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The European Commission Conference:
The Future of Cardiovascular Research in Europe
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The Future of Cardiovascular Research in Europe

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Summary

• The conference brought together leaders from basic and clinical cardiovascular research as well as representatives from the EU institutions (Parliament, Council and Commission) and stakeholders to analyse what had been achieved and suggest strategy for the future. Workshops held before the meeting had analysed specific problems and presentations at the conference informed on important conclusions form the workshops.

• Cardiovascular disease remains the biggest killer of men and women, often in middle age, in developed society. It is the disease that causes more deaths than any other in the world (including AIDS, tuberculosis, malaria and cancer). In a number of European countries more than 50% of all deaths are due to cardio- and cerebrovascular disease. More women die of heart disease than breast cancer. Cardiovascular disease also inflicts great suffering to patients.

• The economic cost, direct and indirect, for the European Union is approximately 300 billion € per year.

• Cardiovascular research has an excellent track record of leading to a better understanding of the normal functioning and the pathophysiology of the cardiovascular system and of translating that knowledge into new treatments. Investment in cardiovascular research brings results.

• The cost of clinical research could be reduced by clinical academic networks. Communication between basic scientists and clinicians needs strengthening. The ‘physician-scientist’ is an endangered species.

• There is need for expansion of research and coordination between EU Member States.

• Research funding remains less than in the United States or Japan.

• There is a danger that industrial research in cardiovascular disease will be moved from the European Union to the United States and India and China.

• The social needs of young scientists need to be taken into account when they change laboratory, which is a necessary step in their career development.

• The research priorities in the next 10 years include understanding the differentiation of cardiovascular cells, predicting atherosclerotic plaque behaviour and thrombosis, understanding how diabetes leads to atherosclerosis, understanding change in heart rhythm that leads to atrial fibrillation and sudden death, the molecular basis of heart failure, imaging of the cardiovascular system, individual tailored treatment, gene and stem cell therapy, understanding the mechanisms of ageing in the cardiovascular system and understanding the cardiovascular vulnerability of women.

• The European Commission is committed to the development of novel concepts of performing pan-European research in the cardiovascular system. There are many outstanding examples of success in both basic and clinical research achieved by EC funded groups.
Contributions

Welcome and Introduction

Philippe Busquin, Commissioner for Research
Prof. Dušan Keber, Slovenian Minister for Health
Ms. Maria del Pilar Ayuso González, Member of the European Parliament

Keynote lecture:

Prof. Sir James Black, King’s College London: Achievements in fundamental research bring benefit for patients

Chair: Prof. Peter Carmeliet, Flanders Interuniversity Institute for Biotechnology and University of Leuven

Prof. Thomas Lüscher, University Hospital, Zürich: Achievements in clinical cardiovascular research

Prof. Daiva Rastenyte, Kaunas University of Medicine: Epidemiology of cardiovascular disease

Prof. Andrzej Rynkiewicz, Medical University, Gdansk: The economic burden of cardiovascular disease in Europe

Prof. Brendan Kennelly, Trinity College Dublin: Cardiovascular research from the perspective of a patient

Prof. Silvia Priori, Maugeri Foundation and University of Pavia: Presentation of outcome from workshop on “Future developments in clinical cardiovascular research”

Prof. Thomas Eschenhagen, University Hospital Eppendorf, Hamburg: Presentation of outcome from workshop “Young scientists in cardiovascular disease research”

Chair: Dr. Ketty Schwartz, INSERM U 582, G. H. Pitié-Salpêtrière, Paris

Dr. Octavi Quintana Trias, Director Health, European Commission: EU activities in cardiovascular research

Prof. Jean-Jacques Mercadier, INSERM U 460, G. H. Xavier Bichat, Paris: Presentation of outcome from workshop on “The next 10 years in cardiovascular research”

Prof. Lina Badimon, Cardiovascular Research Centre, Barcelona: Presentation of outcome from workshop on “Needs for infrastructures for cardiovascular research”

Prof. Anders Svensson, AstraZeneca, Mölndal: Strategy of cardiovascular research in industry

Dr. Volkert Manger Cats, Netherlands Heart Foundation, The Hague: Analysis of funding from different sources

Prof. Sir Charles George, British Heart Foundation, London: Presentation of outcome from workshop on “Coordination of national research activities”

General discussion with chairs and presenters

Summary from rapporteur Prof. John Martin, University College London
Presentations

Introduction

The objective of the meeting was to analyse the recent history and future needs of cardiovascular research in Europe both at the basic and clinical levels. Attendees at the meeting included physicians and basic scientists, politicians and industrialists, as well as stakeholder groups representing patients.

The meeting was opened by an address from the European Research Commissioner Philippe Busquin, the Slovenian Minister for Health, Professor Dušan Keber, a Member of the European Parliament, Ms María del Pilar Ayuso González and Professor Sir James Black, Nobel Laureate.

M. Busquin pointed out that although health care was within the competence of Member States, research was within the competence of the European Commission and that a true European research space has been created. There were many examples of successful organisations working within this space. Research is the future of Europe and this has been emphasised by the heads of state and government. Research growth causes increased quality of life. However, more funding for research is needed to increase the efficiency of what we do and to coordinate national research. The Framework Programme 7 will contain many of these new ideas.

Professor Keber explained that cardiovascular disease was a big problem, particularly in lower social groups, and that the cost to the state was enormous, although data is difficult to obtain, the annual cost is over 300 billion €. He emphasised the importance of patents coming from research in this area. The clinical trials that have to be done are expensive but necessary. It is important that researchers should influence clinical practice in our hospitals. We must beware of social inequality developing within Europe and social vulnerability. There has been success in treating cardiovascular disease, but this must not be limited to richer people and must be spread equitably throughout society. We also have a duty to care for the third world with the products of our research.

Ms Ayuso emphasised the role science plays for the advancement of our societies. She underlined that health research brings benefit to patients, as clearly evidenced by cardiovascular research, which has contributed to the significant reduction in cardiovascular mortality witnessed in the last decades. The past success should be taken as an incentive for further research in the cardiovascular field. Also in light of budgetary constraints, increased overall investment in research is needed in Europe for us to remain competitive in the world.

Sir James Black told a wonderful story about the discovery of beta blockers and their clinical application. He emphasised the importance of ideas in science. What is essential is an interaction between basic research and clinical science. The effect of beta blockers on blood pressure was unpredictable and would not have been recognised except that scientists moved from basic research to clinical research and from there back to basic research again. He also asked the question whether we can cure hypertension. Could the control of blood pressure in its mild early stages stop deterioration? There were many excellent concepts associated with beta blockers that are still not in clinical practice. Again, what is needed is an interaction between basic research and clinical research. The challenges for the future are in heart failure and in understanding systems failure in biology. This will require collaboration with scientists from other disciplines such as mathematicians and engineers.
Presentation of Prof. Brendan Kennelly, a cardiovascular disease patient

Professor of Modern Literature, Trinity College, Dublin, Ireland


The following excerpt from the book is reprinted with permission.

“I had major heart surgery, a quadruple bypass, in October 1996. The day after the operation I had a number of visions (they probably lasted a few seconds, in daylanguage terms). I saw a man made of rain. He was actually raining, all his parts were raining slantwise and firmly in a decisive, contained way. His raineyes were candid and kind, glowing down, into, and through themselves. He spoke to me and took me on journeys. His talk was genial, light and authoritative, a language of irresistible invitation to follow him wherever he decided to go, or was compelled by his own inner forces to go. Yet he gave no sense of being compelled to do anything, he seemed relaxed in his own freedom, he moved calmly and unstopably. He led me to different places (I call them ‘places’) such as my father’s grave, inside my father’s bones, the land of no-language, the place where scars are roads through difficult territories, provinces of history and memory, the place of cold, true cold, and what is that? He took me into brilliant confusions to experience thrilling definitions, or moments of definition. He taught me the meaning of presence, what it means to be truly and fully in somebody’s presence, a process of complete dream surrender to another’s emotional and intellectual reality at its most articulate and vital. He was seeing, hearing and touching phenomena in a way he wished me to imitate so that I might be as real as he. He seemed to want to transfer, frequently with grace and humour, something of his essential being into mine. The interesting thing, now, is that, at this moment, I realise I was stricken in bed, well, my body was, but I was also involved in a number of odysseys and conversations such as I’d rarely enjoyed or endured in the whole of my health, in the joy of my Dayenglish, in the world of explanation without which education would not exist, the explanation which is meant to make us establish, experience, and propagate the reassuring phenomenon of coherence that guarantees us the right answer to the question: Is it sane to be mad, or mad to be sane?

What is vision? It is completely normal when you’re going through it, odd or tricky when you try to speak of it afterwards. The challenge of ‘afterwards’ is connected with ‘afterwords’, how to preserve the normality of the visionary moment without being distorted or even drowned in the familiar sea of Dayenglish. If that normality is not kept and sustained, what is sane and true at the moment of experience will come across as bizarre at the moment of telling. And vision is not bizarre though it may witness phenomena that are hair-raising in the telling. Vision, when experienced, is normal as rain falling on trees, grass, gravel, flowers, weeds, streets, people. Vision waits for us, ready to give itself; we use countless techniques to cut ourselves off from it. If I have failed to capture that normality in this poem, then this poem is a flop. If I have been able to suggest that beautiful and intense normality, then this poem may hold some kind of special interest for readers. This depends on how effectively I’ve persuaded Dayenglish to confront and express nighthappenings. The man made of rain would probably say that if I could surrender to the magical potential of Dayenglish to do the job, then I needn’t worry. Nothing seemed to worry the man made of rain. There was a concentrated joy in him. Well, I enjoyed writing this poem in the cold blue winter of 1996-97, just three months after my operation, in Dame Street.
in Dublin with crowds of young people happily drinking and carousing in the street all night into early morning, and the man made of rain graciously and deftly flowing through ‘afterwards’ and ‘afterwords’ in my mind and imagination. Cold, blue light. Walks along the canal. Cries of lovers or would-be lovers drunk at night, threats and curses flung at the moon. Violence in the streets (you’ll see the blood tomorrow), screams of homeless men beating each other up as they headed for favourite doorways or a place in the Saint Vincent de Paul shelter. They sought shelter in the shade of the Saint as I sought to recreate the sheltering, inviting, guiding, presence of the man made of rain. In ‘afterwards’ and ‘afterwords’. I let these screams invade my being and the paper I wrote on. I wanted to see the dream absorb and transfigure its own violation by the “real”. Time is a fierce river and language must do its poor best to keep up with the flow. Let it flow. The man made of rain would not leave me (not that I wanted him to leave me) until I let his presence flow in the best and only poem I could write for him. Though I appear in the poem, or what I recognise as my “own” voice sounds through it, the poem is essentially a homage to his presence, a map of his wandering discoveries, and an evidence of my inadequate witnessing of those discoveries and that presence. He is a real presence in the poem; I am more an absence longing to be a presence. How, equipped only with ‘afterwords’, could I possibly do justice to those thrilling voyages, excursions, expeditions, flings, conversations, moments of pure light, and pain that makes vision possible? What I feel now, afterwards, is gratitude to the man made of rain: to his raining light, shining gentleness, flowing sympathy, cheeky piss-taking of my hacked body, his smile inviting me to explore, explore, his pity, compassion, love. Dear man made of rain, dear guide, friend, genial pisstaker, (and whoever else you are), I hope you enjoy this ould poem.

