychological background of the patient. The opinions, concerns, and desires of spouses, family, children, and other members of the patients' milieu also often need to be factored into decisions. Some patients are risk-takers while others are very conservative and risk-adversive. Some patients relish statistics and choose therapies logically. Others eschew “science” and smoke, eat too

much, drink too much, take harmful drugs, exercise too little, and rely on herbs, vitamins and alternative medicines.

RCTs that answer clinically relevant questions are clearly needed. We also need more careful observations from experienced clinicians and more observational studies. More patients with complex illnesses need management by specialists as well as primary care physicians. RCTs and evidence-based medicine do not hold as much promise for the future as their advocates posit. We need to convince young physicians and medical students to go back to the bedside and to learn as much as possible about their patients and about the fundamental anatomy, pathology, and pathophysiology of the patients' diseases. Decisions take time, patience, experience, and repeated patient encounters. But these key ingredients are not valued highly in our money-driven managed care dominated environment.

1. Understanding what is wrong with the patient in as much detail as possible
2. Understanding the patient's risks for disease and for complications of potential treatments
3. Understanding the patient – their background, genetics, stresses, socio-economic milieu, psychology, responsibilities, goals etc.
4. Understanding the benefits and risks of potential therapeutic strategies to treat the patient's conditions (often multiple) and to prevent conditions that they are at risk for developing
5. Communicating with the patient and often family members and friends, listening and conveying information, and teaching.
6. The patient and their families' preferences.

Table 3. Factors important in choosing treatment for individual patients.

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STATEMENT

ATHEROSCLEROSIS: THE 21ST CENTURY EPIDEMIC CONCLUDING STATEMENT

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Arterial disease affects most of the world's population causing Heart and Brain infarctions. Cardiac and Cerebrovascular Diseases are the leading causes of death worldwide. Prevention of arterial disease is possible yet largely unaccomplished. Paradoxically, the last decade has witnessed major scientific advances in the prevention and treatment of Vascular Disease. These positive achievements, however, have mostly increased the gap between knowledge and expected results. Effective implementation is most important to reach objectives.

Science is succeeding in the battle of research against Vascular Disease but losing the field of successful patient treatment as reflected by an increasing death toll. In current times, most things change rapidly and in science specially so. Often, even before there is time to test a new hypothesis, drug or device, a more recent one has to be evaluated instead.

Knowledge sharing is the key to scientific progress in any given field. Vascular Disease is unique in that specialists from different medical areas participate in the treatment of the same patient. However, the knowledge from these different vascular experts is not fully integrated since they work in different hospital departments, do research in different laboratories and attend different scientific meetings.

One first step to effectively potentiate the discoveries that will benefit arterial disease is to integrate the efforts from physicians and other experts that specialize in epidemiology, genetics, cardiology, diabetes, vascular neurology, lipids, cognitive impairment and related specialties.

In turn, the aforementioned scientists should present their work in easily understood terms to Governments and other non-medical agencies that have a leading role in the distribution of new resources and knowledge.

At the Vatican Meeting "Atherosclerosis: The 21st Century Epidemic" we contributed by stimulating an inter-specialty collaboration with world opinion leaders.

The following is a Statement based on two days of meetings. After each participant had presented salient issues in their vascular fields, open discussions lead to this statement. We created a short document with a concise and attainable message that identifies the key success factors that must be urgently addressed.

I. Atherosclerosis

1. Atherosclerosis (Vascular Disease) is a *rising epidemic* with severe health and economic consequences for all world regions, affecting men and women in developed and developing countries. Vascular Disease is the leading cause of death worldwide resulting in 17 million deaths per year.
2. Atherosclerosis *begins early in life*, and is a chronically progressive disorder that is initiated and progressively advanced by specific lifestyle conditions and genetic factors.
3. Atherosclerosis is a *systemic disorder* responsible for acute conditions such as MI (heart), stroke (brain) as well as chronic conditions such as cognitive decline and dementia, heart failure, renal failure, peripheral vascular disease.
4. Atherosclerotic disease *worsens exponentially with increasing age* and the burden of atherosclerotic disease is expected to double by 2030 as the population ages.
5. The incidence of *premature atherosclerotic disease is rising* in some parts of the world and threatens to do so globally with the growing epidemic of obesity/diabetes.
6. *New knowledge* from epidemiology, therapeutic trials and technological advances, support the recognition, diagnosis and a new basis for action to fight this atherosclerosis epidemic.

II. Prevention

1. Prevention is the major hope for controlling atherosclerotic Vascular Disease. However, many public campaigns and medical publications focus on acute treatment missing the most effective target: prevention. Prevention provides the opportunity to generate a much clearer, effective and large-scale audience message. Resources are limited and thus must be allocated where there are greater chances for success. Prevention offers this unique opportunity.
2. Risk factor assessment and modification should begin early in life (childhood).
3. Most risk factors that lead to atherosclerosis can be modified by lifestyle changes as opposed to drug or device treatment.

4. Behavioral risk factors include: smoking, unhealthy diet and physical inactivity. Unhealthy diet encompasses excessive salt intake, excessive alcohol intake, excessive carbohydrate intake and trans-fat consumption. Obesity is a result of unhealthy diet and physical inactivity among other factors.
5. Most important risk factors include: hypertension, cholesterol, diabetes and the metabolic syndrome.
6. With the exception of age, gender and family Vascular Disease history, all risk factors are modifiable through behavioral and/or pharmacologic strategies.
7. Primary prevention can reduce the burden of illness through a culture of healthy lifestyle: reducing the prevalence of obesity, smoking, high salt diet, reducing trans-fat intake, replacing some saturated with polyunsaturated fats and avoiding a sedentary lifestyle. Solidarity in primary prevention efforts will benefit both the individual and the society as a whole. Such measures are extremely cost effective.
8. Primary and Secondary Prevention is achieved with control of the medical risk factors: hypertension, high cholesterol, and insulin resistance. Effective treatment reduces the first clinical manifestations of atherosclerosis and subsequent events in those who have already suffered a consequence of atherosclerosis (stroke, MI).
9. Hypertension accounts for approximately 50% of Vascular Disease mortality and thus is the most important modifiable risk factor yet it is largely ignored or undertreated by physicians and patients. White coat hypertension is not a benign entity and should thus be treated as hypertension.
10. In order to achieve the behavioral changes that will reduce atherosclerotic disease, policies and environment must be conducive to (promote) healthy choices. The role of Governments in these areas is crucial. The best approach should be based on a strong intersectorial Government-Health collaboration.
11. Aggregate risk factor reduction can decrease cardiovascular events by as much as 70%. Adequate Secondary prevention measures can reduce vascular event recurrence by 75%.

III. Treatment

1. Acute and chronic treatment strategies for acute coronary events and stroke are proven to reduce disability/death but access to care is often lacking.
2. Effective strategies and medications are generally underutilized even when available and not limited by cost.

3. Interventions to consider: the polypill approach for primary and secondary prevention is a cost-effective, evidence-based approach to prevention. Percutaneous interventions with stenting and surgeries (by-pass and endarterectomy) are effective measures for certain scenarios of coronary and cerebral artery stenosis and occlusions. Recent data shows that pharmacological treatment is an acceptable alternative to invasive revascularization in certain patients with coronary and carotid artery disease.
4. The most cost-effective management of Vascular Disease is one of an integrated atherosclerosis treatment based on a Total Vascular Risk approach. Individuals should be stratified according to their Vascular Risk of developing a vascular event depending on their risk factor profile and objective measurement of arterial atherosclerosis (and not managed solely on the basis of individual vascular risk factor treatment).

