

Cardiovascular disease

Prognostic/diagnostic testing and a raft of new drug targets from genomics promise to transform cardiovascular medicine.

Cardiovascular diseases cause more than 15 million deaths in the world each year, according to the World Health Organization (WHO; Geneva). They account for 50% of all deaths in several developed countries, and more than 50% in Africa and Western and Southeast Asia. They are also the major cause of death in adults. In addition, many cardiovascular incidents are not necessarily fatal, but may impair the ability to lead a normal daily life, resulting in enormous healthcare costs (estimated at \$50–150 billion per year) to society.

However, despite the huge death and disability tolls, there have been significant declines in total cardiovascular disease mortality over the past few decades, due to improved acute and chronic medications and surgical procedures, and lifestyle and diet changes. Because of the incidence and mortality rates, cardiovascular diseases are the subject of enormous investment by the biotechnology and pharmaceutical industries.

Historical perspective

In considering the evolution of drug discovery and development in the cardiovascular area, it is important to realize that the term "cardiovascular disease" refers to a number of

conditions, which WHO classifies into 11 groupings for the purposes of assembling mortality data. These groupings include hypertension with or without renal disease, stroke, atherosclerosis, other diseases of arteries, arterioles, and capillaries, and diseases of veins and lymphatics. In addition, there are six heart disease groups: rheumatic fever/rheumatic heart disease, hypertensive heart disease, heart and renal disease, ischemic heart disease, diseases of pulmonary circulation, and other forms of heart disease¹.

Medicines did not appear for these conditions at the same time, although herb medicines have been used since antiquity. Perhaps the best known of these in use today is digitalis, also known as digoxin and digitoxin. It is derived from the foxglove plant and has been described in medical literature for over 200 years. It is used to treat congestive heart failure, some kinds of congenital heart defects, and is also used to treat certain arrhythmias, as it functions to strengthen the contraction of the heart muscle, slowing the heart rate and promoting the elimination of fluid from body tissues. However, it is not particularly effective in treating coronary artery disease (CAD), which is the leading

cause of death in the US. Until 30 years ago, there were no drugs available to treat CAD. However, the concerted efforts of clinicians and the biopharmaceutical industry have since then produced thrombolytic agents, beta-blockers, parental nitroglycerine, heparin, aspirin, 2b-3a inhibitors, calcium blockers, and a variety of anti-platelet agents, all of which gives doctors a potent arsenal with which to treat cardiovascular diseases.

Nevertheless, medication alone cannot overcome the problems posed by cardiovascular diseases as a whole, and preventative lifestyle changes have emerged as leading contributors to the decline of mortality and disability rates now being seen. For example, the recently completed international Coronary Primary Prevention Trial (CPPT) was a landmark 10-year study that showed conclusively for the first time that reducing low density lipoprotein (LDL) cholesterol and total blood cholesterol can reduce the incidence of coronary heart disease and heart attacks in men at high risk because of significant amounts of plasma cholesterol. This and several other studies confirmed the link between lifestyle, diet, and the chances of having or succumbing to cardiovascular dis-

Table 1. Selected products in clinical trials

Company	Product	Status
Alexion (New Haven, CT) / Enzon (Piscataway, NJ)	Recombinant h5G1 for inflammation following bypass	Phase II, 7/97
Bristol-Myers Squibb (Princeton, NJ)	Lanoteplase tPA for acute myocardial infarction	Phase III
Centocor (Malvern, PA)	Capiscint Mab imaging agent for arteriosclerotic plaques	Phase II
Centocor (Malvern, PA) / Corvas (San Diego, CA)	Corsevin Mab against thrombolytic complications following angioplasties	Phase III
Centocor (Malvern, PA) and Eli Lilly (Indianapolis, IN)	ReoPro Mab for acute myocardial infarction and unstable angina	Market, 11/97
Chiron (Emeryville, CA)	Growth factor for coronary artery disease	Phase II, 1998
Collateral Therapeutics (San Diego, CA)	Gene therapy for angina	Phase I/II, 1999
COR Therapeutics (S. San Francisco, CA) / Schering-Plough (Madison, NJ)	Integrilin platelet aggregation inhibitor for acute myocardial infarction	Phase II
Corvas (San Diego, CA)	Factor VIIa inhibitors for thromboses	Late preclinical
Cypros Pharmaceuticals (Carlsbad, CA)	CPC-111 cell therapy for bypass surgery	Late preclinical
Diatide (Londonderry, NH)	AcuTect peptide for carotid thrombus detection	Market, 9/98
Genentech (S. San Francisco, CA)	Anti-CD18 humanized Mab for acute myocardial infarction	Phase II
Genentech (S. San Francisco, CA)	Second generation tPA for acute myocardial infarction	Market, 4/95
GenVex (Rockville, MD)	BioByPass VEGF angiogenesis gene therapy for cardiovascular disease	Late preclinical
Genzyme (Cambridge, MA)	Recombinant antithrombin against clotting during bypass surgery goat milk-produced human recombinant antithrombin III to reduce bleeding & transfusions in CABG	Phase III, 5/98
ICOS (Bothell, WA)	Hu23F2G Mab for myocardial infarction	Phase II, 2/97
NeoRx (Seattle, WA)	Biostent for vascular remodeling after balloon angioplasty	Phase I
Ribi Immunichem (Hamilton, MT)	Immunomodulator against cardiac ischemia reperfusion injury	Phase II
Schering-Plough (Madison, NJ)	IL-10 for ischemic reperfusion injury	Phase I
Schering-Plough (Madison, NJ)	small molecule thrombin inhibitor (injectable)	Phase I/II
Scios (Mountain View, CA) / Chiron (Emeryville, CA)	Trafermin growth factor for coronary artery disease and peripheral vascular disease	Phase II, 12/96