What?

‘What is my body?’ I asked the man made of rain. ‘A temple,’ he said, ‘and the shadow thrown by the temple, dreamfield, painbag, lovescene, hatestage, miracle jungle under the skin.

Cut it open. Pardon the apparition.’

‘What is my blood?’ I dared then. ‘Her pain birthing you and me, the slow transfiguration of pain into knowing what it means to be climbing the hill of blood, trawling the poisoned sea.’

‘Where have I been when they say I’ve returned?’ ‘Where beginning and end combine to make a picture, compose a sound reminding you that love is a singing wound.

and I could be your friend.’

The man made of rain

I.

Between living and dying is the calmest place I’ve ever been./ He stood opposite me and smiled./ I smiled too, I think, because this was the first time I’d seen a man made of rain though once or twice my heart was chilled by men of ice./ The rain poured through him, through his eyes, face, neck, shoulders, chest, all his body but no rain reached the ground, it ended at his skin.

He looked at me with eyes of rain and said, ‘I’ll be coming to see you now and then from this moment on./ Today, I’m colours, all colours./ Look at me, I’ll be colours again but different next time, maybe./ See my colours today.’
I looked. I saw the flesh of rain. I looked into and through the rain and saw colours I'd never seen before. As I looked, the colours began to dance with each other, some were laughing, some were crying, some said they were lost and were looking for their brothers and sisters, one said he was the colour of work and it saddened him to see how easily he made slaves of men. I looked for the colour of slavery but couldn't find it. I saw the colours of poverty instead like children in O'Connell Street. 'Pick one of us,' they sang in a chorus. 'You'll have a friend for life.' I was indecisive because I was between living and dying and anyway the colours were vanishing into each other like thoughts that cannot stand alone but must seek out other thoughts to stop going mad. Why are thoughts afraid to go mad? The rain is laughing at that fear. I followed the rain of the eyes and saw the terror that makes reason necessary and gives it authority, an educated terror that didn't trust the rain. He never asked me to trust him but I would trust the man made of rain to the lip and into the mouth and belly of eternity, it isn't even a question of trust more of the kind of interest you find when you put aside the fear of dying and look at the light or listen to the sound of water or pay attention to pigeons or her hair when she's unaware or find yourself swallowing a nightsound or like the way a scientist talks of ten dimensions. It is calm in the place beyond trust and especially calm if you walk there in the company of your own hurt, in the company of the man made of rain pouring beside you but more contained than anything in the world except the pain waiting at the white door one cold October evening, leaves falling, traffic ranting, seagulls hovering, swooping like dreams that seek you out for, it seems, the fun of it.

O scars of living, the fun those dreams must have!

I won't have to open the door.

He steps forward, opens it, smiles. I walk in, he vanishes nowhere to be seen, the silver rain is everywhere, the shadows creep into the secret corners of the October evening where live and die secret and open dark and light chaos and wonderplan are wideawake in the heart of sleep.
Speaker Presentations

Achievements of Clinical Cardiovascular Research

Professor Thomas F. Lüscher
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Summary
Ever since the discovery of the circulation by William Harvey in the 17th century, cardiovascular medicine has made considerable progress. However, in the first 300 years progress was very subtle. Indeed, only a few drugs such as digitalis, as discovered by William Withering and later amyl of nitrate introduced by Sir Thomas Lauder Brunton were available. Most of the disease states of the heart and circulation were unknown or not well understood. Indeed, only in the 19th century did the London clinicians Hunter and Jenner suggest an association between calcifications of coronary arteries and sudden death. Also, although the common occurrence of cardiac hypertrophy and shrunken kidneys was noted by Wright in the mid 19th century, blood pressure could only be measured regularly much later and the recognition of the importance for this condition took further time. Efficacious drugs only became available in the 60ies and 70ies of the last century. Many problems were related to the fact that the heart as an inner organ was not very well accessible to the clinicians and, therefore, diagnosis of many today well known diseases was rather difficult. The first physician to make a difference was Lanneac in Paris who invented the stethoscope in 1823 and allowed for the first time clinical diagnosis of many cardiac conditions, in particular valvular heart disease. The discovery of the x-rays by Röntgen in 1900 first allowed to see the heart and eventually made cardiac catheterization possible. Echocardiography was developed 50 years ago and is now common practice as a readily accessible tool to diagnose heart disease. Newer imaging techniques like MRI and CT are currently increasingly utilized in clinical practice.

Cardiovascular medicine became clinically relevant as treatment options were developed, at first bypass surgery as introduced by René Favoloro in 1968 and later percutaneous coronary intervention as introduced by Andreas Grüntzig in 1977. At the same time many drugs were introduced in clinical practice such as aspirin, cholesterol-lowering agents, beta blockers and blockers of the renin angiotensin system, thrombolytic agents and glycoprotein IIb/IIIa inhibitors. The therapeutic potential of cardiovascular medicine was complemented by devices; at first the pacemaker introduced in 1958 by Ake Senning made bradycardic rhythm disorders amenable to therapy. In the 80ies and 90ies implantable cardioverter defibrillators were developed and increasingly used. Most recently, biventricular pacemakers for congestive heart failure became a treatment option.
Thus, in summary, cardiovascular medicine made enormous progress through the development of diagnostic and therapeutic tools that allow to markedly reduce and delay the occurrence of cardiovascular and its complications such as myocardial infarction, stroke and death.

**The Hidden Organ**

Although ancient doctors were able to feel the pulse as a first clinical sign of cardiac action, introduction of the stethoscope by Lanneac in Paris in the early 18th century for the first time made it possible to access the function of cardiac valves and to clinically assess pulmonary congestion. Real progress in cardiovascular medicine, however, only started with the development of new technologies allowing to see the structure of the heart and to measure its activity. The discovery of x-rays by Conrad Röntgen in 1900 provided a technology that at last made the shadow of the heart visible and allowed to judge its overall size. With this technique it became clear that patients with high blood pressure or heart failure had larger hearts than healthy controls. Also, x-rays made pulmonary congestion and pleural perfusion in these conditions visible.

As important was the development of the electrocardiogram by Willem Einthoven in 1985. This technique provided means to quantify heart rate, to understand the electrical excitation and activity of the heart and to diagnose conditions associated with an abnormal ECG such as syncope, rhythm disorders, left ventricular hypertrophy and later myocardial infarction. Einthoven introduced the classical denominations of the various waves in the ECG such as P, Q, R, S and T, which still are in use today.

The discovery of the x-rays also provided the basis for an important development in cardiovascular medicine, i.e. the first cardiac catheterization performed by Werner Forssmann in the local Prussian hospital Eberswalde near Berlin in 1929 using an urethral catheter on himself that he introduced through the antecubital vein into his right atrium. Although, this seminal self-experiment opened the door to cardiac catheterization, Werner Forssmann was not privileged to pursue that as his colleagues did not allow him to go into that direction. Indeed, he became an urologist only to remember his heroic experiments when he heard about the Nobel Prize he received in 1953 together with Alexander Cournand. Today coronary angiography is the gold standard to diagnose coronary artery disease and the basis to perform percutaneous coronary interventions as introduced by Andreas Grüntzig in 1977 at the University Hospital in Zürich, Switzerland.

However, there are several limitations to the left ventricular angiogram and coronary angiography, respectively as they only visualize the “shadow picture” of the left ventricular cavity and the coronary vasculature. They do provide only limited information about cardiac valves, their structure as well as the vascular wall of the coronary circulation where the atherosclerotic process that is responsible for coronary disease and acute myocardial infarction really takes place. Furthermore, cardiac catheterization remains invasive and does have a certain complication rate, although it has dropped considerably to less than 1% in the last decades.

Another approach to visualize the heart was inspired by marine ultrasound in the 1960s and led to development of echocardiography, a non-invasive tool that with current equipments allows to visualize cardiac structure and function in a very appropriate manner. However, there are limitations to echocardiography: In particular it is still dependent on the experience and skills of the operator involved. Furthermore, the coronary circulation can still not be visualized on a
regular basis with this technique. The newer technique of magnetic resonance imaging, although more cumbersome to perform, provides more accurate and observer-independent information on the structure and function of the heart and in addition also allows to quantify myocardial function and perfusion more precisely. The biggest progress, however, recently has come from multi-slice computer tomography which allows not only to visualize the cardiac chambers, valves and major vessels, but also the coronary arteries, particularly with the new 64-slice technique that provides a remarkable resolution. Hybrid technologies combining computer tomography with positron emission tomography are moving towards a “one stop shop” that remains the vision of cardiac imaging. Ideally, one would like to have an imaging modality that not only provides information about the structure of the cardiac chambers, its valves and the major vessels, but also on the coronary arteries and perfusion of the myocardium. Furthermore, the most important challenge of cardiac imaging is the characterization of coronary plaques that are responsible for acute coronary syndromes. Although remarkable progress has been made by the use of intravascular ultrasound experimentally, it is quite difficult to assess plaques appropriately in the clinical setting.

What is Clinical Research?

In cardiovascular medicine, as in any other specialties, integration of various levels of research has proved to be crucial to enhance our knowledge about the function of the heart and circulation as well as the origins of major diseases. The introduction of physiology, cell biology and molecular biology has remarkably stimulated the understanding of the heart and the vasculature. Translation of the knowledge gained at the basic level, however, does require patient-oriented research and the new tools of clinical epidemiology to confirm hypothesis gained in small series of patients in larger patient populations. Indeed, the introduction of the principles of evidence-based medicine to clinical research of the heart and circulation prove to be extremely productive. In the last 30 years, thousands of large randomized clinical trials have been performed in all fields of cardiovascular medicine, thereby markedly advancing our knowledge in the treatment of hypertension, hyperlipidemia, myocardial infarction and heart failure.

Although genetic techniques allow characterizing rare monogenetic diseases such as hypertrophic cardiomyopathy, long QT-syndrome and other familial cardiovascular diseases, little has been gained for the understanding of the major disease entities such as coronary heart disease, hypertension, just to mention the most frequent ones. Although several single nucleotide mutations of genes involving the renin angiotensin system, the eNOS system and others do have some relation to clinical syndromes in cardiovascular medicine, their contribution is disappointingly low. Thus, the complex interaction of multiple gene mutations with life style and other environmental factors must be well characterized in the future.

Congenital Heart Disease

In the middle 1950s of the last century, congenital heart disease was the first disorder of the heart and the circulation that was amenable for treatment. Indeed, pioneers in cardiac surgery started to close the open Botalli duct, atrial septal and ventricular septal defects and other congenital disorders. Although initially perioperative mortality was huge, the development of the heart lung machine, the improvement of techniques in anaesthesia as well as availability of
modern diagnostic tools led to a marked improvement in outcome. More recently, techniques allowing to operate on more complex congenital disorders such as the Senning procedure, the Switch operation and others have allowed to prolong life also in children with malformations of the heart that previously led to premature death in these patients.