IV. Education

1. There is a major shortage of “vascular neurologists” in both high- and low-income countries. There should be a change in focus in the education of all physicians to more strongly emphasize evidence-based primary prevention of Vascular Disease.
2. Education focused on school children, especially targeted to create sustainable healthy behavior and sustainable control of risk factors. Both in Elementary and High School levels subjects covering Health Promotion and Disease Prevention should be part of the mandatory curriculum or could even replace subjects such as anatomy, biology or similar.
3. Telemedicine has been proven effective in selected world regions. This experience should be extrapolated and proven as a reliable alternative for treatment of Vascular Disease patients in most world areas without direct access to physicians with expertise in Vascular Disease.
4. There is significant asymmetry between the medical and general population knowledge in the different vascular fields. Knowledge in stroke lags significantly behind that about coronary heart disease. This limitation in knowledge worsens the fact that stroke incidence has increased 100% in low- and middle-income countries over the last 40 years. This and other gaps should be reduced via effective medical and population education.
5. Engage the media to promote education on Vascular Disease knowledge for a healthy lifestyle, Vascular Disease Prevention, and the need for rapid access to treatment.

6. Produce easily accessible (through multiple medical journals and internet) and understandable guidelines for management of Vascular Disease. Present guidelines are redundant, complex and not geographically, economically and culturally sensitive. If not understandable and applicable by physicians worldwide, they are not serving their natural purpose.

V. Research

1. Studies are essential to understand the pathobiology of the disease (atherogenesis, related thrombosis, lipid biology, vascular inflammation), and for the development of more potent anti-atherogenic medications.
2. Implementation (Translational Type 2) research is necessary to understand how to achieve most effective health/clinical outcomes in the wide variety of populations, to optimize the treatment of individual patients (personalized medicine). Monitoring and evaluation of cardiovascular health programs is essential to improve health outcomes.
3. Further research is necessary to discover the yet unknown risk factors that contribute to atherosclerosis and the occurrence of vascular events in persons with atherosclerosis. In the same line, knowledge is lacking to explain the occurrence of events in people without vascular risk factors and the absence of events in elderly people with multiple risk factors (i.e. outliers).
4. Greater coordination between the industry and academia would lead to a larger spectrum of the research needed for knowledge progression.
5. Many different and complex mechanisms are involved in the genesis of arterial disease: oxidative stress, cellular apoptosis, ion channels, cell migration, and inflammation are all pieces with a role in the vascular damaging process. An isolated approach to research by the different vascular specialties delays discoveries. Basic science researchers, epidemiologists, genetic experts, lipid and glucose specialists, cardiologists and vascular neurologists should work closely together and ensure that information exchange is sufficient to advance their mutual learning process.

VI. Health care policies

1. Policy development is essential as well as multidisciplinary and multi sector research.
2. Special efforts should be devoted to low- and middle-income countries where 85% of vascular events occur.
3. Developed, high-income regions should coordinate efforts to promote effective action in developing, low-income countries. This could be achieved politically at Government level, through financial support with

- research grants and identifying scientists and physicians that could function as representatives and valid translators of each country's necessities.
4. Develop an overarching Policy Framework with key components; Protection/Promotion/Prevention, Health care, Monitoring of risk factors and determinants which provides a life course approach to cardiovascular health.
 5. Advocate to place Cardiovascular/Non-communicable diseases in the development agenda and give due recognition to health in all public policies. A coordinated call to action should engage governments, church, food distributors, media, education, non-governmental organizations, and health professionals.
 6. Invest adequately on prevention focusing lobbies on tobacco control policies, reduction of salt, and high content carbohydrate and trans-fat in processed foods, replacing some saturated fats with polyunsaturated ones, providing opportunities for healthy choices and empowering people, particularly children.
 7. Medical societies related to Vascular Disease should join forces and mandate that Governments worldwide include Vascular Disease Prevention as a priority in their agendas. Public Health campaigns should include validated Vascular Disease Prevention information. Public Hospitals should have Multispecialty Vascular Prevention Clinics and Stroke Units organized following particular geographic needs and possibilities.
 8. Provide fair financing for health care moving towards universal coverage and address equity gaps so that services are based on need rather than ability to pay. Strengthen primary care for early diagnosis and reorient health systems.
 9. There is a unique opportunity for the Church, through its schools, ministry, and care of the sick to make a major contribution in fighting the epidemic of atherosclerosis in high- and low-income countries.

Conclusions

The present generation of physicians has the duty and responsibility to make Vascular Disease Prevention the number one priority in the World's health agenda. Scientists with the active collaboration of Governments, NGOs, the Church and other religious orders should ensure that Vascular Disease Prevention translates from wishful thinking to reality. The next generation should see this endeavor accomplished and focus efforts on genetics, biotechnology, nanorobotics and other novel approaches for the treatment of selected patients in whom prevention is not effective.

Tables

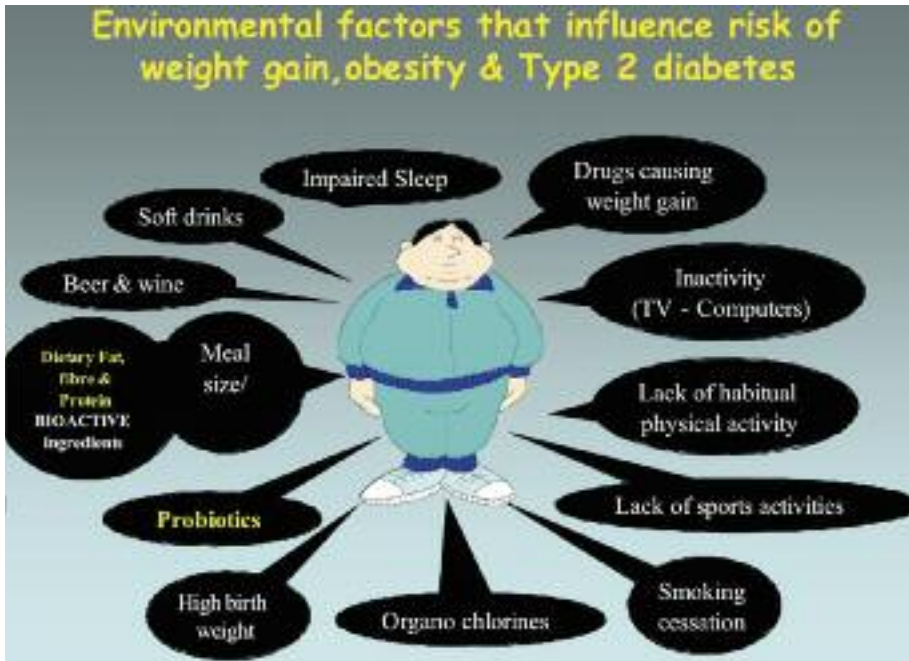


Figure 1.



Figure 2.



Figure 3.

So what should we eat and drink to maintain a healthy body weight, and to prevent T2D & CVD ?

- ❑ Reduce fat to 30-35 % of energy
 - Less Saturated fat (except from cheese and dark chocolate), and more polyunsaturated
- ❑ Increase protein to 20-25 %
 - Lean unprocessed meat, dairy products, fish, and vegetable proteins
- ❑ Keep carbohydrate ~ 40-50 %
 - with emphasis on whole grain food, fruit and vegetables
- ❑ Reduce sugar-rich soft drinks
- ❑ Alcohol in moderation
 - Wine and beer preferable
- ❑ Daily physical activity

Figure 4.

