WORKING
PAPER

An overview of cardiovascular disease and research

EDWARD NASON

WR-467-RS

January 2007

Prepared for Project Retrosight

EUROPE

Preface

This working paper has been prepared for the International consortium of cardiovascular disease (CVD) research funders involve in Project Retrosight. Project Retrosight is investigating the payback on CVD research in four countries (Australia, Britain, Canada and New Zealand). The main objective of this suite of documents is to provide an overview of the CVD situation, CVD research and the funding systems in place for CVD research.

This background information will be useful in providing context to the case studies of specific CVD research projects that form the majority of Project Retrosight. Each country involved in the project will produce 4-16 case studies of research conducted around the early 1990s, following the outputs and outcomes from that research. The case studies will use the Payback framework used by the UK study team in previous health research studies.[1]

This document provides an overview of the key background issues involved in this study of research into CVD. These are:

- An introduction to CVD, including the different forms of the disease, risk factors and the impact on both people and countries.
- An introduction to CVD research, covering the different areas of CVD research, the key advances, high-impact research and future expectations for research.

This is a living document that can be updated when new advances are made, new information comes to light, or if researchers from specific countries have information on the CVD research or general health research funding situation within their country.

Also contained within this suite of documents are overviews of the CVD situation (from disease burden through to research funding system) for each country involved in the study; a research pack that identifies the way to approach research looking at payback on CVD research; and an overview of the literature on "research on research" – how to assess the impact of funded scientific research.

[1] Studies for the Arthritis Research Campaign (ARC), the English Department of Health (DH) and Economic and Social Research Council (ESRC) in the UK and research for the Alberta Heritage Foundation for Medical Research (AHFMR) in Canada have used the "payback" methodology to understand the impact of funded research and the key drivers, facilitators and inhibitors of this impact.

RAND Europe is an independent not-for-profit policy research organisation that serves the public interest by improving policymaking and informing public debate. Its clients are European governments, institutions, and firms with a need for rigorous, impartial multidisciplinary analysis. This report has been peer-reviewed in accordance with RAND's quality assurance standards[2] and therefore may be represented as a RAND Europe product.

For more information about RAND Europe or this document, please contact:

Edward Nason
Analyst
RAND Europe Cambridge
Westbrook Centre
Milton Road
Cambridge. CB4 1YG. UK

Tel: +44 (0)1223 353 329
Fax: +44 (0)1223 358 845
Email: nason@rand.org

Dr. Steven Wooding
Senior Analyst
RAND Europe Cambridge
Westbrook Centre
Milton Road
Cambridge. CB4 1YG. UK

Tel: +44 (0)1223 353 329
Fax: +44 (0)1223 358 845
Email: jgrant@rand.org

[2] For more information, see http://www.rand.org/about/standards/

Contents

Table of Figures

Table of Tables

Abbreviations

ACE (inhibitors)	Angiotensin Converting Enzyme
AIDS	Auto Immune Deficiency Syndrome
BHF	British Heart Foundation
CAD	Coronary Artery Disease
CHD	Coronary Heart Disease
CT	Computer Tomography
CVD	Cardiovascular disease
DALYs	Daily Adjusted Life Years
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
HDL	High Density Lipoprotein
HIV	Human Immuno-Virus
IOTF	International Obesity TaskForce
LDL	Low Density Lipoprotein
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
PE	Pulmonary Embolism
PET	Positron Emission Tomography
VSD	Ventricular Septal Defect
WHO	World Healt Organisation
YLD	Years Lived with Disability
YLL	Years Life Lost

CHAPTER 1 Cardiovascular disease overview

As the largest single cause of death on the planet,[3] cardiovascular disease (CVD) in all its forms is an important and life or death matter. CVD is not a single disease, but a cluster of diseases and injuries that affect the cardiovascular system (the heart and blood vessels). These are most commonly diseases of the heart and of the blood vessels of the heart and brain. In general they affect people in later life (with incidence rising sharply after the 30-44 age range), although, according to a leading cardiologist, by around 35 years old, most who will get a form of CVD already have the beginnings of the disease.[4]

1.1 Typology of disease

As mentioned, CVD is actually a collection of diseases affecting the cardiovascular system. These include: coronary heart disease; angina; stroke; rheumatic heart disease; congenital heart disease; peripheral arterial disease; aortic aneurysm and dissection; deep vein thrombosis; and other, less common, cardiovascular diseases.