A major event in cardiovascular medicine and surgery was the first cardiac transplantation performed by Christiaan Barnard in Cape Town in 1968. Although surgeons of that time including also Norman Shamway, Ake Senning and others readily mastered the surgical technique, immunological problems leading to chronic rejection of the organ limited the use of this procedure in patients with end stage cardiac disease. Through the introduction of cyclosporine by Novartis in the 70ies, organ transplantation became more and more a routine procedure at least in patients below the age of 65 years.

**Cardiovascular Risk Factors**

The major progress in the understanding of atherosclerotic vascular disease that accounts for most of morbidity and mortality in Western countries came from experimental and epidemiological studies. After Anichtkov's seminal observation that feeding rabbits with a high fat diet leads to formation of atherosclerotic plaques, the Framingham Study had confirmed on an epidemiological basis that high cholesterol, hypertension, smoking and diabetes are major risk factors for the development of coronary artery disease, myocardial infarction and stroke. Indeed, while Admiral Ross T. McIntire, the personal physician of President Franklin D. Roosevelt, in 1945 still was able to state that the fatal cerebral haemorrhage that killed the President "came out of the clear sky", we know today that hypertension is a major cardiovascular risk factor for stroke, myocardial infarction and death. While in Roosevelt's time no effective drugs were available, today we have multiple molecules interfering with the renin angiotensin system, water handling by the kidneys, calcium channels as well as the sympathetic nervous system. Thus, currently almost all patients with high blood pressure can be well controlled with medical therapy, although compliance of patients and doctors remains a problem. With appropriate blood pressure control fatal or non-fatal strokes can be reduced by almost 50% and coronary heart disease by a disappointingly low 15%. Thus, hypertension is the first cardiovascular risk factor that has been characterized through experimental studies, systematic clinical experience, cohort studies and finally small randomized trials and more recently by huge therapeutic studies involving more than 40'0000 patients. With the application of evidence-based medicine it was possible to demonstrate that lowering of blood pressure is efficacious in reducing cardiovascular morbidity and mortality and that blood pressure should indeed be lowered to normal levels particularly in diabetic patients.

Although cholesterol has been recognized as a risk factor already in the Framingham cohort, the efficacy of cholesterol lowering by HMG-coenzyme-reductase inhibitors only could be demonstrated in the early 90ies of the last century. Until today numerous randomized controlled trials in patients after myocardial infarction, unstable angina, or with only elevated cholesterol have demonstrated a profound risk reduction with statins making these drugs a standard therapy in patients with coronary artery disease as well as in the primary prevention of this disease process. While statins are particularly efficacious in LDL lowering, they only minimally affect HDL cholesterol levels, which are inversely related to coronary artery disease. Indeed, in patients with the metabolic syndrome, an increasingly frequent disease entity in a
society with an ever increasing prevalence of obesity, low HDL levels are particularly important. Thus, new drugs affecting HDL levels may represent the next step in cardiovascular prevention. Although currently available drugs such as fibrates and niacin do have some effect on HDL, the novel cholesterol ester transport protein inhibitors are even more promising.

With the increasing average weight of Western societies and the increasing prevalence of obesity in the US but also in Europe and India, the metabolic syndrome typically presenting with central obesity, hypertension, dyslipidemia and insulin-resistance and later diabetes may become a major epidemic in the future. Indeed, already today an increasing number of adolescents and young adults show signs of the metabolic syndrome. As diabetes is still difficult to control and associated with lipid disorders and hypertension, this development may markedly affect the incidence and prevalence of atherosclerotic vascular disease in the future in spite of the progress made in the past. Also, since most attempts to control body weight with dietary measures have failed, major progress in this area only can be achieved by the development of new drugs interfering with appetite control in the central neurohormones involved in it.

**Coronary Artery Disease**

Originally, coronary artery disease was only amenable to medical treatment. Indeed, the first drug introduced by Sir Thomas Lauder Brunton in 1867 was amyl of nitrate, which was soon replaced by nitroglycerine. Beta blockers and calcium antagonists, two other compounds that are efficacious in treating myocardial ischemia and angina pectoris, were only introduced in the 70ies and 80ies of the last century. Surgical treatment was for the first time introduced by René Favoloro in 1968 when he performed venous bypass surgery using a saphenous vein of a patient to revascularise a stenotic coronary segment. Later internal mammary artery grafts were added with remarkably better long-term outcome. Randomized studies comparing medical treatment with surgical therapy in the late 70ies and 80ies demonstrated a superiority of bypass surgery in terms of morbidity and mortality in the long-term particularly in patients with main stem disease and three-vessel disease.

With the introduction of percutaneous coronary intervention (PCI) in 1977 this less invasive procedure became an increasingly important alternative. Although originally hampered by a high restenosis rate of about 30% to 40%, the method was considerably improved by an introduction of coronary stents in the mid 80ies. Particularly since the problem of stent thrombosis was solved by the introduction of ADP antagonists interfering with platelet activation, stents have been increasingly used and are now employed in over 90% of the procedures. With this technique the restenosis rate could be reduced by about 20% on average. Several randomized trials comparing balloon angioplasty and/or stenting to bypass surgery have shown that both procedures have a similar morbidity and mortality rate in the long run; however, percutaneous interventions are prone to a markedly higher re-intervention rate due to the problem of restenosis. Through the introduction of drug-eluting stents (releasing either rapamycin or paclitaxel) in the last couple of years, restenosis could be reduced to less than 5% both in uncomplicated patients and well as patients with diabetes and bypass graft disease. Ongoing trials will be performed to determine whether with this new technique percutaneous interventions are equal to bypass surgery even in complex patients with three vessel and main stem disease. If so, percutaneous interventions may substitute for a bypass surgery in the majority of patients, because of their relative non-invasiveness and lower costs due to shorter hospital stays.
Myocardial infarction

A major event in patients with atherosclerotic vascular disease is acute myocardial infarction that originally had a mortality rate of more than 50%. With the introduction of cardioversion as introduced by Bernhard Lown in the early 60ies, mortality could be reduced to about 30%. Then, in the 80ies the introduction of aspirin, thrombolytic treatment and beta blockers further reduced the fatal outcome in this syndrome. Today, percutaneous coronary interventions with pre-treatment of the patients with glycoprotein IIb/IIIa has led to a mortality rate of less than 10% in most patients. Thus, today percutaneous coronary intervention is the treatment of choice in most patients with acute coronary syndrome, in particular those with ST-segment elevations and/or elevated troponin levels. This also has led to shorter hospital stays after myocardial infarction and more rapid resosocialization of the patients.

Secondary Prevention

After an acute coronary event, secondary prevention remains an important aspect of medical management since the event rate in untreated patients remains rather high. Various randomized trials have shown that treatment with aspirin, an ADP antagonist such as clopidogrel, beta blockers as well as an angiotensin converting enzyme inhibitor reduces the occurrence of major adverse cardiac events considerably. With optimal treatment today event rates over two years are in the range of 18%. A further reduction of the cardiovascular event rate might be achieved with new therapeutic approaches, in particular elevation of HDL cholesterol by novel CETP inhibitors or other drugs, possibly the reduction of homocystein on more efficacious patient selections through genetic characterization of the patients.

Inflammation and Coronary Artery Disease

A new development, already suggested by Rudolf Virchow in the mid 19th century, has been the discovery of the importance of inflammatory markers in diagnosing and predicting cardiovascular disease. Indeed, many studies have shown that C-reactive protein and other acute phase proteins such as serum amyloid protein A, interleukin and others are predictive of future cardiovascular events. As it appears, acute inflammatory peaks may act as triggers of acute coronary syndromes and may explain why some patients continue to have stable angina, while others develop coronary occlusion after symptoms or out of the blue. Inflammatory mediators may destabilize coronary plaques, leading to plaque rupture and/or erosion with thrombus formation and vascular occlusion. Although statins do have some anti-inflammatory action and are able to reduce C-reactive protein levels, no specific anti-inflammatory treatment has been characterized so far. Novel approaches are currently tested in ongoing trials, e.g. with COX 2 inhibitors, a class of drug which is able to reduce the expression of this pro-inflammatory enzyme and to reduce C-reactive protein levels and possibly other novel molecules.

Arrhythmias

Although irregular heartbeat is symptomatic in many patients, most arrhythmias are not dangerous. Indeed, even supraventricular arrhythmias such as AV-re-entry and Wolf-Parkinson-White Syndrome rarely lead to fatal complications, but remain a problem for
quality of life. The most frequent supraventricular tachycardia is atrial fibrillation that increases in frequency with increasing age and particularly in the elderly is associated with cerebrovascular events. AV-re-entry, WPW Syndrome as well as more recently atrial fibrillation are now amenable to ablation treatment and in many instances these arrhythmias can be cured by this procedure. In other patients, anti-arrhythmic drugs, in particular beta blockers and amiodarone may be used. In patients with atrial fibrillation both drugs are useful for rhythm control and possible cardioversion into sinus rhythm. Most importantly in these patients anticoagulation or the use of the new oral thrombin inhibitors markedly reduce the occurrence of embolic cerebrovascular events.

Life threatening arrhythmias such as ventricular tachycardia and fibrillation can be caused by genetic diseases such as long QT-syndrome, which has been characterized as a mutation of proteins of channels responsible for potassium and sodium transport in the myocardium. Also, in cardiomyopathies such as hypertrophic cardiomyopathy, right ventricular cardiomyopathy and non-compaction of the myocardium such arrhythmias occur. Progress in gene therapy may provide a cure in these patients as well; however, many technical problems have still to be solved until such a treatment may become available.

In patients with coronary artery disease ventricular tachycardia and fibrillation are a common problem and a major cause of sudden death particularly after acute myocardial infarction. Unfortunately, medical treatment has mainly been shown to be ineffective or even harmful. Therefore the development of implantable cardioverter defibrillators (ICD) has been a major progress. Many randomized trials have now shown that ICDs do prevent sudden death in patients after acute myocardial infarction, reduced ejection fraction and in particular in those with wide QRS-complexes as well as in patients with severe forms of cardiomyopathies.

**Heart Failure**

Heart failure is the final common pathway of most cardiac diseases including coronary artery disease, hypertensive heart disease, valvular heart disease and congenital heart disease. Heart failure may involve systolic and/or diastolic dysfunction. ACE-inhibitors or angiotensin receptor antagonists, diuretics, beta blockers and spironolactone are efficacious in the treatment of patients with systolic heart failure. Each of these drugs does improve symptoms and survival of patients with systolic heart failure. Although digitalis was one of the first drugs introduced into cardiology, randomized trials have shown no survival benefit, although symptoms may improve. With modern treatment, the yearly mortality of heart failure of up to 20% could be reduced to 5-10%. Unfortunately, in the long run most patients succumb to their disease. Therefore, the need for additional treatment modalities remains an issue; unfortunately, new drugs such as endothelin antagonists and vasopeptidase inhibitors have proven to be inefficacious. It is hoped that newly developed treatment strategies aiming to improve myocardial function such as stem cell therapy will provide new treatment options in the future.