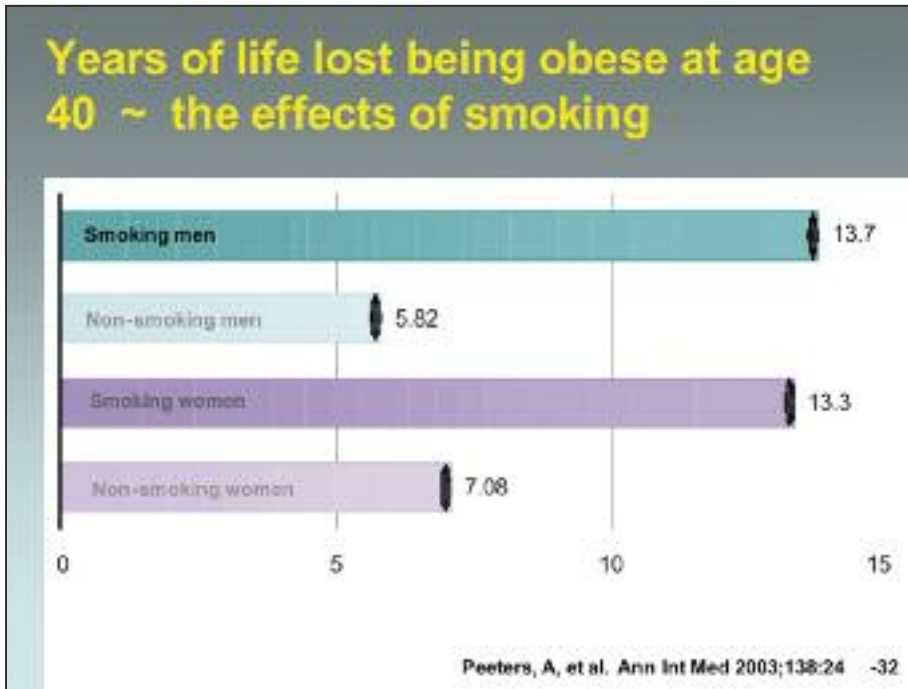


Figure 5.

HYPERTENSION C. Estel, M.D., Ph.D.

NNT: AN EXAMPLE COMPARING HYPERTENSION AND OTHER TREATMENTS

		YEARS	EVENT	NNT
NASCET	>70%	2	Stroke	8
NASCET	50-69%	2	Stroke	20
NASCET	<50%	2	Stroke	67
ACAS	>60%	2	Stroke	83
Aspirin	Prim. P.	5	MI	200
	Second	2	MI	55
		2	Stroke	200
		2	death	83
Statins	Second	2	Stroke	52
		2	MI	58
AF		1	death	66
		1	Stroke	33
Exercise		1	death	333
Hypertension	BP 140/90	6	death	30
HYVET	BP 150/80	2	death	40
	BP 180/110	5	death	19

Figure 1.

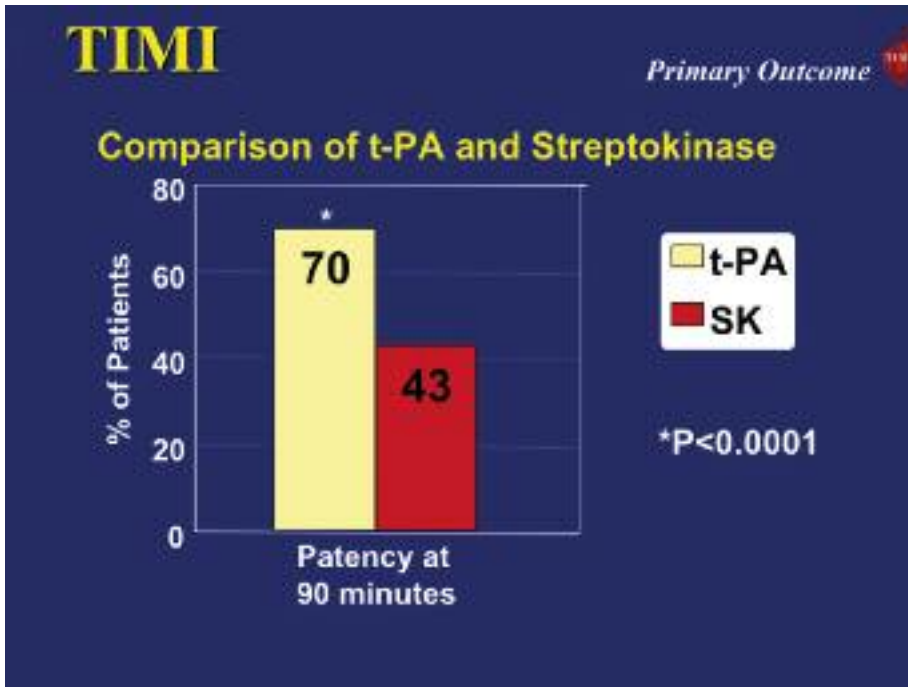


Figure 2. Data from: The TIMI Study Group. (1985) The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med* 312:932-6.

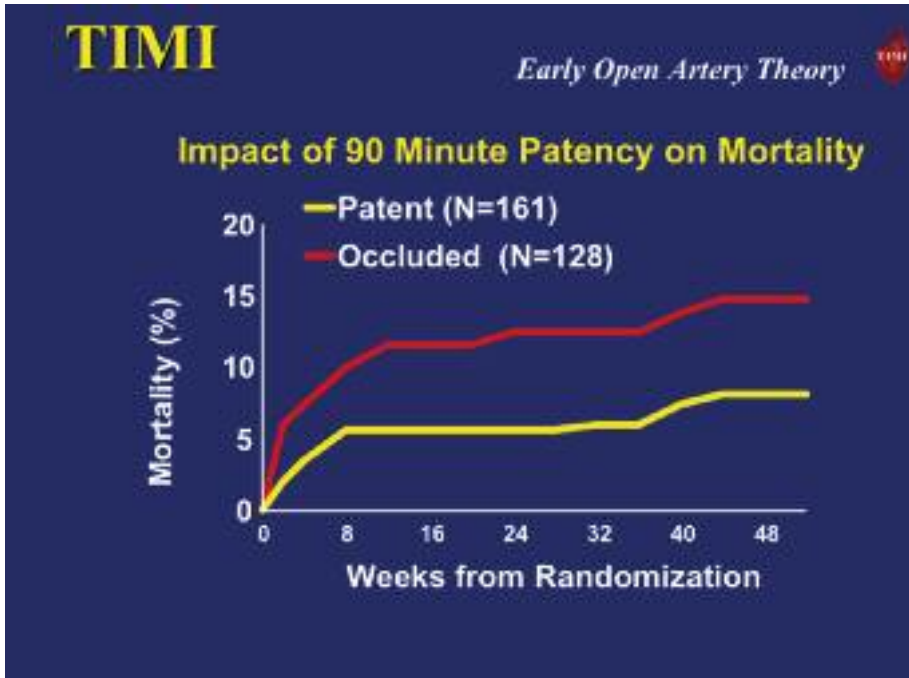


Figure 3. TIMI Phase I: Life table cumulative mortality rates by perfusion status at 90 minutes. From: Dalen, J.E., Gore, J.M., Braunwald, E., *et al.* (1988) Six and twelve-month follow-up of the Phase I Thrombolysis in Myocardial Infarction (TIMI) Trial. *Am J Cardiol* 62:179-85.

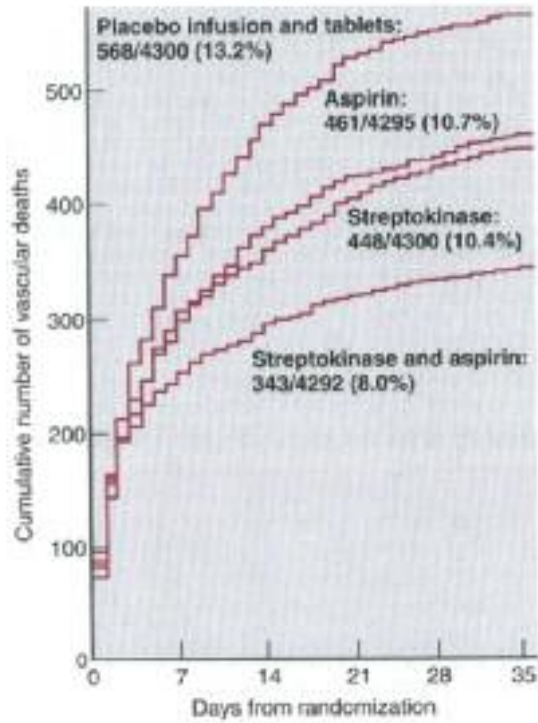


Figure 4. Cumulative vascular mortality in days 0-35. Patients allocated (i) active streptokinase only, (ii) active aspirin only, (iii) both active treatments, and (iv) neither. From: ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. (1988) Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2:349-60.