Source: Biovista (www.biovista.com)

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ease, and have helped direct some of the development of new drugs toward cholesterol-lowering modes of action and related mechanisms.

Current state

Even though the risk factors that increase the chances of cardiovascular disease are well known (cholesterol and other lipids, cigarette and tobacco smoke, diabetes mellitus, high blood pressure, obesity, physical inactivity)² and there is a wide variety of medications to treat or ameliorate conditions that arise, the number of surgical procedures performed in the US alone in response to cardiovascular disease is simply staggering.

In 1996 alone, 1.2 million diagnostic cardiac catheterizations, 600,000 coronary artery bypass graft procedures, 150,000 cardiac pacemaker procedures, 450,000 percutaneous transluminal coronary angioplasty procedures, 130,000 endarterectomy procedures, and 80,000 heart valve procedures were performed². The numbers change in varying degrees over time for each of these procedures, and most are still increasing, although at lower rates than in the past.

These types of surgeries can be very expensive, and the associated costs due to hospitalizations are also enormous, spurring the development of preventative medications and post-procedure drugs to help with the recovery process. Table 1 is a summary of drugs in development for heart disease as a whole. There are multiple approaches under development, ranging from angioplasty gene therapies to monoclonal antibodies to coagulation modulators. In addition, there are efforts by several companies to develop better imaging agents for the detection and monitoring of cardiovascular disease progression.

As previously mentioned, cholesterol-lowering drugs are at the forefront of development, although the American Heart Association recommends that "Drug therapy can be considered for patients who, in spite of maximal dietary therapy, regular physical activity and weight loss, need further treatment for elevated blood cholesterol levels."²

Here, the drugs of choice for elevated LDL cholesterol are the bile acid sequestrants—cholestyramine and colestipol—and the vitamin nicotinic acid (niacin), which have been shown to reduce the risk for coronary heart disease. There are associated side effects; however, they are not considered serious. Another class of drugs is the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, such as lovastatin, pravastatin, and simvastatin. So-called statin drugs are very effective for lowering LDL cholesterol levels and have few immediate short-term side effects. They function by interfering with key events in the synthesis of cholesterol. Other drugs

include gemfibrozil, clofibrate, and probucol, which are effective to varying degrees for lowering elevated triglyceride levels, and combination therapy for patients who do not respond adequately to single drug therapy is increasingly being adopted.

Finally, at present, a constant stream of new data support some basic truths about risk factors and the importance of effective prevention. One recent report from Australia shows how increased blood pressure is directly responsible for more than 50% of stroke deaths and for about 25% of deaths from coronary heart disease in Eastern Asia³. The same study suggests how even modest reductions in blood pressure could have a very significant impact on the number of deaths.

Industry challenges

Even though there is now significant experience with the various drugs used to treat cardiovascular diseases, clinicians and the industry are still challenged by some of the

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findings. For example, while thrombolytic drugs (e.g., streptokinase and accelerated tissue plasminogen activator [tPA]) have been successful since being introduced as the standard management for myocardial infarction 13 years ago, only about 50% of patients achieve unrestricted flow within 90 minutes of administration. This has led to a search for better drugs, including genetically modified tPA and an older agent, staphylokinase⁴. These efforts highlight the need to balance the discovery of new drugs and the incremental improvement of already-existing ones. Industry and clinicians alike are constantly examining the already-existing collection of available drugs for modified applications or combinations.