Diastolic heart failure is extremely common particularly in elderly women and leads to comparable symptoms such as systolic heart failure. Unfortunately, most treatment strategies have proved to be of limited benefit in these patients. Although angiotensin receptor antagonists do reduce cardiovascular death and hospitalizations slightly, no satisfying treatment modality has been found so far.
Conclusion

Thus, cardiovascular medicine has evolved in the last 500 years since the seminal work of William Harvey. In the last 50 years, cardiovascular science has grown into an impressively efficacious discipline of medicine allowing the treatment of most patients with cardiovascular disorders. Although tremendous progress has been made, the disease entity remains a major cause of mortality and morbidity in Western countries and also in India and in the future in China. Main reasons for the remaining importance of cardiovascular disease are the aging Western society, the increase in body weight in Western as well as developing countries leading to the metabolic syndrome and an increasing incidence of diabetes as well as the high prevalence of smoking. Therefore, efforts and progress has to be made to cope with this problem.

References

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Cardiovascular disease (CVD) that includes cerebrovascular stroke and coronary heart disease (CHD) is the leading cause of death and disability among adults. It kills 4 million Europeans each year and is responsible for nearly a half of all deaths occurring in the population. About a half of all deaths from CVD are from CHD and nearly one third - from stroke. CVD is the main cause of deaths among men aged 25-64 years as well as among those aged 65 years and over. Among women of the younger age, CVD as a cause of death is competing for a first place with cancer whilst it causes nearly two thirds of all deaths among those aged 65 years and over [1].

In the year 2000, incidence of fatal coronary events was 166 cases per 100,000 male European population aged 25-64 years, and 46 - among female population or about three times higher than that among the populations of the same age in countries of the European Union (EU). In countries of Central, Southern and Eastern Europe (CSEE), incidence rates were a bit lower compared with the European average, but still more than twice higher that that in the EU and Nordic countries. European average for incidence of fatal coronary events among those aged 65 years and over was 1674 among male and 1182 - among female population or nearly twice higher the average of the EU countries [1].

In the year 2000, an average of incidence of fatal cerebrovascular events in the European male population of the younger age group was 66 cases per 100,000 and that among women - 37 cases. Very similar rates were observed among male and female populations of CSEE countries. Like in case of CHD, incidence rates of fatal cerebrovascular disease in the EU and Nordic countries were more than 3.5 times lower compared to European and CSEE average, and made 18 and 11 cases per 100,000 population among men and women, respectively. In the age group of 65 years and over, rates were naturally much higher than those in younger age group, and again, the difference between rates in the population of Europe as the whole and in the populations of the EU made more than 200% [1].

During the last two decades a steep decline was observed in both mortality from CHD and mortality from cerebrovascular disease in a number of industrialised countries world-wide and in Europe. In five Nordic countries, mortality from CHD among the population aged 25-64 years decreased by 160%, and among those aged 65 and older - almost twice. To the same extent mortality rates decreased in the younger-age populations of the EU countries while the decline by 46% among the population over 65 was not so steep. Much different trends were those for Europe as a whole and for CSEE countries. Up to early nineties, an increasing trend was observed in CSEE countries reaching its highest point in 1992-1993. Since then, a flattening in mortality trend occurred in the population aged 65 years and over while a decreasing trend was observed among those of the younger age group. The latter resulted in the decline of mortality rates by 60% over the last 7 years. There were no major differences in time trends in mortality from CHD between men and women of the two age groups [1].
During the last 20 years the most pronounced decline in mortality from cerebrovascular disease was observed in the EU populations. In the age group of 25-64 years, mortality rates dropped by more than 100%, and that in the older age group - almost by a half. A clear downward trend was also observed in the populations of Nordic countries although it was less steep compared to the EU countries and to the trend in mortality from CHD. For CSEE countries, a flat trend was observed in both age groups for almost 15 years with some acceleration in decline after 1994 in the age group of 25-64 years. For Europe as the whole, mortality from cerebrovascular disease has declined by 20% among those aged 65 years and over. After reaching a peak in 1994, cerebrovascular disease mortality rates decreased by 18% over the next 7 years in the population of the younger age group. As in case of CHD, patterns of trends in mortality from cerebrovascular disease followed the same direction among both men and women of the two age groups [1].

Although official mortality statistics data are most easily obtainable and most frequently used for cross-country comparisons, mortality statistics provides just very general information about the epidemiology of the disease, and reliability of these data has been questioned for years. In order to improve the prevention and control of CVD, to set public health priorities and determine appropriate actions, morbidity data are required. Nevertheless, morbidity data are rarely available in the different countries and when available, they are very rarely comparable [2]. The comparability of data across countries depends on standardisation, case definition, completeness, proper linkage, common diagnostic criteria and validation procedures [2].

The WHO MONICA Project was a multicentre study, involving formation of population-based registers [3]. It produced valid and reliable information on fatal and non-fatal acute coronary and cerebrovascular events in different populations during the years 1983-1995 [4, 5, 6]. During the last 5 years of the MONICA study period, the highest attack rates of coronary events, that exceeded 600 cases per 100,000 population per year, were observed among the male populations aged 35-64 years in United Kingdom, Finland and Poland, while the lowest ones, about 250 cases - in the populations of Switzerland, Spain, France and Italy. Among women of the same age, again, the highest rate was registered in UK - between 260-170 cases, followed by Poland - 158 cases, and Denmark - 134 cases. As among men, the lowest rates among women were those in France, Spain and Italy - about 40 cases per 100,000 population [5].

The average annual stroke event rates in the last 5 years of registration were the highest ones in the populations of Lithuania and Finland, and the lowest ones - in Italy, Sweden and Denmark. Among men, stroke attack rates varied between 345 cases in Lithuania and 121 cases in Italy, and that among women, between 164 cases in Lithuania and 61 case - in Italy [6].

There was substantial heterogeneity in the trends in coronary event trends over 10 years, ranging from less than -6% to more than +3% per year in men and women. The event rates declined in most populations [4, 5]. Those with the increasing trends were from the Eastern European countries and Spain. Among men, CHD declined statistically significantly in 24 out of 39 populations while among women the declining trend was significant just in 14 populations with a lot of uncertainty in others.

Substantial heterogeneity was also observed in the trends of stroke attack rates although range limits of the trends were a bit narrower: between less than -4% and more than +4% per year among both genders [4, 6]. On the other hand, uncertainty in trends was even more pronounced compared to that in coronary events, as statistical significance was reached just in two populations among men and in 4 - among women.
While the cerebral and myocardial vasculature are different, the occurrence of stroke and CHD is related to common risk factors (RF) such as level of blood pressure, hypercholesterolemia, tobacco smoking, and body mass index. One of the key questions addressed in the WHO MONICA Project was to what extent changes in event trends can be attributed to changes in the levels of classic cardiovascular RF in the population [2]. When the effects of all individual RF were combined into a risk score and a time lag was taken into account, the association between trends in coronary-event rates and in risk score appeared to be rather modest, with the percentage of variation explained of 22% in men and just of 10% in women [5]. Stronger association was found between trends in stroke event rates and risk score in women with percentage of variation explained of 36%. In men, however, the association was very weak and negative, suggesting other factors to be in operation [6].

The variation that remains unexplained in regression analyses is attributed to the imprecision of measurements, complexities in the relationship between RF and event rate changes, and other possible factors, such as socioeconomic status, ethnic and cultural background, food consumption, etc., driving changes in event rates [5, 6]. It looks like in many populations factors other than changes in the population load of classic cardiovascular RF constitute an important part of the driving force for changes in coronary- and stroke event rates.

In conclusion CVD remains the number one killer in Europe with a substantial difference in CVD mortality rates and trends in mortality rates between the EU and CSEE countries. During 10-year study period of the WHO MONICA Project, trends in stroke event rates were less clear than that in CHD events, and trends in CVD event rates were less clear among women compared to men. Variations in CHD and stroke trends between populations can be explained only in part by changes in classic cardiovascular risk factors. All said above proves an urgent need for further, more extensive research in the field of cardiovascular disease.

References
The economic burden of cardiovascular disease in Europe

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To consider the economic burden of a disease one needs to take into account several categories of costs: Clearly, the direct medical costs need to be considered. These consist of costs for outpatient care such as the fees for doctor’s visits and diagnostic procedures, the costs of drugs and the costs created by referral to the emergency room. The costs for inpatient care include the costs for general care in the hospital, the costs for critical care and the price of frequent and often costly interventions.

Indirect costs of disease relate to productivity losses due to morbidity or due to partial or total disability and also due to premature death. Difficult to quantify but also very important are the psychological costs of disease.

Figures in Europe would have to be analysed for every individual country. Since it can be assumed that in many respects the figures from the United States will be similar to those from European countries, they were presented.

The total cost of CVD in the United States in 2004 is close to 300 billion €. Heart disease accounts for the largest proportion of this cost followed by coronary heart disease, hypertensive disease, stroke and heart failure. On average the direct costs are about 2/3 of the total costs. The direct costs consist of about 45% hospital costs, about 17% nursing home costs about 15% costs for physicians and other health care professionals, 19% costs for drugs and about 4% home health care costs. The share of the different direct costs changes between the different types of CVD. For example, in the case of hypertensive disease the costs for drugs have a relatively larger share (38% - double the overall average) and the hospital costs have a relatively smaller share (10% - 1/4 the overall average) than for the other disease categories. The indirect costs of CVD account for 38% of the total costs. Whereas for coronary heart disease the direct and indirect costs are almost the same, for congestive heart failure, the indirect cost is only about 10% of the direct cost.

Based on the figures in the United States it can be assumed that the economic burden of CVD in Europe is very large.

It is also interesting to note that the amount of money spent on treating coronary artery disease in Europe differs by a factor of six: In the year 1999 In the United Kingdom only about 42 € per head were spent on treating this condition, whereas in Germany more than 250 € were spent. A large part of this difference is accounted for by the differing number of percutaneous transluminal coronary angioplasties that are being performed.

With the enlargement of the EU the already existing differences in overall health care spending per capita are becoming even larger, ranging from about 500 € in Poland to 2500 € in Germany. Disability-adjusted life years is one measure for the burden of disease. The health research spending by the National Institutes of Health in the United States correlates quite well with this DALY figure for a large range of diseases. In consequence there is a large amount of funding for CVD.
Strategy of cardiovascular research in industry

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Cardiovascular diseases have a huge impact on global health, and are estimated to account for 17 million deaths annually. Not only Europe and North America are affected; cardiovascular diseases are the leading cause of death in most regions of the world, with the exception of Sub-Saharan Africa. Morbidity and premature mortality can be translated into medical need, and the need for better and more effective treatments can be seen as an opportunity for the pharmaceutical industry to develop medicines, to fill these needs. Thus, it is logical that cardiovascular therapeutic classes represent around one quarter of worldwide pharmaceutical sales.

The global environment for health care providers and the innovative industry is rapidly changing, due to changes in demography with an ageing population. Global socio-economic trends and lifestyle changes are creating an epidemic of obesity, type 2 diabetes and all the cardiovascular complications that are associated with these conditions. New guidelines tend to recommend more strict treatment goals, and to focus more on total risk reduction than on control of individual risk factors. This development over a limited period of time, together with better-informed patients, will create huge new demands on health care providers.