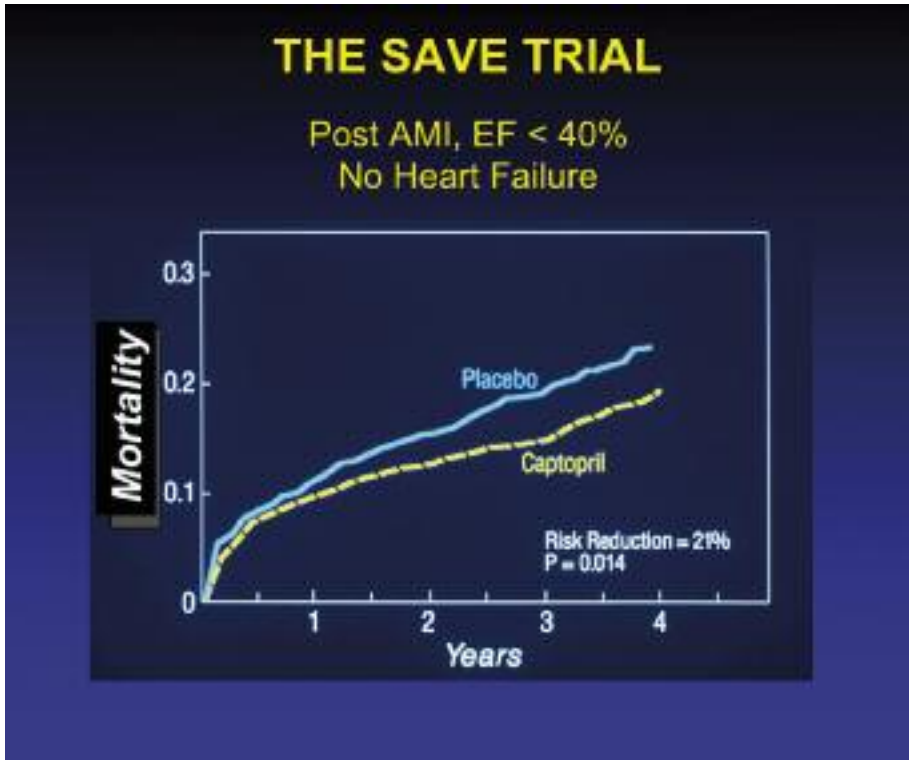


Figure 5. Cumulative mortality from all causes in the SAVE trial. From: Pfeffer MA, Braunwald E, Moya LA, *et al.* (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med* 327:669-77.

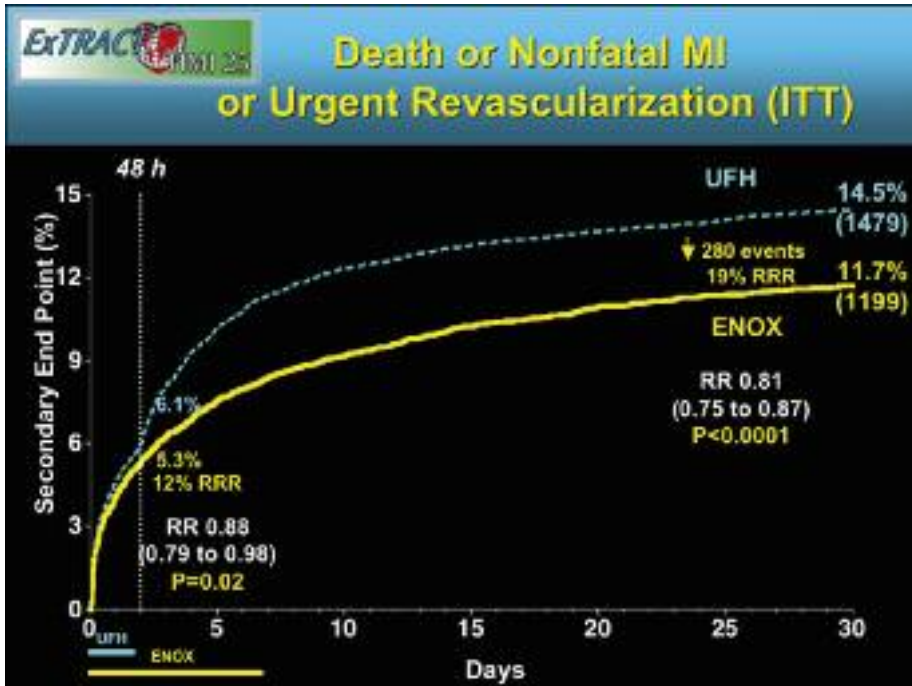


Figure 6. Death, non-fatal myocardial infarction or urgent revascularization, comparing ENOX (enoxaparin) and UFH (unfractionated heparin). ITT = intention to treat. From: Antman, E.M., Morrow, D.A., McCabe, C.H., *et al.* (2006) Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 354:1477-88.

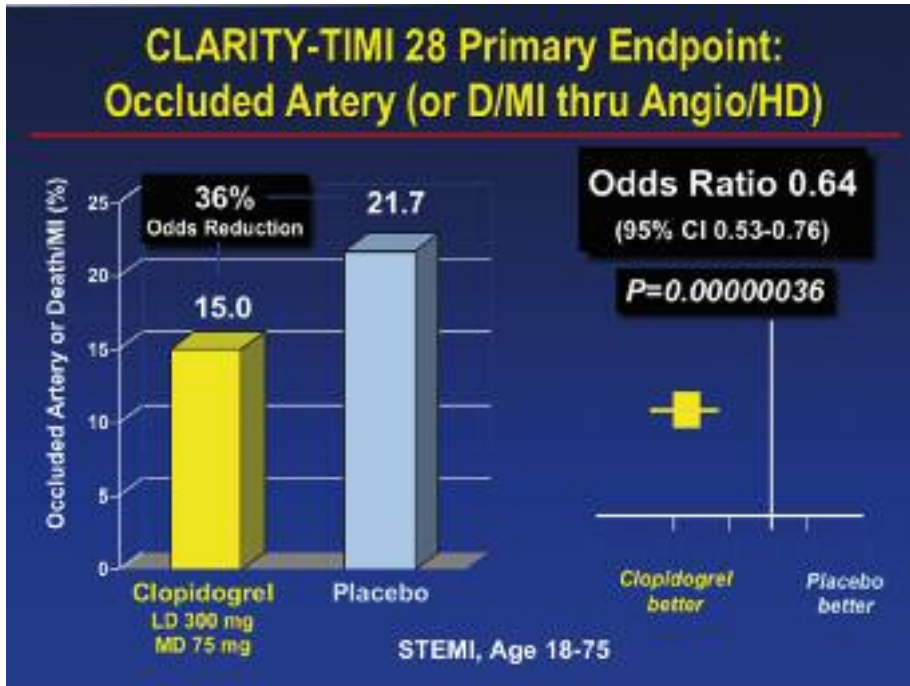


Figure 7. LD = loading dose. MD = daily maintenance dose. From: Sabatine, M.S., Cannon, C.P., Gibson, C.M. *et al.* (2006) Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 352:1179-89.