Since it is essentially pharmaceutical companies that have developed or market all the major cardiovascular disease drugs, another challenge for the industry is whether there are any opportunities for young biotech companies to be involved in the field. Of course, this question is relevant to all disease areas. The answer lies in the fact

that competition between pharma and biotech companies is not a bad thing—and more importantly, many of the advances that will lead to next-generation medicines are increasingly being discovered and developed through their early stages by biotechs. During the later stages of clinical trials, when increased expenses necessitate partnerships, biotechs are then likely to partner with pharmaceutical companies. Thus, the fact that pharma dominates the commercial exploitation of medicines in this area should not detract biotech companies from entry. There will always be a need for better drugs that are effective in a broader population range than currently available, and biotech companies are ideally suited to discover and develop these.

Future directions

Cardiovascular medicine has had to move with the times, and in addition to improved surgical procedures and drugs, it is beginning to make use of the flood of genomic information emerging from tissue-specific sequencing projects. This has ushered in the field of molecular cardiovascular medicine, which is based on databases of genomic information from cardiovascular tissue. For example, a recent report analyzed more than 76,000 expressed sequence tags (ESTs) from 13 different cDNA libraries of the cardiovascular system⁵. Northern analysis of the data identified widely expressed genes, and also ones that were tissue- or development-stage specific.

The future will no doubt see these efforts applied to healthy and diseased cardiovascular tissue from cross-sections of populations, and is likely to result in improved understanding of molecular contributors to these diseases. This, in turn, will be of enormous assistance in the design of new drugs.

In addition, the correlation between gene polymorphisms and specific cardiovascular diseases is also likely to become increasingly important. A recent report showed how the Cys242Thr polymorphism of the *p22phox* gene was related to angiographic coronary artery disease and endothelial function. The gene is thought to play a critical role in the generation of superoxide anions in the vessel wall, which may help control vascular oxidant stress, which in turn impairs endothelial function which arises during CAD. Although the Cys242Thr polymorphism was reported to confer a protective effect on CAD risk in a Japanese study population, in a study of US patients, it did not appear to confer protection from endothelial dysfunction or CAD⁶. This shows the importance of understanding gene variability and the multifactorial nature of these diseases, and helps prevent making generalizations across populations. In addition, it helps focus on specific molecular tar-

gets on the basis of these variations, which is the essence of the burgeoning field of pharmacogenomics (see Pharmacogenomics, pp. 40–42).

Another future development is the increased identification and use of molecular markers of cardiovascular disease for early diagnosis and prevention. For example, cardiac troponins are selectively released by damaged myocytes. The specificity of this event is high enough that it has resulted in improvements in the diagnosis of acute cardiac ischemic disorders, and has also enabled clinicians to predict more reliably the risk and outcome scenarios for patients⁷.

The future will also see the identification of more new potential molecular targets for cardiovascular disease. For example, a recent report describes the correlation between scavenger receptor BI, which is a cell surface receptor for selective high-density lipoprotein (HDL) cholesterol uptake in the liver and in other tissues, and the regulation of HDL metabolism, and protection against atherosclerosis in animal models⁸. Should these results also apply to humans, this will become another new target for drug development in the future with major potential benefits.

In addition, our understanding of the correlations between cardiovascular disease

and patients in other high-risk groups, such as those receiving renal transplants, will continue to be refined. These patients often have major cardiovascular disease complications and left ventricle hypertrophy, which correlates with adverse prognosis. A recent report shows how certain types of immunosuppression regimens received by these patients may correlate with increasing risk of cardiovascular disease⁹. These are significant clinical correlations whose underlying reasons are still some time away but which will continue to be addressed and refined.

Finally, the future will see appropriate emphasis being placed on a third component of cardiovascular disease propensity, in addition to the traditional two, which are genetics and the environment. The third component is the prenatal environment and so-called prenatal “programming”, with increasing research being devoted to it. For example, there are suggestions that the development of the renin-angiotensin system and its importance in renal development may be linked to hypertension and thus ultimately cardiovascular disease¹⁰. Although still in its infancy, this line of thought and work is likely to yield significant insights into the full range of factors that affect the development and progression of heart disease.

Conclusions

Cardiovascular disease's effects on world health and the economics of healthcare are devastating. Nevertheless, a vast array of drugs, improved surgical procedures, early diagnosis and prevention, and lifestyle and diet changes are helping to control it to a considerable extent. In the near future, pharmacogenomic capabilities will help us understand diseases in terms of specific genetic contributors, and spur the development of effective new drugs that will help bring this plague under control.

Reprinted from Nature Biotechnology 17, 930–931 (1999).

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