Europe and the Western world are struggling to meet health care needs and to control health care costs. The Developing world is moving in the same direction; India is today the country with the greatest estimated number of patients with type 2 diabetes. In this situation, access to medicines has become an area of focus. In developing countries, the cost of drugs may make them difficult to afford. However, in developed countries, the cost of pharmaceuticals generally represents 10 - 15% of the total health care expenditure. Still, this is a significant proportion, and may be seen as an easy target for savings. Thus, we see recommendations to use the drugs that are cheapest in the short-term perspective, e.g. diuretics in hypertension, even though “at the population level, the use of antihypertensive drugs with a documented diabetogenic potential is hardly a wise choice” (E. Ferrannini and Kozakova M. J. Hypertens. 2003 Aug;21(8): 1459-1462).

An example of the choices that will have to be made is emerging in the treatment of atrial fibrillation, where the risk of stroke increases dramatically with age. Yet, with increasing age, fewer and fewer patients are being treated with the only available oral anticoagulant, warfarin. The reasons for not treating those at highest risk are related to the well-known complications associated with the use of warfarin and its narrow therapeutic range. For the first time in more than half a century, truly innovative medicines are being developed in this area of high unmet need. The question is whether these drugs will be made widely available to patients in need, or if budget holders responsible for the cost of drugs will discourage the use, potentially at a high cost to the total health care budget, and to patients and their families.
Europe accounts for 26% of the world pharmaceutical market and the US for 51%; according to IMS Health World review 2003. The imbalance is even more obvious when looking at sales of new medicines, launched during the period 1998-2002, where 70% of sales were in the US and 18% in Europe. Since 1990, a dramatic shift has occurred in pharmaceutical R&D expenditure. In 1990, about 50% more was spent on R&D in Europe than in USA, but in 2000 USA spent one third more than Europe, and in 2002 this difference had increased to 40% more than Europe. This is, with some delay, being translated into new molecular entities (NME), where Europe was far ahead with 97 NMEs vs. 52 for US in the period 1988-1992. In 1998-2002 USA was ahead with 77 NMEs vs. 68 for Europe. The direction is clear, and European pharmaceutical companies are adjusting, moving R&D out of Europe, reducing the proportion of their total R&D being spent in Europe from 73% to 59% from 1990 to 1999 according to EFPIA.

The pharmaceutical industry will invest where it is cost effective, where talent is available and researchers can be recruited. The reduced emphasis on clinical research in many European countries will have long-term impact on the potential to participate in high quality clinical R&D initiatives. This is the part of pharmaceutical development that generates the final steps in bringing new therapies to the patients. It is also the most costly part of pharmaceutical development, engaging clinical researchers not only within the industry, but also at hospitals and universities as well as in primary care. AstraZeneca has recently started a Clinical Research Unit in Shanghai, and is expanding operations in Bangalore and in the US, but has also expanded R&D facilities in Europe. However, if new medicines are not reimbursed, recommended and prescribed, the question is whether development will be located in these countries. Pharmaceutical industries have been criticised for performing studies in developing countries, and the Declaration of Helsinki states that at the conclusion of a study, patients should have access to the best therapeutic methods identified by the study (DoH, item 30). What will happen to clinical development if new innovative and effective medicines are not made available to patients? This question would have been seen as purely rhetorical as regards Europe a few years ago, but may be asked by ethics committees, and by the pharmaceutical industry, in the near future.

With investment moving outside Europe, important decisions will be made elsewhere, support to local universities will be reduced, as will employment opportunities. For clinical as well as pre-clinical researchers, this will mean fewer opportunities to participate in the development of novel treatments, and for patients potentially mean later access to effective new treatments. For society as a whole, it may mean a net financial loss (The Economist, Jan 31st 2004, p 53-54: “The trouble with cheap drugs”).

In summary, the demographic changes, the increasing cardiovascular disease burden and emerging new technologies will create huge challenges for society, and for the pharmaceutical industry. Europe has traditionally been a dominant force in this area, but pharmaceutical industry is now expanding much faster outside Europe. Transparent and fast regulatory processes, renewed emphasis on clinical research, and the ambition to make new and innovative medicines available to those in need, are all important factors for retaining a healthy pharmaceutical industry within Europe.
European Union contribution to research

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There are a number of challenges for European research. Europe does not invest enough and funding is fragmented. These problems must be overcome and a favourable environment for research and innovation needs to be created. To achieve this we must work on creating a European Research Area. Activities towards this goal include for example networks of research centres, common infrastructures, better coordination of European and national research programmes, encouragement of risk investment through the European Investment Bank (EIB) and increase of the mobility of human resources. This mobility should include senior managers, not just students. It is evident that a more comparable career structure in the different Member States would be very helpful in this. Regarding the overall budget available it must be remembered that only about 6% of the public funding for biomedical research is administered at the European level. If one considers public and private investment, the share is even smaller with about 2%. Within the limited resources considerable and increasing sums have been made available for biomedical research and cardiovascular research in particular.

Framework Programme 6 (running from 2002-2006) is the financial tool available at EU level to work towards the reinforcing of the European Research Area. About 2/3 of the funding is spent on a total of 7 Thematic Priorities, the first of which is ‘Life sciences, genomics and biotechnology for health’ with a total budget of more than 2.2 billion €. The focus in life sciences research is on genomic research, which is justified by the scientific advances in recent years. Within this framework translational research studies including clinical investigations are being funded. In all projects appropriate participation of industry and especially SMEs is essential.

A number of questions need to be answered for the further development of our research funding. Such questions include whether patients should be involved in the decision making process. The European Directive on good clinical practice raises issues for the conduct of academic clinical trials. The funding of clinical trials with a high public health benefit needs to be addressed.
Analysis of funding from different sources

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Funding for cardiovascular disease research comes from three main sources. The public provides a large part of the infrastructure for CVD research in the form of medical schools, universities, and other public research institutes. It also pays for medical research or similar funds. In particular the pharmaceutical industry contributes considerable amounts to cardiovascular research. Finally, in a number of countries private foundations fund cardiovascular research to a considerable degree.

In addition to the three main sources, in some countries the health insurance schemes provide funding for CVD research directly related to health care.

The funding streams for cardiovascular research in The Netherlands were presented as an example.

Trying to provide figures for funding of CVD research is hampered by the fact that normally only figures for overall health research are available (no disaggregated figures by disease area), that figures are available only for some countries (mostly from northern Europe and the USA) and that these figures date back a few years. Whereas the overall funding for health research in relation to the population varies by a factor of two, the relative funding from different sources varies more. In other words, the total (relative funding) is roughly equivalent in a number of northern European countries and the USA but the sources for these funds differ significantly.

For example, the share of public funding for health research ranges from 24% in the UK to 63% in Germany. The share of industry in the overall funding is lowest in Germany with 35% and highest in Sweden with 66%. Private foundations contribute only 1% to health research funding in Germany but 10% in the UK.

In conclusion it is striking that the share of public funding for health research differs to such a large degree between countries. So far there are few if any initiatives to coordinate health research in general or cardiovascular research in particular between countries.
Workshop presentations

Coordination of National Cardiovascular Research Activities

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Representatives of medical research councils, institutes and non-government organisations from ten EU countries were surveyed by means of a questionnaire.

Six of them sent representatives to a workshop held in Brussels on 1 March 2004 and a seventh subsequently provided additional information.

Common themes which emerged were:

• Cardiovascular research is funded by several agencies in each of the countries
• Their financial contribution varies markedly
• Research into cancer receives greater funding than does cardiovascular disease
• Most research funders operate in response mode

Most research funders are constrained by a lack of available funds and their terms of reference. Furthermore, international cooperation was more prevalent than cooperation at national level.

In this millennium, there are signs that cooperation amongst funders at national level is progressing. There are useful examples evident in Germany and the United Kingdom for which there is preliminary evidence of added value.

Such alliances can lead to the sharing of knowledge, the saving of money and the division of responsibilities. They provide an opportunity for discussion and debate leading to scientific agreement and the establishment of a consensus on key issues.

Successful alliances are predicated on a number of core principles which have recently been identified by the European Heart Network based in Brussels.

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Young Scientists in Cardiovascular Disease Research

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There was general agreement between the participants of the workshop that the attractiveness for young people to enter science is decreasing throughout Europe. This appears to be, to a large extent, not specific for CV research, but a general problem of science in Europe. The participants tried to (1) identify major problems and (2) to suggest potential solutions that could be offered by the EU.

The major problems are low total spending on research compared to the US, the narrow individual salary range compared to other fields, especially to clinical practice (particular clinical cardiology), and to the US in particular, bureaucracy and strict regulations, general lack of freedom to achieve scientific and business ideas, rigidity and hierarchy of science structures with the consequence of intransparent career chances, few permanent positions (depending on country), insufficient integration of basic, clinical and applied science, too few MD-PhD programs, relatively low social status of researchers (depending on country) and in medicine the trend towards a more practical/professionalized medical curriculum that increases the gap between fundamental research carried out by non-medical departments/researchers and the medical community.

Specifically, major hurdles that prevent mobility of young scientists in Europe are lack of competitiveness of EU science, structures in guest country that impose unnecessary difficulties for families to join the scientist, structures in home country that do not promote mobility ("local networks are often more important than scientific achievements"), lack of intra-European competition for good scientists, language problems, and bureaucracy of travel grant application.

Finally, the discrimination against women in many European countries, both psychologically and in terms of practical limitations (e.g. insufficient places for children day care), was felt to be one of the central problems for science. It leads to the paradoxical situation that women makes up more than 50% of science/medical/pharmacy students, but less than 10% of leading positions. This is an unacceptable waste of human potential.

During the course of the workshop it became increasingly clear that the efforts of the EU commission to improve European competitiveness remain necessarily symptomatic and inefficient as long as the structural problems of the national and European science are not being solved. It is unlikely to be enough to put more money in the system without achieving a political solution.

Several practical ideas are already partly implemented in recent EU activities.

Postdoc scholarships should include repatriation grants

Postdoctoral fellows who want to come back from another EU country or the US after a postdoc time do not find an open position or they have to work under conditions which do not allow competitive scientific research (e.g. in clinics). As a consequence, the postdoctoral
experience helps the guest country, but is lost for the sending country. Postdoc scholarships should therefore include repatriation grants, e.g. 3 years postdoc outside + 3 years inside Europe. Such a system gives a clear perspective for young scientists to make a career back in their home country.

Open EU science to non-EU nationals
European science needs more young brilliant scientists than Europe generates and Europe has to compete with the US and Japan for the best worldwide. The Marie-Curie program already addresses this problem, but should be expanded, should be open to all nationals and not restricted to EU nationals, and should increase the relative proportion of running costs and equipment as compared to individual salaries.

The EU should put pressure on national governments to facilitate foreigners and their relatives to work in the EU

The EU should reserve some money for “high risk projects”
Presently, grants are primarily given to already successful projects. This is a safe method, but sometimes obstructs brilliant young scientists to enter the system. A small (5%?) fraction of the budget should be reserved for high profile, high risk projects that did not show success yet, but have highest potential, are not standard, not “me too”, not arising from the present the state of the art.