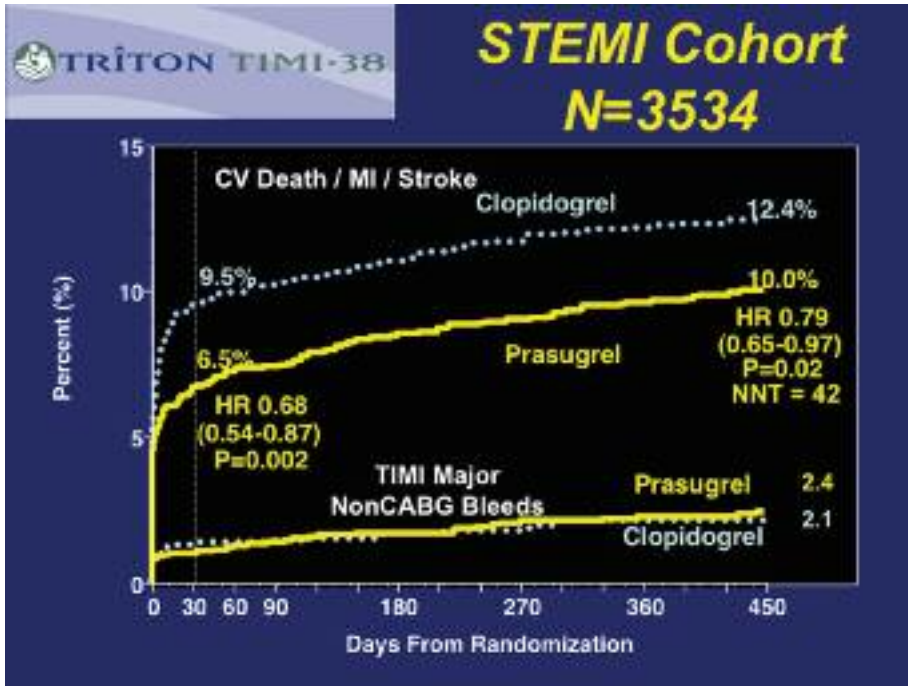


Figure 8. From: Montalescot, G., Wiviott, S.D., Braunwald, E., *et al.* (2009) Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial. *Lancet* 373:723-31.

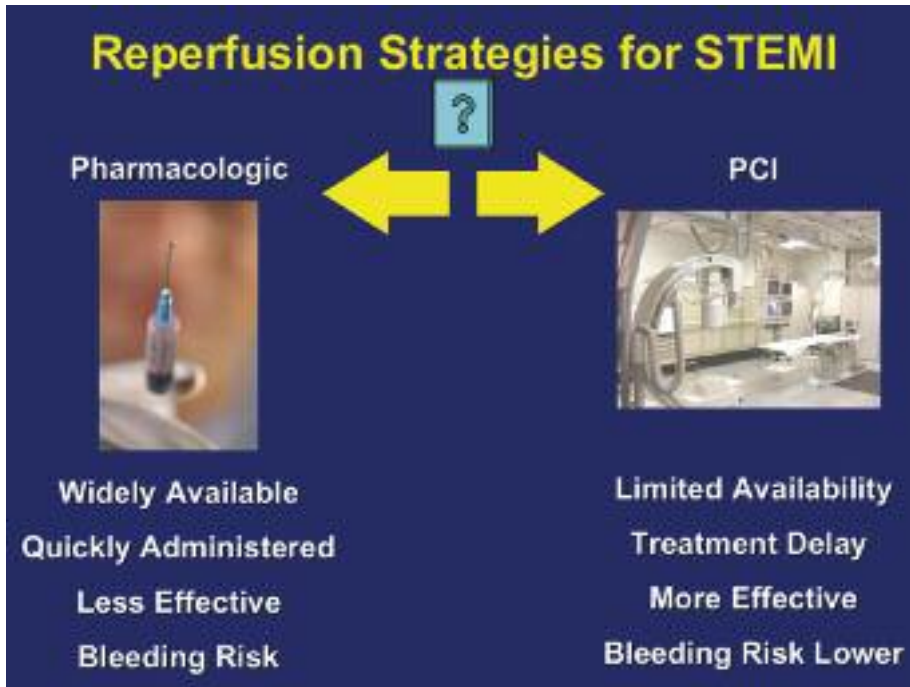


Figure 9. Comparison of the two approaches to reperfusion in ST-elevation myocardial infarction (STEMI). The advantages and disadvantages of each approach are outlined at the bottom. PCI=percutaneous coronary intervention. From: Antman, E.M. (2008) ST-elevation myocardial infarction, in Libby, P. *et al.* (eds): *Braunwald's Heart Disease*, 8th ed. Philadelphia: Elsevier. pp 1233-1299.

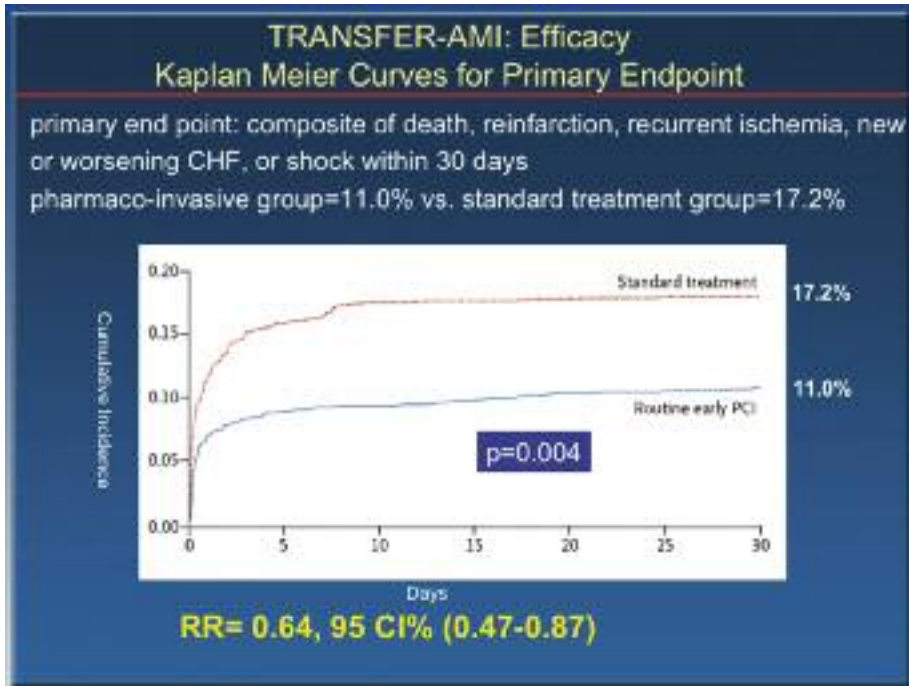


Figure 10. Kaplan-Meier curves for the primary endpoint at 30 days. The primary end point was the composite of death, reinfarction, worsening heart failure, or cardiogenic shock within 30 days. (see text) PCI denotes percutaneous coronary intervention. CHF = congestive heart failure. From: Cantor, W.J., Fitchett, D., Borgundvaag, B., *et al.* (2009) Routine Early Angioplasty after Fibrinolysis for Acute Myocardial Infarction. *N Eng J Med* 360:2705-18.