1.1.1 Coronary heart disease

Coronary heart disease (CHD), also called coronary artery disease (CAD) and atherosclerotic heart disease, is the end result of the accumulation of atheromatous plaques[5] within the walls of the arteries that supply the myocardium (the muscle of the heart). While the symptoms and signs of coronary heart disease are noted in the advanced state of disease, most individuals with coronary heart disease show no evidence of disease for decades as the disease progresses before the first onset of symptoms, often a "sudden" heart attack, finally arise. After decades of progression, some of these atheromatous plaques may rupture and (along with the activation of the blood clotting system) start limiting blood flow to the heart muscle. The disease is the most common cause of sudden death.

1.1.2 Angina

The pain associated with very advanced CHD is known as angina, and usually presents as a sensation of pressure in the chest, arm pain, jaw pain, and other forms of discomfort. The

[3] WHO (2004) "Atlas of Heart Disease and Stroke", available at http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html

[4] From interview with a BHF professor of cardiovascular sciences, on 15th May 2006

[5] Abnormal inflammatory accumulations of macrophage white blood cells.

word *discomfort* is preferred over the word *pain* for describing the sensation of angina, because it varies considerably among individuals in character and intensity and most people do not perceive angina as painful, unless it is severe. Angina is essentially a cramp in the heart muscle.

1.1.3 Stroke

A stroke is an acute neurological injury whereby the blood supply to a part of the brain is interrupted, either by arterial blockage or rupture (haemorrhage). The part of the brain perfused by a blocked or burst artery can no longer receive oxygen carried by the blood; brain cells are therefore damaged or die (become necrotic), impairing the function of that part of the brain. Stroke can cause permanent neurological damage or death if not promptly diagnosed and treated.

Strokes can be classified into two major categories: ischemic and hemorrhagic. Ischemia can be due to thrombosis (clotting), embolism (clot or obstruction from elsewhere in the body), or systemic hypoperfusion (reduction of the blood flow to all parts of the body). Haemorrhage can be due to intracerebral haemorrhage or subarachnoid haemorrhage. ~80% of strokes are due to ischemia.[6]

1.1.4 Rheumatic heart disease

Rheumatic heart disease is a condition in which the heart valves are damaged by rheumatic fever caused by streptococcal infection. Rheumatic fever is an inflammatory disease that can affect many of the body's connective tissues — especially those of the heart, joints, brain or skin. Anyone can get acute rheumatic fever, but it usually occurs in children five to 15 years old. The rheumatic heart disease that results can last for life. Every year at least eight out of every 1,000 babies born in the UK have some sort of heart defect.[7] About half of these babies have a minor defect and will not need any treatment but the rest will need either medical treatment or surgery.

1.1.5 Congenital heart disease

Congenital heart disease is a broad term that can describe a number of different abnormalities affecting the heart, all of which are abnormalities of the heart's structure and function caused by abnormal or disordered heart development before birth. In some cases, such as *coarctation of the aorta*, it may not present itself for many years and a few lesions such as a small ventricular septal defect (VSD) may never cause any problems and are compatible with normal physical activity and a normal life span. Some congenital heart diseases can be treated with medication alone, while others require one or more surgeries. The risk of death from congenital heart disease surgery in the USA has dropped from approximately 30% in the 1970s to less than 5% in most cases today. Box 1 shows some of the major congenital heart diseases, taken from the British Heart Foundation (BHF) website (www.bhf.org.uk).

