Cardiovascular diseases: The earliest cure is prevention

Netherlands Platform
for Cardiovascular Research
of the Netherlands Heart Foundation

1. Introduction

Applications of the knowledge and innovative technologies deriving from scientific research have produced considerable success in the past few decades in the battle against cardiovascular diseases. Examples include the treatment of myocardial infarctions in the acute stage and the introduction of stents. These developments have significantly reduced the acute cardiovascular mortality.
However, in the Netherlands cardiovascular diseases will not fade away in the 21st century, on the contrary:

- Simple the fact of the **aging** of the population will lead to an increase in the total number of cardiovascular patients by 45% to 1.3 million patients in 2020. There will be a shift from acute to chronic forms, like heart failure.
- In addition, the number of cardiovascular patients will also increase due to **unhealthy nutrition** and **obesity** (RIVM-report 'Ons Eten Gemeten', Measuring our food).
- In 2000 there were about 860,000 cardiovascular patients in the Netherlands, including 400,000 women. An increase will primarily be noted in the number of women dying of coronary heart disease.

The consequence of these developments is an **increase in the health care services**.

Worldwide, currently 17,000,000 people die annually due to cardiovascular diseases. This is 31% of the total number of deaths. In comparison, 3,000,000 people die of AIDS annually.
If no action is taken, cardiovascular diseases will form the greatest contributor by far to the burden of care and disease in the world in 2020 (Lopez: Global Burden of Disease report).

This memorandum intends to outline a number of paths in cardiovascular research that needs to be followed to arrive at improved diagnostic and treatment methods, also in terms of prevention. Only by following such a path, it will be possible to develop specific knowledge to counteract the threatening new epidemic of cardiovascular diseases. The success of this type of research will depend to a great extent on the effectiveness of translating the various findings from fundamental research into clinically useful applications. The fundamental molecular (genome) research continues to produce potential targets for therapy. Also, the number of substances (drugs, nutriceuticals) with a possibly favourable effect is growing rapidly due to the very efficient modern synthesis and screening methods. The translation of these results to clinical practice remains a restricting factor in medical innovation and should therefore be supported.

2. Clinical Analysis

Since the 1960s the focus has been on acute, highly qualified care: coronary care and stroke units, cardiovascular surgery, ptca, peripheral bypass surgery and stenting techniques. These important developments derive from the concentration on so-called 'after the event' care. Nevertheless, atherosclerotic disorders of the coronary vessels, the cerebral and peripheral arteries are still responsible for a large part of the mortality and morbidity among the Dutch population. In 2002 the cause of death was cardiovascular disease in 35% (> 48,000 patients) of all deaths in the Netherlands. There can be no doubt that all the investments are worth the efforts that have been made. But it has recently become clear that a significant reduction in morbidity and mortality can only be achieved through prevention and an integrated biomedical approach.

As a result preventive cardiology is nowadays in the picture. In the past few years the influence of a healthy diet and lifestyle on coronary heart disease has become clear. Also preventive

interventions in patients after a heart infarct seem to have influence on mortality risk. Changes in lifestyle, but also other forms of preventive interventions seem to get integrated in treatment strategies to reduce mortality and morbidity. Many blanks are still present within these treatment strategies, which require a preventive biomedical (and pharmacological) approach.

In the past few years, new risk factors have been added to the list of classic risk factors for cardiovascular disease like smoking, hypertension, obesity and a raised cholesterol level. These include diabetes mellitus, disorders in the metabolism of lipoproteins, clotting and fibrinolysis. For some of these new risk factors the cause is obvious. But the majority are more complicated when it comes to diagnostics, genetics and counselling of the affected patient and family members. According to one estimate, around 15% of the Dutch population suffers from a lipid-aberration, often associated with other risk factors for atherosclerosis, the 'metabolic syndrome'. To be able to treat and advise patients and their family members optimally, a multidisciplinary, integrated research and patient care (**translational research**) is required. Only in this way the research possibilities can be optimally utilised.