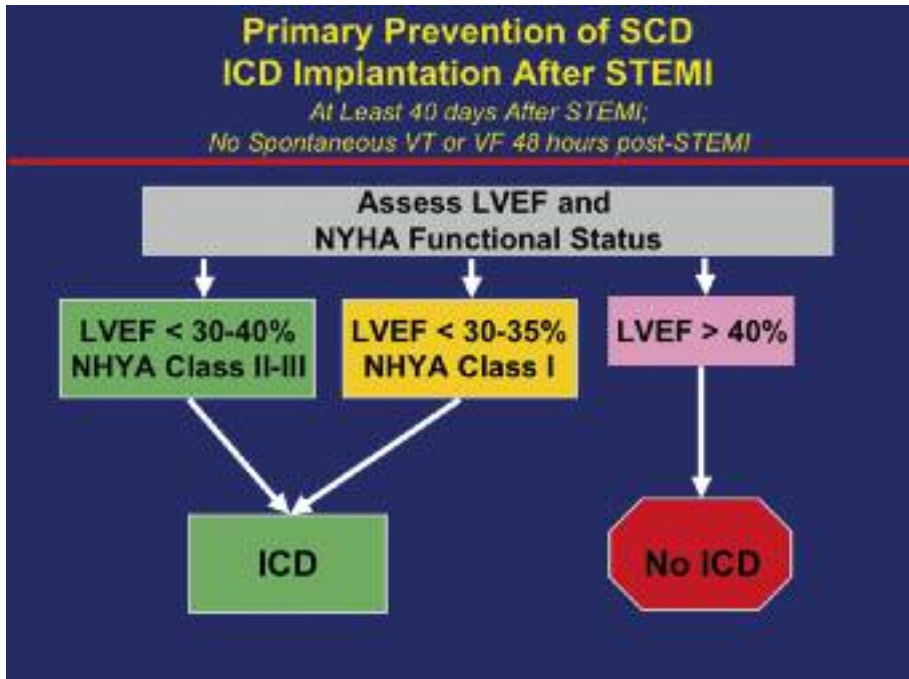


Figure 11. Algorithm for implantation of an implantable cardioverter defibrillator. (ICD) in ST-elevation myocardial infarction (STEMI) patients without ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) more than 48 hours after STEMI. The appropriate management path is based on measurement of left ventricular ejection fraction (LVEF). EF measurements obtained 3 days or less after STEMI should be repeated before proceeding with the algorithm. Patients with EF less than 30 to 40 percent at least 40 days post-STEMI are referred for insertion of an ICD if they are in New York Heart Association (NYHA) Classes II or III. Patients with a more depressed LVEF less than 30 to 35 percent are referred for ICD implantation even if they are NYHA Class I. Patients with preserved left ventricular function (LVEF >40 percent) do not receive an ICD post-STEMI. From: Antman, E.M. (2008) ST-elevation myocardial infarction, in Libby, P. *et al.* (eds): *Braunwald's Heart Disease*, 8th ed. Philadelphia: Elsevier, pp 1233-1299. Modified from: Zipes, D.P. *et al.* (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden death. *Circulation* 114:e385-484.

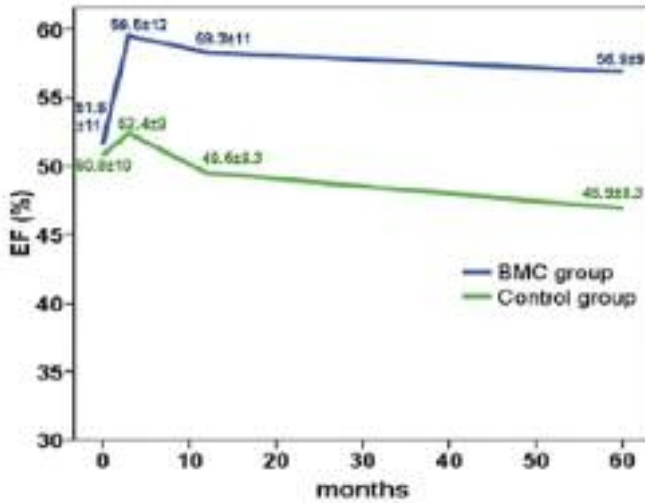


Figure 12. Ejection Fraction over the course of time after bone marrow cell (BMC) therapy in patients with AMI in comparison with the control group. Ejection fraction (EF) improves significantly in the BMC group. The initial beneficial effect of BMC therapy, as evidenced by a significant improvement of EF after 3 months, was longstanding after 60 months. In contrast, the EF decreases in the control group. AMI = acute myocardial infarction. From: Yousef, M., Schannwell, C.M., Köstering, M., *et al.* (2009) The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. *J Am Coll Cardiol* 53:2262-9.

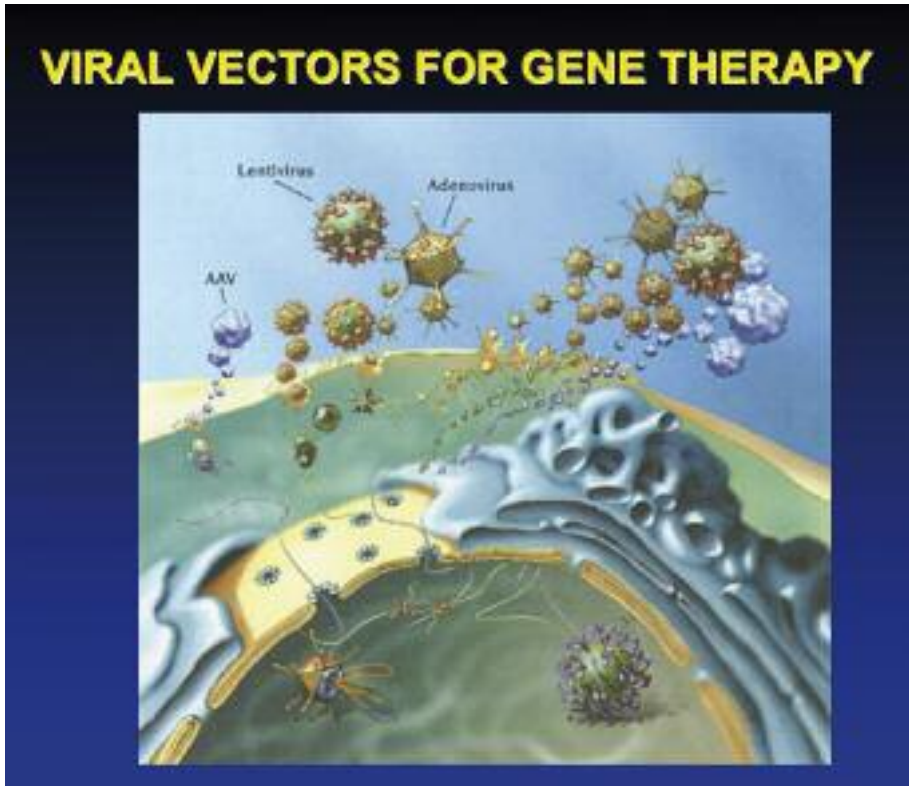


Figure 13. Virus-mediated gene transfer. The figure depicts the three major virus vectors used for cardiac gene therapy. Once the vector has gained access to the cardiac interstitium, the vectors attach to cell surface receptors or integrins, enter the cell by vesicular transport, traverse the cytoplasm, and enter the nucleus. Adeno-associated virus (AAV) and lentivirus provide persistent transgene expression, as the transgene becomes integrated into the host chromosome. Adenovirus provides extrachromosomal expression. From: Hammond, H.K., Tang, T. (2009) Gene therapy for myocardial infarction–associated congestive heart failure: how far have we got? *Dialogues CV Medicine* 14:29-36. Modified from: Perkel, J.M., Slayden, C., Swift, A. Viral mediated Gene Delivery, Poster. www.sciencemag.org/products/posters/GeneDeliveryPoster.PDF Washington DC, American Association for the Advancement of Science.