- Tetralogy of Fallot

[6] http://www.urmc.rochester.edu/smd/Rad/stroke.htm

[7] http://www.bhf.org.uk/hearthealth/printout.asp?secID=1&secondlevel=77&thirdlevel=362&artID=500

- Transposition of the great vessels
- Tricuspid atresia
- Total anomalous pulmonary venous return
- Hypoplastic left heart/right heart
- Ventricular septal defect (VSD)/ Atrial septal defect (ASD)
- Patent ductus arteriosus (PDA)
- Aortic stenosis
- Pulmonic stenosis
- Atrioventricular canal (endocardial cushion defect)

Box 1. Major forms of congenital heart disease

1.1.6 Peripheral arterial disease

In peripheral arterial disease, the arteries that supply the blood to the legs become narrowed or completely blocked off. The narrowing of the artery usually occurs in the upper part of the leg. The disease is caused by a gradual build-up of fatty material within the walls of the artery (atherosclerosis). The presence of atheroma can also cause a blood clot (or thrombus) to form, blocking off the artery completely. People with peripheral arterial disease are also likely to have narrowing of other arteries in the body. If there is narrowing in the arteries that supply blood to the heart, it can cause angina or a heart attack. If the arteries to the neck are affected, it can interfere with the flow of blood to the brain and may cause a stroke.

Aortic aneurysm and dissection

An aortic aneurysm is a balloon-like swelling of the aorta that can rupture causing large internal bleeding (dissection).

Deep vein thrombosis

A deep vein thrombosis (DVT) is a blood clot (thrombus) that develops in a deep vein, usually in the lower leg. Deep vein thrombosis can cause pain in the leg and can potentially lead to complications. About 1-3 people in 1000 develop a DVT each year in the UK.[1] A DVT usually develops in a deep vein in the leg but it can occur elsewhere, such as the arm. Deep veins pass through the centre of the leg and are surrounded by the muscles. A DVT is different to blood clots that form in a separate set of veins (called superficial veins) that lie under the skin. These clots are called superficial thrombophlebitis and are less serious.[2]

It is uncommon for DVT to cause any further problems but potential complications include Pulmonary Embolism (PE) and post-thrombotic syndrome. PE happens when a piece of the blood clot breaks off and travels in the bloodstream to become lodged in the lungs and block blood flow. This can happen hours or even days after the formation of a clot in the calf veins. It may cause chest pain and shortness of breath. Post-thrombotic syndrome happens if a DVT damages the valves in the vein, so that instead of flowing upwards, the blood pools in the lower leg. This can result in pain, swelling and ulcers on the leg.

1.1.7 Other cardiovascular diseases

These could include tumours of the heart, vascular tumours of the brain, disorders of the heart muscle (cardiomyopathy), heart valve diseases and disorders of the lining of the heart.

1.2 Disease burden

Prevalence of disease is notoriously difficult to estimate in a population since it requires an idea of those not presenting for healthcare and undiagnosed cases. In terms of global prevalence of CVD, this task is almost impossible since there are multiple countries reporting prevalence in slightly different ways and a number of different conditions making up CVD that can be interpreted in different ways. Throughout this section, the USA is commonly used as an example of disease burden statistics, since the USA has high levels of CVD and well kept statistical records. The figures for Retrosight study countries will be covered in country specific reports as part of the overview suite of documents.

As an example of prevalence though, the USA estimated the number of cases of CVD in 2003 at 71.3 million; this is over 1 in 4 Americans.[8] Of these 71.3 million cases, around 13.2 million were coronary heart disease cases and around 5.5 million were stroke. Prevalence rates for the study countries involved in Project Retrosight are shown in the country specific profile documents.

1.2.1 Change over time

Currently, 17 million people worldwide die of CVD each year.[9] Due to improvements in treatment, the mortality due to CVD has dropped in developed countries in the last 10-15 years. However, there remain problems in developing countries and there are a number of foreseeable problems that will affect developed countries in the coming years. As obesity and diabetes, two major risk factors for CVD, prevalence increase across the world (they are predicted to increase worldwide by 700 million people by 2015[10] and around 140 million people by 2025[11] respectively), there is expected to be a corresponding increase in CVD cases.[12]

1.2.2 Geographic spread

Despite statistics often being quoted for the rise in CVD due to obesity, poor diet and lack of exercise in developed countries such as the USA and UK; it is not just a disease of the developed world. In fact, CVD is more of a threat to those living in developing countries