The exponential increase in knowledge about the (patho-) biology and physiology of complex cellular processes in the vascular wall make new risk stratifications and therapies possible. Examples include inhibition of thrombus formation and of cell migration, along with neo-intima proliferation. In addition, gene therapy is being developed, such as genetically modified endothelial cells on vascular stents and interaction with cell-specific receptors, which enable the delivery of genetic material – aiming for gene expression. Pharmacogenetics will ultimately lead to an optimalised risk stratification and therapy for the individual patient. In the future, these patients will no longer be burdened with a combination of all possibly effective universal therapies; each patient will receive an individually optimalised rational mix of treatment strategies. For an effective application and evaluation of combinations of these new pathophysiological vascular wall concepts and therapies, **a multidisciplinary and 'from bench to bedside' integrated – thus translational – approach** is essential.

3. Progress

The burning question is which scientific developments are in need of a stimulus to produce the greatest improvement in health in the cardiovascular field for both patients and the general public. In other words, what fields of scientific research are laying the groundwork for the prevention and treatment of cardiovascular diseases?
The most important advances in the field of cardiovascular disease research are currently being made in:

1. genomics and the rapidly rising star proteomics: more generally, **molecular medicine**
2. the possibility of assessing the form and function of the heart and vessels with e.g. **imaging techniques**
3. **regenerative medicine**

3.1 Molecular Medicine

This concerns progress made in the field of molecular medicine, including genomics, which should lead to **an increase in the options for diagnostics and preparing risk profiles**. Genomics is considered the first link in the chain from molecule to patient. This link contains knowledge about mutations and variations in the DNA which can lead to cardiovascular disease or an increased risk of it. In addition, it also includes knowledge about changes in gene expression, metabolism and physiology during the pathogenic process. These changes can serve as biological indicators for prognosis, diagnosis and progression of the disease and as potential targets for therapeutic interventions.

New developments in this field focus primarily on the preparation of genetic risk profiles using snp-profiling (snp = single nucleotide polymorphisms). Due to improved technical possibilities, this method is important not only in the area of fundamental research, but also in the care and prevention of cardiovascular diseases in terms of a better risk estimation. It is expected that snp-profiling of 'susceptibility' genes will become part of the standard diagnostics. We still need genetic epidemiological research to ascertain whether individuals and patients with a raised genetic risk can be identified in this way and whether that will lead to more effective prevention and treatment.

To achieve the above-mentioned developments in the field of genomics, we need:

- to stimulate genomics and **genetic epidemiology** research, utilising large databases with clearly phenotyped individuals. Joint efforts between different areas of expertise at the national and European levels will be required.
- to develop personalised drugs: 'one pill for the patient', based on the individual gene profile (**pharmacogenetics**)
- to **educate** cardiologists regarding the application of genetics in everyday practice.

The last point matches a number of action items from the Medical Biotechnology Agenda 2004 prepared by the Ministry of Health, Welfare and Sport.

All of this should make abundantly clear that implementation of the existing knowledge in everyday practice is an important point for attention. Other areas of expertise like proteomics and immunology are also involved in the further development of fundamental knowledge about the processes leading to cardiovascular diseases. This includes knowledge about gene regulation and expression, biochemical signalling systems, (trans) localisation and function of proteins in the cell, cell processes, organ function and structure, and the function of the whole organism under both normal and pathological conditions.
All of this knowledge is essential for the development of new strategies for prevention and therapy.

3.2 Imaging and Processing Technology

Other novel developments are taking place in the field of imaging and processing technology. They have made it possible to visualise in better detail and to quantify the morphology and function of the heart and vessels. They include primarily new methods like IVUS ('intravascular ultrasound'), MRI ('magnetic resonance imaging'), CT ('computed tomography'), SPECT ('single-photon emission tomography'), PET ('positron emission tomography'), EBT ('electron beam tomography') and vital and molecular imaging at the cellular and organ levels. The technological advances with these methods are still being developed, but currently much attention is being paid to their application to clinical problems regarding diagnostics. Especially the **non-invasive techniques** are promising and very important. These methods enable us through better screening **of presymptomatic individuals to identify people at great risk early**. This will lead to better possibilities for prevention and a shift from a diagnostic to a more preventive application ('active prevention'). It is also possible that this development will stimulate the establishment of vascular medicine. By using non-invasive methods to visualise the heart and the entire circulatory system, we shall gain new insights allowing us to make informed decisions about the patient's complete health profile. The technology can also be employed in research into the effects of drugs or when implementing therapeutic surgery.
Examples of potential applications include:

- Detection of (preclinical) atherosclerosis, focussing on the unstable plaque and its composition, especially in the coronary vessels, the carotid artery and the iliac artery.
- A second area of interest is the microcirculation, particularly 'target organ damage'.
- A great example of 'vital imaging' is the visualisation of apoptosis (programmed cell death) of cardiomyocytes.
- Modern labelling and microscopic techniques can make translocation of proteins in the living cell visible (molecular imaging and live cell imaging).