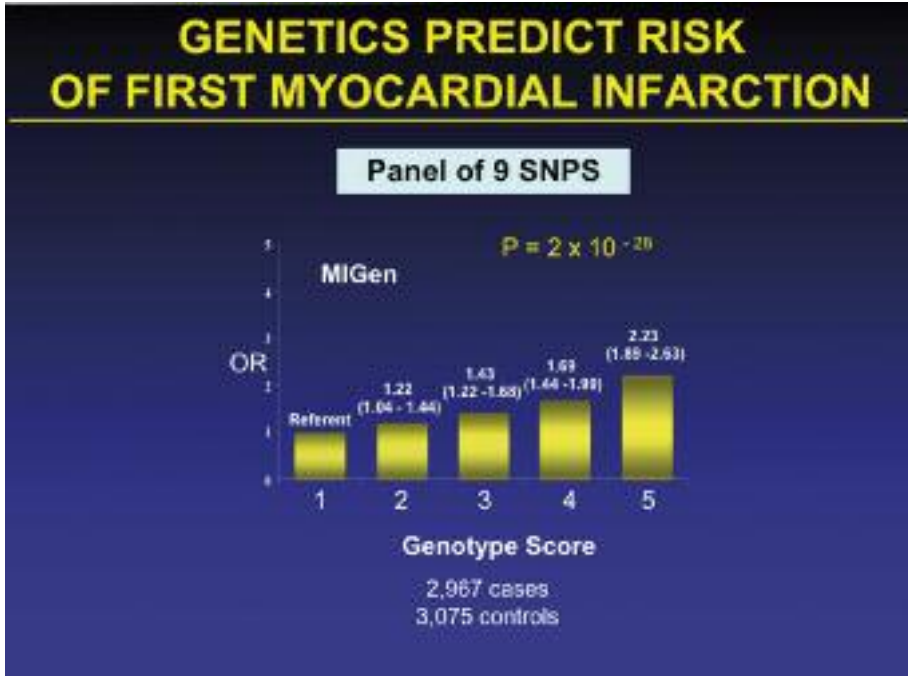


Figure 14. Genetic risk prediction of first myocardial infarction. O.R. = odds ratio; SNP = single nucleotide polymorphism. From: Kathiresan, S., Voight, B.F., Purcell, S., *et al.* (2009) Genome-wide association of early-onset myocardial infarction with single nucleotide polymorphisms and copy number variants. *Nature Genetics*. 41:334-41.

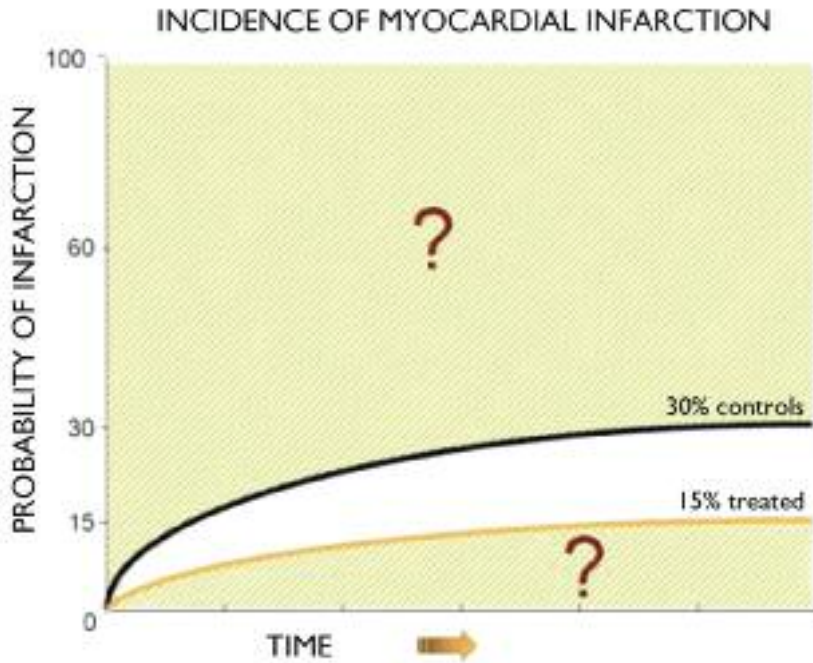


Figure 1. The diagram illustrates a preventive intervention that reduced the rate of MACE by 50% in patients with an average risk of 30%. This is remarkable, yet 15% of the treated patients had events despite treatment, and the remaining 70% had no events with no treatment. Socio-economic, clinical, and psychological factors demand a shift of research from the white area to the hashed areas.

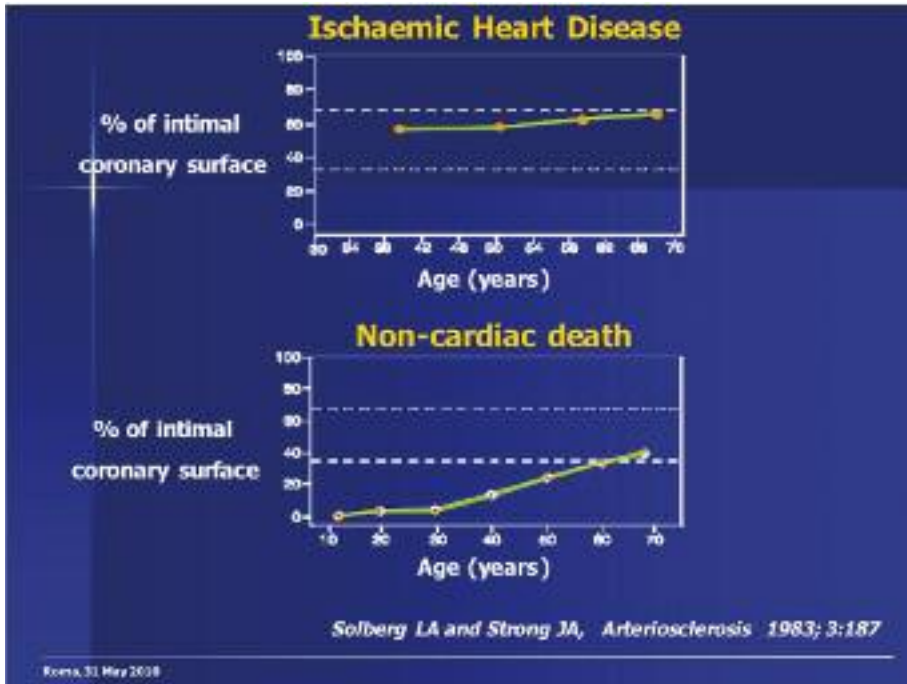


Figure 2. Percentage of the intimal surface of the major coronary arteries covered by raised fibrous plaque in patients dying of IHD and in controls. Data from the Oslo study, one of the centers involved in the International Atherosclerosis Project; the results from the other centers were similar. The percentage of the intimal surface of the coronary arteries covered by raised fibrous plaques in patients dying of IHD (A) was, on average, higher than that found individuals dying of noncardiac causes (B), but there is considerable overlap between the two groups (mean values are indicated by open circles connected by dashed lines). Many patients in the IHD group had less than one-third of the intimal surface of the coronary artery covered by plaque; conversely, many individuals in the control group had more than two-thirds of the intimal surface covered by plaque. Some individuals have no plaques, even in old age, indicating that the process is not an inevitable consequence of aging (modified from ref. 5).

	OCSP		OXVASC		Rate ratio	p
	Number of cases	Standardised incidence	Number of cases	Standardised incidence		
All intracerebral haemorrhages						
<75 years	28	0.10 (0.07–0.14)	18	0.06 (0.03–0.08)	0.53 (0.29–0.95)	0.03
≥75 years	27	1.55 (0.96–2.13)	34	1.44 (0.95–1.92)	0.91 (0.55–1.51)	0.72
Overall	55	0.21 (0.16–0.27)	52	0.16 (0.12–0.20)	0.72 (0.49–1.05)	0.08
Fatal intracerebral haemorrhage						
<75 years	11	0.04 (0.02–0.07)	10	0.03 (0.01–0.05)	0.74 (0.31–1.74)	0.49
≥75 years	15	0.86 (0.42–1.30)	19	0.81 (0.44–1.17)	0.91 (0.46–1.81)	0.79
Overall	26	0.10 (0.06–0.14)	29	0.09 (0.05–0.12)	0.87 (0.51–1.46)	0.59

Data are cases per 1000 per year (95% CI) or rate ratio (95% CI).