The EU should provide simple travel grants for short-term collaborations
True collaborations work at the bench and on the postdoc/researcher level. This fruitful interaction should be supported by the EU.

More importantly, a fundamental change of the EU funding system was found to be necessary in order to:

1. Make a commitment to the freedom of research: Freedom is the main driving force for brilliant people to do basic science and not other jobs where they can earn considerably more money with similar qualifications.

2. Make a strong and long-lasting commitment to basic science: Basic science is the necessary requirement for any kind of applied science and economic progress. The EU should encourage and support the fast track from basic science to industrial application, but should not make applicability the major measure of quality. Teaching programs in schools should encourage science. Public campaigns would be a possibility to increase public interest in science.

3. Increase inter-European competition, because this will automatically generate fruitful collaborations: As long as national research is a “closed-shop affair”, i.e. the institutes/clinics only compete with each other on a national scale, the speed of structural improvement will be slow. An open competition for EU grants would allow talented young researchers to do excellent research in their home country. Such teams will be crystallization points and would brake up rigid local structures.

4. Forget about large networks: Networks sound good, but do not work if they are exceeding a few groups. Big groups prevent the exchange of ideas, of hot data, secrets and therefore tend to produce mediocre results. Big groups reduce the degree of personal commitment to the network. Big groups are expensive and multiply bureaucracy.
5. *Create a science-driven European funding agency such as the NIH, MRC or DFG* (“bottom-up”): The idea to stimulate excellence by feeding the scientific community with questions/subjects generated by politics, public or pressure groups as done in the 6th framework program is conceptually wrong. Good science is driven by individual ideas. Good scientific collaborations need time, personal relations and commitment. Scientific collaborations should be established before the grant. There should be no restriction of grants to specific fields or networks. Such an open grant system would automatically stimulate inter-EU competition and break up national structures that adversely affect scientific efficiency.

6. *Give maximal freedom, but ask for results*: Reduce paperwork to the absolute minimum; this saves time, money and energy for research. Define the aims, but not the method (“we give you the money, you produce the papers/patents/well educated postdocs…”). Define the consequences (“if you do not produce papers/patents you will never get anything anymore”). Give global budgets, i.e. allow the principal investigator to define him/herself what he/she needs to pursue the project in terms of personal, instruments and running costs. Allow a realistic time frame (rather 4 than 2 years).

7. *Provide an open, simple and transparent peer review process* that will be accepted by the scientific community as the reference funding source in EU research, to replace well functioning national agencies such as the MRC or DFG and to stimulate excellence, the reviewing structures of the funding agency need to be as transparent and simple as possible. Any political influence should be structurally excluded. Reviewers should be proposed by EU countries, and relevant scientific societies, and then voted in a democratic process throughout Europe.

8. *Age does not matter, but achievement does*: It is good to promote young scientists. On the other hand, it is counter productive to prohibit appointments of professors after the age of 54 regardless of their efficiency, and to limit work at the university strictly at 65. There has to be a place for brilliant people who want to work and can prove that they do work productively at any age. This would open up the perspective for young scientists.

Taken together, the main conclusions from the workshop “Young Scientists in Cardiovascular Disease Research” were that a public effort is necessary in Europe to increase the public interest in science, to move from the present “top-down” to a “bottom-up”, investigator-driven science funding approach by the EU, to make a strong commitment to basic science, a strong commitment to excellence according to scientific standards and to scientific freedom.

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Needs for infrastructures for cardiovascular research

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Professor Lina Badimon emphasised the importance of horizontal research techniques that could be applied over a wide area of disease, for example stem cell and gene therapy.

What was needed are:
(i) animal facilities containing a series of tools: mice, fish, xenopus, drosophila and also, in some cases, pigs and monkeys;
(ii) large clinical databases;
(iii) an amplification of biophysics facilities: for example nuclear magnetic resonance and crystallography.

Local European Union centres for functional genomics and biobanks are needed. A danger is that we will suffer from data overload and must discover the means of dealing with this.

Building a European infrastructure for science is important not only for European science itself, but also to stop European researchers going to the United States.

Participants:
Prof. Lina Badimon, Barcelona, Spain
Prof. François Cambien, Paris, France
Prof. Desmond Fitzgerald, Dublin, Ireland
Prof. Javier Muñiz, La Coruña, Spain
Future developments in clinical cardiovascular research

Professor Silvia Priori

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Despite the fact that Cardiovascular (CV) Research has achieved important results in reducing CV mortality, CV diseases remain the dominant cause of death in all European countries. In order to win the next battles, a further effort in clinical and basic research needs to be accomplished. Accordingly, if we want to achieve better prevention of atherosclerosis and coronary artery disease, to develop better treatments for acute coronary syndromes and heart failure and to reduce the toll of sudden cardiac death, just to name a few of the challenges, we need to focus our resources toward a coordinated research that can rapidly and effectively move from hypothesis generation to clinical testing.

It has been the objective of this workshop to investigate the problems faced by the community of investigators involved in cardiovascular research in addressing pressing scientific issues. The panel has identified the presence of obstacles that limit the development of these areas of research and analyzed the impact that a reduction of scientific innovation may have on health care in Europe.

The panel concluded that there are matters that need to be urgently addressed in order to ensure the progression of research in cardiovascular science.

Inadequate funding for clinical research

Clinical research is suffering because of continuous and progressive reduction of financial support. In USA, Japan, Canada the share devoted to research is 2.6-2.8% of GNP, in Europe the share is around 2%. Accordingly, the paucity of economical resources represents the first hurdle to the development of CV research. The organisation of clinical trials, registries, databases is perceived as a “second rank research that can be supported by industry” and this attitude, shared by several governmental funding agencies, underscores the fact that these type of projects provides not only the foundation of the epidemiology of diseases, but also the objective assessment of the efficacy of, drugs, devices, diagnostic modalities. There is no understanding that in order to address in a thorough way clinical questions, it is not possible to rely only on a limited number of larger clinical trials. On the contrary different methodologies (registries, observatories etc.) need to be applied as they do not provide redundant information; rather they offer different and complementary information. Each of them suffers of limitations that may bring to the wrong conclusion, on the contrary it is only when results collected with different methodologies are pulled together, they provide an answer that is closer to reality.

Clinical trials have been considered as the gold standard in clinical research because of their controlled methodology (randomization, blind methodology, sample size adequate to achieve the statistical significance).
However, even in areas in which we have large scale clinical trials, we still need further research because it is now well established that clinical trials introduce a selection in the population of patients and therefore they may not reflect the same situation that is encountered in clinical practice. In this respect, epidemiological observatories may provide additional and most valuable information.

The prevailing attitude in clinical research may become that of “not repeating” trials: this is supported on the assumption of saving resources by not replicating investigations. The danger of this approach is that assessment of the value of novel therapies should be performed through extensive comparison with the efficacy of conventional therapies, with different study designs, inclusion of specific subgroup of patients (women, elderly, ethnic subgroups). Furthermore adequately long follow up is advisable to ensure that benefit is maintained over time (particularly when trials are interrupted for “benefit” after a short follow up). Once an adequate number of clinical trials are available it is important that surveys are conducted in order to evaluate in clinical practice therapy prescription, patients’ compliance, costs, long term safety.

This more exhaustive model for obtaining information on therapies, interventions, diagnostic procedures may seem costly but it may eventually be cost effective by avoiding premature introduction of new and costly therapies in clinical practice.

**Lack of exploitation of the academic centres for coordination of clinical research**

Among the consequences of the reduced support for clinical research the panel has identified the increasing cost of clinical research and of clinical trials. These costs need to be contained in order to be able to perform more investigations as needed. At preset time however clinical trials are mainly performed by professional organizations (Clinical Research Organizations; CROs) thus under-utilizing the potential of academic facilities that can organise trials at a lower cost. It has been estimated (Lancet 2003; 360:1866) that the cost of trials ranges between 5000 and 10000 Euros per patient enrolled. Outsourcing to CROs and payment of honoraria to investigators contribute to the high costs, these costs could be reduced when networks of academic centres run clinical trials. As an additional benefit, academic centres may have a stronger interest in the investigation topics unrelated to drug development.

**Reduced attractiveness of research tracks for physicians**

Another important issue that has been identified as an obstacle to the development of clinical research is the perceived lack of attractiveness for the professional figure of the “physician-scientist” that has resulted in a reduction of MDs interested in pursuing research.

*The panel has identified several causes for this worrisome trend: tighter control of health-care resources has limited the opening of positions for academic medicine. At the same time, industry’s growing involvement in research (from the basic science to clinical trials) has created a competition for attracting young, brilliant investigators. The cost containments required by healthcare systems have reduced the number of program that allow medical doctors to perform research activities, thus discouraging young doctors from entering in the research arena. This policy may effectively increase the efficiency in patients’ care within the hospitals but it leads to the loss of a key element for the development of clinical science.*
This is particularly dangerous considering that even within the academic medical training the support of MD-PhD programs is diminishing.

**Conclusions**

The difficulties identified by the members of this workshop encountered in the promotion and performance of clinical research in cardiovascular sciences, are creating a gap between basic science and clinical practice that is an obstacle to the development of transitional research. Incentives need to be developed at European level and at national level in order to promote and protect research activity among physicians.

The panel of clinical and translational scientists involved in this workshop believes that we need to achieve the following objectives have to be pursued to ensure that the development of cardiovascular medicine is not slowed:

- Raise awareness on the importance of cardiovascular diseases for public health
- Inform decision makers on the need for increased public funding for clinical trials to avoid inappropriate selection of topics and patients
- Promote education on science, clinical research and translational research by creating programs that encourage young doctors to engage in research.
- Increase the interaction between basic scientists and clinicians in order to maximize the application of novel developments into the clinical arena
- Attract industry to invest in translational research in Europe
- Support the development of networks for clinical trials in Europe

**Participants:**

**Workshop was held through e-mail exchange**

Prof. Silvia Priori, Pavia, Italy  
Prof. Maarten Simoons, Amsterdam, The Netherlands  
Prof. Frans Van de Werf, Belgium  
Prof. Karl Svedberg, Göteborg, Sweden  
Prof. Patrick Serruys, Rotterdam, The Netherlands  
Dr. Marie Claude Maurice, France  
Prof. Jean-Pierre Bassand, Grenoble, France  
Prof. Attilio Maseri, Milano, Italy  
Prof. Michel Betrand, Lille, France  
Prof. Amadeo Betru, Barcelona, Spain  
Dr. Aldo Maggioni, Firenze, Italy  
Prof. Robert Wilcox, Nottingham, UK  
Prof. Helmut Drexler, Hannover, Germany  
Prof. Karl-Heinz Kuck, Hamburg, Germany  
Prof. Kim Fox, London, UK  
Prof. Peter Schwartz, Pavia, Italy  
Prof. Günther Breithard, Münster, Germany
Workshop on Cardiovascular research in the next 10 years

Professor Jean-Jacques Mercadier

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I. Introduction, general goal of cardiovascular research

This report summarizes the individual presentations and discussions which took place during the workshop that was held in Brussels on 5 March 2004 and the presentation given by J.-J. Mercadier on the behalf of the workshop participants at the conference on the Future of cardiovascular research in Europe held in Brussels on 19 March 2004.