To extend the application of these techniques to clinical problems, we need:

- Multidisciplinary approach by the involved clinical and preclinical areas of expertise.
- Development of new radiopharmaceuticals for the labelling of various biomarkers used in molecular nuclear cardiology.
- Application-oriented research into the validation and practical application of these new imaging techniques. Eventually, the predictive value of these methods and the effectiveness of intervention in persons analysed in this way will also have to be examined more closely in terms of a cost/benefit analysis.

3.3 Regenerative Medicine

The therapy for cardiovascular disorders has improved immensely in the past hundred years. It has involved developments in the fields of intervention cardiology, surgery and new drugs. This trend will undoubtedly continue and lead to even better optimalisation of the various techniques and surgical and medical treatment methods. In addition, we can expect that **new therapeutic methods will be developed** based on new insights produced by genomics and physiomics research.

Examples of these new therapeutic methods include:

- Gene therapy. A relatively small number of cardiovascular diseases are caused by improper functioning of only one gene or protein. For these disorders for which no effective therapy exists, somatic gene therapy could provide a solution. Through local application of the gene in question in a suitable expression system, the desired protein will be produced at the correct time and location, which could prevent the consequences of the disorder. In addition, better insights into the pathological processes leading to cardiovascular diseases could allow us to identify new targets for gene therapeutic interventions, leading to interventions in the disease process. This could include the temporary halting of atherosclerosis and restenosis and the stimulation of angiogenesis and arteriogenesis, the formation of new blood vessels in tissues in which the blood circulation is limited as the result of a vascular problem (reversed remodelling).
- Cell therapy, the 'repair' of damaged vessels and hearts through the transplantation of stem cells. Studies in animal models and now in patients have shown that the transplantation of stem cells or (autologous) skeletal muscle cells which have the capacity to develop into healthy heart cells is a promising new approach in the treatment of acute myocardial infarction and heart failure.
- Endovascular therapy of the aorta, carotids and leg vessels.
- Heart support and artificial heart
- Artificial vessels (large, aorta aneurysm, and small, diabetic foot)
- New strategies with regard to therapy compliance. Primarily, new technologies of administering drugs will play an important role here.

4. Translational Research

Translational research is defined as research involving collaboration between clinical and non-clinical research groups. The results of fundamental, productive research come to be applied in practice.
This definition is the one used in the report 'Onderzoek onderzocht' (Research investigated) from the Netherlands Federation of University Medical Centres. In this report lists of authors of publications were examined for information regarding the departments to which the authors were affiliated. One interesting finding is that groups which appear at first glance to be publishing in more fundamental fields like cell biology or physiology actually publish in more clinically oriented scientific fields, like cardiovascular research. The **collaboration between clinical and non-clinical groups** is reflected in this finding. It emphasizes once more how effectively organised the university research into cardiovascular diseases is into main themes and/or institutes, in which both clinical and non-clinical groups participate.
It also indicates how unique the Netherlands is due to the combination of fundamental and clinical research in the University Medical Centres.

We are aware that translational research is defined differently in other fields, like oncology. To ensure clarity, we find it more suitable to use the generally accepted definition as formulated by the Netherlands Federation of University Medical Centres.

Individual stimulus programmes in the field of cardiovascular diseases generally target the scientific careers of clinicians. In the Netherlands Heart Foundation, the Dr. E. Dekker programme, which supports both clinical and fundamental researchers, has been very successful. About three-quarters of the recipients awarded the highest funding in this programme are currently professors. The Dr. E. Dekker programme also stimulates various successive stages of a person's (clinical) scientific career.

Both the level of organisation and the stimulus programmes have strengthened the translational component of cardiovascular research. An excellent tradition in this has been established in the Netherlands. The importance of translational research in the current status of medical science/life sciences is clear: many new molecular targets and many more improvements in the treatment of cardiovascular diseases. The current therapies are mostly symptomatic and often not causal, let alone preventive.
At the same time, we have to be aware that rapid developments in molecular biology research threaten to isolate it from clinical research.