Figure 1. Incidence of intracerebral haemorrhage per 1000 per year in OXVASC and OCSP standardised to the 2001 population of England and Wales. Reprinted with permission from Lovelock C.E., Molyneux A.J., Rothwell P.M., *et al.* Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurology* 2007;6:487–93.

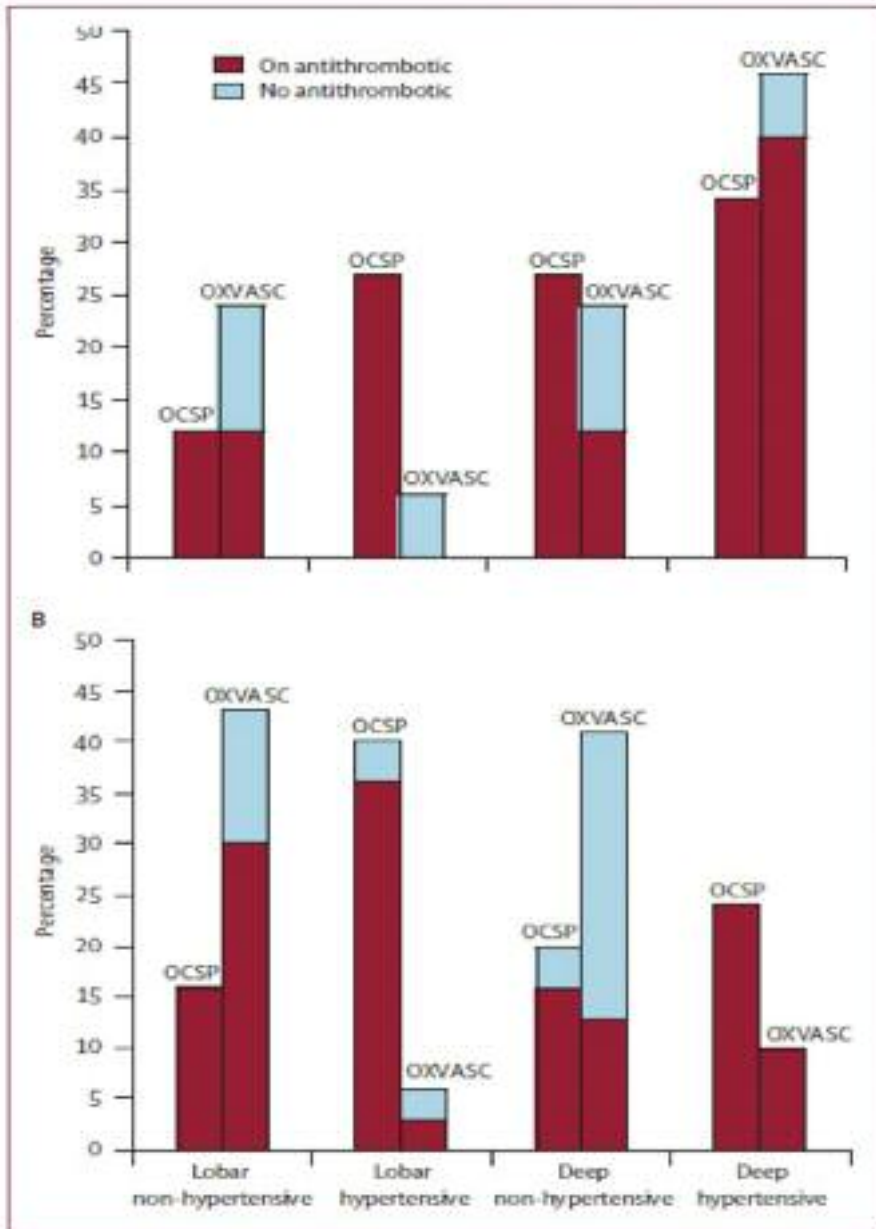


Figure 2. Proportions of hypertensive and non-hypertensive deep and lobar intracerebral haemorrhages in OCSF and OXVASC. Reprinted with permission from Lovelock C.E., Molyneux A.J., Rothwell P.M., *et al.* Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. *Lancet Neurology* 2007;6:487-93.

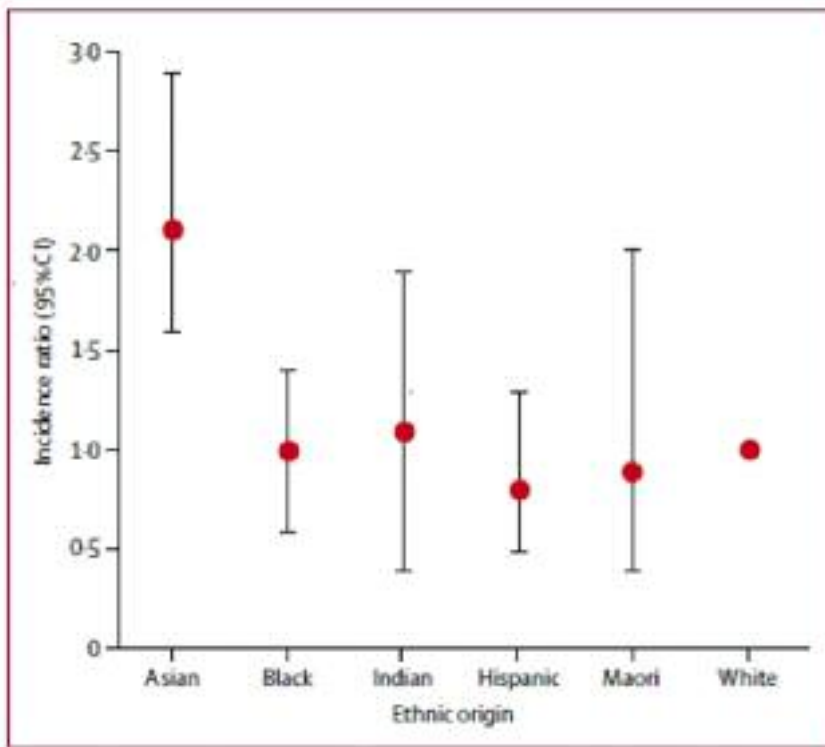


Figure 3. Intracerebral haemorrhage incidence ratios in ethnic groups. White ethnic origin was taken as reference because it was the ethnic group with the largest number of patients with intracerebral haemorrhage. Circles are means and bars are 95% CI. Reprinted with permission from van Asch C.J.J., Luitse M.J.A., Rinkel G.J.E., *et al.* Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurology* 2010;9:167-76.



In carrying out its distinctive service, the Pontifical Academy of Sciences always relies on the data coming from science and the Magisterium of the Church. In particular, concerning the present study group [on *The Signs of Death*], Christian Revelation also invites the man of our times, who in many ways seeks the real profound meaning of his existence, to face the theme of death casting his eye beyond human reality in its purest form and opening his mind to the mystery of God. Indeed, it is in the light of God that the human creature better understands himself and his final destiny, the value and meaning of his life, a precious and irreplaceable gift of the almighty Creator.

Benedict XVI, Letter dated 8 September 2006 to his venerated Brother H.E. Msgr. Marcelo Sánchez Sorondo, Chancellor of the Pontifical Academy of Sciences, concerning the working group on *The Signs of Death*, 11-12 September 2006.

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