Cardiovascular (CV) diseases are a major source of morbidity and mortality in western countries. There is no epidemiological information available on the impact of CV morbidity and mortality at the level of Europe as a whole but in the United Kingdom for instance, the mortality due to CV diseases in men under 65 is 42% compared to 32% for cancer (British Heart Foundation, www.dphpc.ox.ac.uk/bhfprg/stats/). This points to the importance of supporting CV research by sustained funding by national and European institutions, both to decrease this morbidity and mortality and the corresponding societal and economical burden on European health care systems.

As for other chronic diseases, the general goals of CV research can be summarised as follows:

• to improve the treatment of CV diseases
• so as to prolong patients’ life expectancy
• or at least improve their quality of life
• at best prevent CV diseases
• the whole contributing to improve the efficiency of European health care systems resulting in a decrease in the societal burden of the diseases.

It has been acknowledged by the workshop participants that important breakthroughs have been accomplished during the past few decades regarding the decrease of CV death in two main areas: coronary heart diseases mortality has decreased markedly mainly due to early treatment of acute coronary syndromes and the development percutaneous coronary angioplasty. However, this decrease appears somewhat artificial since rescuing patients at the acute phase of myocardial infarction results in increasing the number of candidates for late heart failure. Heart failure mortality has decreased due to the development of powerful new pharmacological interventions, many of them derived from findings of basic research. In contrast, the incidence of sudden cardiac death mainly due to ventricular arrhythmias is increasing, and given the impossibility to identify each individual at risk, currently available prevention procedures (implantable defibrillator) applied to all patients potentially at risk would largely exceed the capacities of European health care systems. The same applies to resynchronization pacemaker therapies to improve the functional state or survival of patients with heart failure.
Therefore it appears that some kind of plateau has been reached in the treatment of CV diseases and that further decrease in mortality and morbidity will only arise from the progresses of basic CV research. Indeed, in already established diseases, the development of new therapeutic approaches can rely only on the understanding of the pathophysiological processes allowing to stop or even reverse them. Regarding prevention, it can only be achieved through an in depth understanding of the pathophysiological processes leading to the disease state. Still in the field of prevention, only basic research will allow to determine the individual risk to develop a given disease and to actually benefit from a given treatment.

Accordingly, there has been an unanimous agreement of all workshop participants on the fact that the main goal of CV research is to increase our knowledge and understanding (1) of normal processes occurring within the cardiovascular system (and at the interface of this system and others for instance, the central nervous system) from conception to ageing and death and (2) of the pathophysiological mechanisms leading to cardiovascular diseases: only basic research allowing to decipher the most basic molecular and cellular mechanisms of normal cardiovascular development and function and pathological processes affecting the cardiovascular system, and to identify individuals at risk not only to develop the disease but also to benefit from treatments, will allow to progress on the path of CV diseases treatment and prevention.

II. The continuum of cardiovascular diseases

Most CV diseases result from degenerative processes and therefore from complex interactions between each individual’s genetic background (including gender) and environment. Such interactions start from conception and continue throughout life until ageing and death. Among the well known CV risk factors, not only cigarette smoking, but also hypertension, diabetes and dyslipidemia can be regarded as external factors exerting environmental effects on the heart and vessels resulting, together with the influence of the genetic background, in the development of a number of pathophysiological – but also adaptive – processes. Along this path of interactions occurring throughout life, heart attack or more generally acute coronary syndromes, only represent a brief part of a very long pathophysiological process, namely atherothrombosis and the tip of the iceberg since other sites of atherosclerosis are ignored until the revealing event (for instance stroke in the territory of carotid arteries). In this scheme, the occurrence of a myocardial infarct opens the phase of compensatory mechanisms in an attempt to maintain arterial pressure and cardiac output both at rest and during exercise. The progressive failure of these adaptive mechanisms together with the progression of many pathophysiological processes lead to the stage of chronic heart failure on one hand, and the progression of atherothrombosis on the other hand. Importantly, acute coronary syndromes, compensated heart function following MI, heart failure and even risk factors such as hypertension or diabetes favour the occurrence arrhythmias and sudden death. Since each and every step of this pathological process leading from conception to death is a potential target for treatment and/or prevention, and therefore an area for basic CV research, the rest of this synopsis will follow the natural history of the pathophysiological processes throughout life. The specificities of female gender and of ageing throughout all physiological and pathophysiological processes described below have been emphasized. Their importance has been considered as justifying specific research to be included systematically in each research programme and not as a distinct topic of this report.
III. Development of the cardiovascular system
Whereas the normal development of the cardiovascular system is a very active field of CV research, many advances are still required to better understand the pathophysiology of congenital heart diseases (CHD), both with respect to the dysfunction in the normal developmental process leading to CHD, but also with respect to specificities of foetal adaptive and pathophysiological processes in response to the hemodynamic overload resulting from the cardiac defects. Since the proliferation of cardiac myocytes stops several weeks or months after birth, it is clear that adaptation of the foetal heart to the increased (or decreased) hemodynamic load resulting from the various types of cardiac defects will be different from that occurring at the adult stage, thus requiring specific – eventually comparative – research. Regarding upstream processes, it is clear that cardiac and vascular regenerating therapies (see below) will progress only from our increased knowledge and complete understanding of the molecular mechanisms governing cardiac and vascular myocyte commitment and differentiation from embryonic stem cells and the very early stages of cardiogenesis and vasculogenesis. At last, interest has been brought recently to the impact of environmental factors on the developing CV system, a field that has been largely neglected to date by CV research. Given the increased smoking rate among young women and the increase in the “non conventional” risk factors such as obesity among the same population, it seems that a special interest should be given to the development of specific research in this field.

IV. Atherothrombosis
On the way to heart attack, stroke and other organ damage is the atherothrombotic process which results, at a given time of the natural history of the atherosclerotic process, from a complex interaction, still incompletely understood, between a given plaque and a given blood at a given place of a given vessel.

Atherosclerosis is a multifactorial disease for which a number of risk factors have been well identified, including hypertension, hypercholesterolemia, smoking, diabetes, and ageing. However, growing evidence suggests that the individual burden of currently known cardiovascular risk factors is not the only determinant of atherosclerosis. Aggressive therapy with the lipid-lowering drugs statins has substantially reduced cardiovascular risk in the setting of both primary and secondary prevention; in general, these drugs provide a 25% to 40% relative risk reduction in major adverse cardiovascular events such as death, myocardial infarction, and stroke. However, statin treatment fails to prevent 60% to 75% of events, and even with more aggressive treatment of conventional risk factors atherosclerosis will probably not be eradicated.

The atherosclerotic process starts early in life and there are reports of atherosclerotic plaques already present in the foetal aorta from normocholesterolemic and hypercholesterolemic mothers. Moreover, clinical research has revealed that severe clinical manifestations of atherosclerosis are due to “unstable” plaques prone to fibrous cap rupture or plaque surface erosion, which triggers thrombus formation and vessel lumen occlusion, rather than lumen stenosis stemming from exaggerated plaque growth. This points to the need for research on the mechanisms governing the development of atherosclerosis not only in adults but also during earlier developmental stages (including prenatal as pointed out above) starting from plaque occurrence (the onset of atherosclerosis) through its progression to plaque rupture or erosion leading to thrombus formation. A special emphasis should be given to a number of specific aspects of this process:
• the role of the vessel wall remodelling (changes in size, thickness, stiffness…)
• the contribution of platelets and endothelial dysfunction to atherosclerosis
• the role of inflammation and cell apoptosis in the occurrence of plaque rupture
• conversely, the mechanisms of non-inflammatory plaque thrombosis
• the responsibility of specific blood alterations (blood vulnerability) in the occurrence of the thrombus.

On the therapeutic side, research should be focused on plaque stabilization and regression and on determination of specific immune profiles favouring the development of atherosclerosis and the associated possibility to develop specific vaccination procedures.

The association of a number of characteristics of the vessel, of the plaque and of the blood should allow to define unstable plaques, thus allowing to identify people at risk to experience an atherothrombotic event. It is noteworthy that sudden cardiac death remains the most common and often the first manifestation of coronary heart disease and is responsible for 50% of the mortality from cardiovascular disease in the developed countries. Risk profiling should benefit from advances of genetics, proteomics, and physiomics such as parameters of endothelial dysfunction and from advances in imaging techniques. Taken together, these approaches, by identifying individuals at risk, should allow us to conceive novel diagnostic and therapeutic approaches aimed at predicting and preventing the first acute vascular ischemic event leading to heart attack or stroke, and at promoting the functional recovery of organs injured by ischemia.

V. Conventional and “new” risk factors

Because of major changes in life style which have occurred during the last few decades, western countries are facing an epidemic of obesity, diabetes and metabolic syndrome. In fact, together with heart failure, type 2 diabetes is the only chronic disease the incidence of which is going to increase during the next decades. Research should be specifically dedicated to the pathophysiological mechanisms through which these pathological conditions contribute to atherosclerosis and myocardial dysfunction. Besides these well identified factors, research should also be dedicated to the mechanisms by which other factors such as psycho-social stress (professional, marital…) contribute to these processes and to the worsening or recurrence of several disease states such as myocardial infarction or heart failure.

VI. Angiogenesis

A specific attention has been paid, during the workshop, to angiogenesis and to therapeutic manipulations of the angiogenesis process. Indeed, an excess in vessel growth contributes to a number of diseases such as cancer, blindness in the context of diabetes, arthritis or even obesity. Such diseases could benefit from the therapeutic use of angiogenesis inhibitors. Conversely, diseases such as heart and limb ischemia, stroke, baldness and fracture could benefit from the development of new proangiogenic agents able to stimulate vessel development and thus improve the vascularisation of ischemic tissues. In this respect, research on the use of endothelial progenitor cells and other progenitors derived from bone marrow should be favoured, with a special focus on processes to mobilize these cells from bone marrow and make them better proliferate in vitro. The use of large morpholino knockdown screen in the zebrafish and tadpole to discover novel angiogenic candidates has been emphasized.
VI. Myocardial injury and protection

The myocardium downstream a stenotic atherosclerotic plaque suffers from a number of different injuries. The most common is the more or less pronounced ischemia which results from insufficient oxygen supply to the myocardium during effort due to the stenosis. However, it has been shown that such brief episodes of ischemia occurring before the prolonged episode resulting in myocardial necrosis decrease the necrotic surface area. This process of natural protection of the myocardium, known as “preconditioning”, offers a broad spectrum of mechanisms and signalling pathways that could be fruitfully used to decrease the size of myocardial infarction. This is also the case of ischemic episodes occurring once coronary flow has been restored known as “post conditioning”.

Spontaneous or therapeutically-induced reperfusion following myocardial infarction has both beneficial and detrimental aspects. Indeed, the restoration of the coronary flow in the territory of the occluded vessel is actually beneficial. However, reperfusion is responsible for an additional stress to the injured myocardium mainly due to the occurrence of an oxidative stress. This is responsible for a burst of cardiac myocyte apoptosis which adds to the apoptosis and necrosis due to the ischemia itself. The importance of the role of mitochondria as sensors and effectors of these pathophysiological processes as well as targets for cardioprotective therapies is now well established.