5. Industrial Activity

In general, it can be ascertained that larger companies like Philips, Organon and Unilever have focussed an important part of their research on cardiovascular diseases.
Philips Research recently started a study in the field of Molecular Imaging with Philips Medical Systems. The aim of the study is the introduction of new modalities which can increase the applicability of existing Philips apparatus. The ultimate goal of Philips's efforts is the introduction of Molecular Imaging as technology in human clinical diagnostics and therapy. Philips's interest in cardiovascular diseases derives from its existing broad range of apparatus especially developed for this area of application. The expectation is that using Molecular Imaging will not only advance our insights into the disease process, but also allow the earlier detection of cardiovascular diseases and the creation of individualised therapy.
Organon, the pharmaceutical business unit of Akzo Nobel, has an important research site in Oss.

Organon Research has initiated together with the University of Maastricht a large-scale programme in the area of atherothrombosis.
The aim of Organon's efforts is the development of innovative drugs for the treatment of atherothrombosis. In general, the identification of new drug targets and the development of new drugs based on genomics.

Traditionally, Unilever has always been interested in nutrition and its relation to health. Therefore, Unilever Research is particularly interested in cardiovascular diseases. The Netherlands Heart Foundation together with Unilever Research and Wageningen University is supporting a large-scale programme about the effects of different omega-3 fatty acids in the prevention of cardiovascular diseases. The aim of these activities is to introduce optimally composed food products on the market.

Alongside the big names mentioned above, there are also some middle-sized companies working in the field of cardiovascular diseases. In the area of apparatus, for example, Medtronics and Piemedical are active and in the area of nutrition, Numico is active.

Furthermore, a relatively large number of start-up companies are being developed around the university knowledge centres, like Farmatarget and Synapse which are doing important work mainly in the development of certain diagnostic/therapeutic products.

In this way, cardiovascular research significantly stimulates new forms of activity in both the large companies and the spin-off industry.

6. Why the Netherlands?

There are a number of reasons why the Netherlands could take the lead in Europe in the above-mentioned areas of expertise in cardiovascular research:

- The cardiovascular research done in the Netherlands is of a demonstrably high quality. We can refer to the cited report 'Onderzoek onderzocht' (Research investigated) from the Netherlands Federation of University Medical Centres (2004), which reveals that of all medical research the Dutch cardiovascular research has the highest international impact. That statement is supported by a study by Schaper et al. (1999), and by the disproportionately large number of contributions submitted from the Netherlands to the meetings of the American Heart Association and European Society of Cardiology. The research in question scores as excellent in the latest
-report on health research (1999).

- As mentioned earlier, the organisational structure of research into cardiovascular diseases is excellent. The Netherlands is unique due to the combination of fundamental and clinical research in the University Medical Centres. In these centres research into cardiovascular diseases is effectively organised into main themes and/or institutes.

- This research is coordinated on a nation-wide level by the Netherlands Platform for Cardiovascular Research of the Netherlands Heart Foundation. By properly coordinating the research, improvements in quality are sought. Similarly, the available infrastructure in the Netherlands can be utilised as effectively as possible in this way.

- As cited above, research into cardiovascular disease has already advanced along the path of translational research. In the Netherlands this path has been shown to be of international quality. This clearly distinguishes cardiovascular research from that in other areas, e.g. cancer research.

7. Conclusions/Recommendations

Within cardiovascular research in the Netherlands, the translational component has established a strong basis and built up an excellent tradition. At the same time, we can ascertain that the rapid developments in fundamental molecular medical research is threatening to isolate it again from clinical research. **Action in the Netherlands and Europe must be taken** to prevent this happening. The present memorandum points out the areas in which this could happen.
At the start of the 1990s, the Netherlands Heart Foundation decided to establish a long-term programme to introduce the developments happening in molecular biology into cardiovascular research and to eliminate the lost ground which had accumulated.
For the Netherlands Heart Foundation, providing this successful stimulus was a significant investment, but within the global research setting it was small scale and had a limited impact. We did gain valuable experience in setting up and managing the Molecular Cardiology Programme. **That model will have to be used again now.**