Accordingly, research in this area of CV diseases should focus on the mechanisms of cardioprotection against myocardial ischemia and especially on the mechanisms of short-lasting and long-lasting protection, pre- and post-conditioning, their signalling pathways and the end-effectors of cardiac protection with a special focus on the central role played by mitochondria (K-ATP channels, permeability pores…). Research should be dedicated also to the mechanisms of apoptosis and necrosis of cardiac myocytes and the apoptosis/necrosis balance with a special interest given to the development of anti-apoptotic therapies. At last, research should be dedicated to the detrimental aspects of reperfusion (ischemia-reperfusion injury vs. limitation of infarct size) with special interest in the molecular mechanisms, the role of mitochondria and the potential therapeutic strategies.

VII. From heart attack to heart failure

Following myocardial infarction, the heart undergoes a profound remodelling which associates changes in size and shape of the left ventricle (LV), an increase in mass of the non-infarcted myocardium accompanied by alterations in gene expression. Such a process occurs also in a number of cardiomyopathies of known (gene mutations, viral, toxic…) or still unknown origin when the increase in left ventricular size is a trigger for the remodelling process. It is well established now that some of these features are beneficial/adaptive whereas others are harmful. The molecular mechanisms responsible for the transition from compensated/compensatory hypertrophy to failure are currently not understood. However, many arguments support the hypothesis that such a transition occurs once the harmful mechanisms have exceeded the beneficial/adaptive ones.

This points to the need for research on signalling mechanisms of LV hypertrophy, remodelling and transition to heart failure with a special focus on identifying the harmful vs. beneficial pathways and in both cases, the pathways for mechano- vs. neurohumoral signals, the spatial and time-domain confinement of signalling action with a special interest paid to Ca2+ as a signalling...
molecule for regulation of gene expression. At last, in the process of transition to heart failure, a special attention should be paid to the role of post-translational protein regulation vs. gene expression. Research should be developed on how to inhibit detrimental signalling pathways and post-translational regulations and promote beneficial ones.

Both clinical experience and recent research have shown that in face of a myocardial injury (infarction, mechanical overload…) or stress (toxic…) of similar amplitude, the outcome will markedly differ from patient to patient pointing to individual susceptibility and to the role of functional genetic polymorphisms acting as susceptibility and modifier genes in the development and evolution of the disease. Recent data have also shown that patients do not respond equally to similar therapeutic interventions pointing to the existence of “pharmacogenomic” polymorphisms responsible for individualised response to each drug. Research on these susceptibility factors has to be developed, focusing not only on the intermediate phenotypes but directly on the gene polymorphisms involved.

VIII. Ventricular arrhythmias and sudden cardiac death

The incidence of sudden cardiac death (SCD), which is usually linked to ventricular fibrillation, itself resulting from acute coronary occlusion or chronic ischemic heart disease is increasing (1/1000/year) with, in general, no pre-event symptoms. Following the CAST study (Cardiac Arrhythmia Suppression Trial Investigators, 1989) that provided the first demonstration that the classical antiarrhythmic drugs (i.e. Na⁺ channel blockers) increased mortality and therefore were more harmful than beneficial, the arrhythmia community was left with the idea that the therapeutic agents they had been used for decades were detrimental and that only old drugs such as β-blockers could reasonably be used in clinical practice. There was a persistent need for an alternative to classical antiarrhythmic drugs, until it was demonstrated in patients with prior myocardial infarction that implantation of a defibrillator improved survival, making it a recommended preventive therapy. However, these devices are very costly, and their cost-effectiveness for secondary prevention of life-threatening ventricular arrhythmias seems to be only moderate. Alternative therapeutics based on novel pharmacological targets are still needed to control cardiac arrhythmias, as the classical targets (e.g. cardiac ion channels) have failed to meet expectations. Most recent advances in the understanding of ventricular arrhythmias and SCD have resulted from the elucidation of molecular mechanisms responsible for monogenic diseases affecting cardiac rhythm. Although these diseases concern only a small subset of patients, their deciphering induced determinant insights in our understanding of the complex mechanisms leading to acquired arrhythmias and sudden cardiac death. As is the case of heart failure, the field is now moving from monogenic to complex/multigenic diseases with the role of susceptibility and modifier genes.

In this area of CV diseases also, and all the more because many cases of SCD occur with no pre-event symptoms, specific efforts have to be oriented towards identification of patients at risk with the identification of biomarkers (gene polymorphisms, intermediate phenotypes…). This will be possible only if large European clinical data bases and biological banks incorporating well defined populations of patients with increased SCD risk can be created. Animal models of SCD are also required as well as high throughput stress tests allowing to identify SCD phenotypes in animal with a null phenotype.
IX. Atrial fibrillation

As ventricular arrhythmias, atrial fibrillation (AF) is rarely familial and most often results from a complex and longstanding degenerative process similar to that experienced by the ventricles during heart failure. Although rarely immediately lethal, supra-ventricular arrhythmias and especially AF are responsible for both serious individual handicaps and a considerable social burden, which is expected to increase enormously with population ageing. Indeed, 1% of all adults and up to 20% of very elderly people have atrial fibrillation, which is a factor in about one-third of all strokes. In addition, the anticoagulant therapy often required for chronic AF can cause bleeding and other complications, which aggravate morbidity, mortality and the burden for society. This points to the need to advance our understanding of the mechanisms underlying AF and other often preceding supra-ventricular arrhythmias, with the dual aim of identifying individuals at risk and of developing novel therapeutic approaches.

As that of ventricular arrhythmias, the complex pathophysiology of AF can be summarised as interactions between a substrate, a triggering event, and the modulation of the two by various neuro-hormonal systems. Research will have to focus on the role of major pathophysiological processes such as inflammation, oxidative stress, apoptosis, extra-cellular matrix remodelling and neuro-hormonal modulation in each in case. As in the case of heart failure, in addition to alterations in gene expression, post-translational regulations will have also to be considered. Innovative research will also require large patient data bases and tissue banks, and the development of pertinent experimental models.

X. New therapies

The development of new therapeutic approaches of CV diseases is a major goal of CV research in the next ten years. This comprises two major aspects: the development of new therapies (gene therapy, stem cell therapy, assist devices…) and the development of individually tailored therapy based on pharmacodynamic and pharmacokinetic characteristics specific for each patient. New strategies for gene therapy will have to be developed targeting regulatory sequences of gene promoters (stimulation of gene transcription, inhibition of transcription factors…) as well as specific signalling molecules using for instance the RNAi technology. Regarding heart failure, in parallel with stem cell therapy, research on the very early stages of cardiac development and on the mechanisms of cardiac myocyte differentiation should allow understanding how adult cardiac myocytes have exited cell cycle and therefore should facilitate the development of regenerating therapies. A special interest will have to be paid to prevention therapies i.e. therapies delivered early/upstream during the pathophysiological process so as to prevent the degenerative process rather than to reverse it. This essentially refers to all procedures that can be undertaken at the time of myocardial reperfusion to save ischemic myocytes, prevent the additional stress of reperfusion, and prevent LV remodelling by pharmacological and/or cellular intervention on the scar. Workshop participants have unanimously deplored the insufficient pre-clinical validation of cell therapy clinical trials, the performance of small, unblinded clinical trials with poor statistics and have pointed to the need for coordinated European initiatives in this area as well as in the area of individually tailored therapy and therapy modifier genes.
XI. Organisational aspects

Although out of the scope of this workshop, workshop participants insisted on the importance to make available to the research community at the European level appropriate tools to speed up the discovery of new genes and pathways. This includes:

- Large patient cohorts, data bases and biobanks
- Large bioinformatics facilities allowing rapid data analysis
- High throughput mutagenesis centres (zebrafish, tadpole, mouse…)
- Standardized procedures allowing concerted patient and animal phenotyping

XII. The 10 priorities of cardiovascular research for the next 10 years

1. Basic biology of cells of the CV system – Development
2. Healing/regeneration of ischemic tissues
   - normal and pathologic angiogenesis – therapeutic potential
   - stem cell commitment and differentiation towards cells of the CV system
3. Predicting and preventing the first atherosclerotic event
   - plaque development mechanisms
   - plaque imaging
   - mechanisms of plaque stability/instability
   - blood vulnerability
   - platelets & atherosclerosis
   - endothelial cell and micro-vessel dysfunction
4. New risk factors: obesity, diabetes, metabolic syndrome
   - mechanisms leading to atherosclerosis / cardiac dysfunction
5. Developing cardiac protection against ischemic and other injury
   - pre- & post-conditioning, necrosis/apoptosis, role of mitochondria…
6. Predicting & preventing sudden cardiac death and severe arrhythmias
7. Understanding the molecular basis, predicting & preventing heart failure
   - signalling of remodelling
   - mechanisms of transition to heart failure
   - modifiers of heart failure
8. New therapies
   - individually tailored therapy
   - myocardial regeneration, gene therapy, cell therapy
   - assist devices
9. Molecular mechanisms of physiological ageing
10. Cardiovascular vulnerability of women
XIII. Workshop participants:

Vascular experts:
Prof. Peter Carmeliet (Belgium)
Prof. Elisabetta Dejana (Italy)
Prof. Desmond Fitzgerald (Ireland)
Prof. Ingrid Fleming (Germany)
Prof. John Martin (UK)
Prof. Andrew Newby (UK)
Prof. Otto Smiseth (The Netherlands)
Prof. Alain Tedgui (France)

Cardiac experts:
Dr. Connie Bezzina (The Netherlands)
Prof. Denis Escande (France)
Prof. Gerd Hasenfuss (Germany)
Prof. Antoon Moorman (The Netherlands)
Prof. Bohuslav Ostadal (Czech Republic)
Dr. Ketty Schwartz (France)
Prof. Karin Sipido (Belgium)
Prof. Ajay Shah (UK)

Coordinator:
Prof. Jean-Jacques Mercadier (France)
Final discussion

The meeting ended with a discussion between Dr Quintana and delegates. Many points of importance arose.

- There is a need for increased research funding in the European Union. In particular, there is a need to increase research funding allocated by the European Commission.
- The possibility of the European Commission funding EU Chairs in universities was considered.
- There is a need for all scientists to be non-partisan and to have a wide view of research in Europe.
- There is a need to form alliances between researchers within the European Union.
- There is a need for movement of senior managers, not just junior researchers, to spend time in different departments.
- There is a need to include cardiovascular disease in Framework Programme 7, particularly because of the track record of productivity in that area and the importance of the disease.
- There is a need to form research teams in Europe.
European Commission

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On 19 March 2004 the European Commission organised a conference on The Future of Cardiovascular Research in Europe. The conference brought together leaders from basic and clinical cardiovascular research as well as representatives from the EU institutions (Parliament, Council and Commission) and stakeholders to analyse what had been achieved and suggest strategy for the future. Workshops held before the meeting had analysed specific problems and presentations at the conference informed on important conclusions from the workshops. In this booklet summaries of the different presentations at the conference as well as conclusions drawn in the discussion amongst participants are presented.