---

[8] Thom et al. (2006) "Heart Disease and Stroke Statistics - 2006 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee", *Circulation*, **113**, e85-e151

[9] WHO (2004) "Atlas of Heart Disease and Stroke", available at http://www.who.int/cardiovascular_diseases/resources/atlas/en/index.html

[10] http://www.who.int/mediacentre/factsheets/fs311/en/index.html

[11] http://www.eatlas.idf.org/Prevalence/

[12] The burden of CVD (% of DALYs lost worldwide) is expected to rise from 10.4% to 11.6% by 2030, see WHO (2004), Op cit

than to those in the developed world. [13] For example, of the global burden of CHD, over 60% is in developing countries. India, China and Russia have the largest death tolls due to CHD, with Lithuania and Bhutan also having very high rates. These figures are mirrored by those for stroke, with the same three countries having the largest number of deaths per annum. In terms of DALYs (Disability Adjusted Life Years)[14] lost due to stroke, only two countries have figures of over 20 DALYs lost per 1000 population; these are Mongolia and Kyrgyzstan. This means that Mongolia and Kyrgyzstan have an exceptionally high impact of CVD on their populations. Overall, these figures show that the developing world has a very real CVD problem and one that is predicted to become even more prevalent as treatment and prevention become more successful in the developed world. [15]

This does not mean that CVD is not a problem in developed countries, far from it. In high income countries 18% of all DALY's lost are due to CVD; but this figure is only 10% in low and middle income countries. As an example, stroke is the single biggest cause of major disability in the UK. [16]

1.2.3 Mortality and morbidity

In terms of global mortality, CVD is the largest single contributor to the 57 million deaths registered by the WHO in 2002[17]. In fact, CVD causes more deaths globally than cancer and HIV combined (Figure 1). In current terms, nearly 100 times as many people a year are killed by CVD than by war.

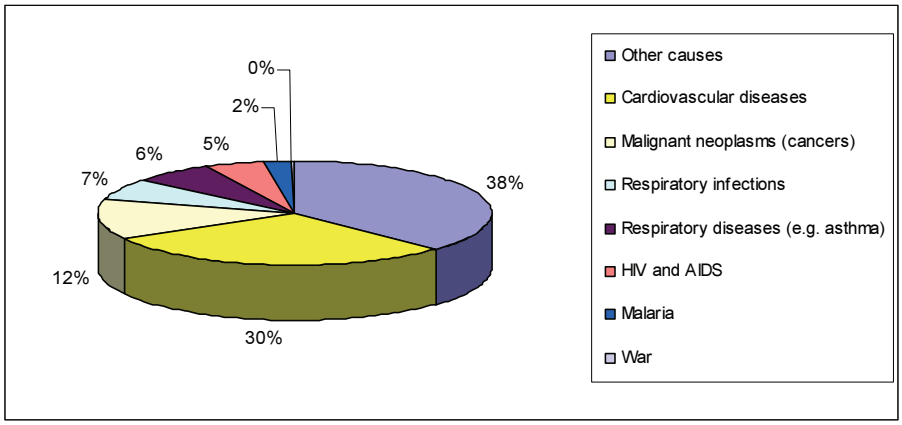

Figure 1. Global mortality in 2002 by major causes (millions)

Source: WHO global mortality figures, available at:
www.who.int/healthinfo/statistics/gbdwhoregionmortality2002.xls

[13] Figures on the global burden of CHD and Stroke are taken from: WHO (2004)

[14] DALYs are calculated by taking the sum of two components; average or expected Years of Life Lost (YLL) and Years Lived with Disability (YLD) using the formula: DALY = YLL + YLD. This takes into account the effect on both length and quality of life.

[15] WHO (2004)

[16] Ibid

[17] Ibid

Since CVD is a term that describes several different conditions, it is important to clarify exactly what the particular causes of disease burden are in terms of mortality and morbidity. The WHO Atlas of Heart Disease and Stroke (2004)[18] breaks down the 16.7 million deaths due to CVD globally into deaths due to CHD, stroke, rheumatic heart disease, inflammatory heart disease, hypertensive heart disease and other forms of heart disease (Figure 2).

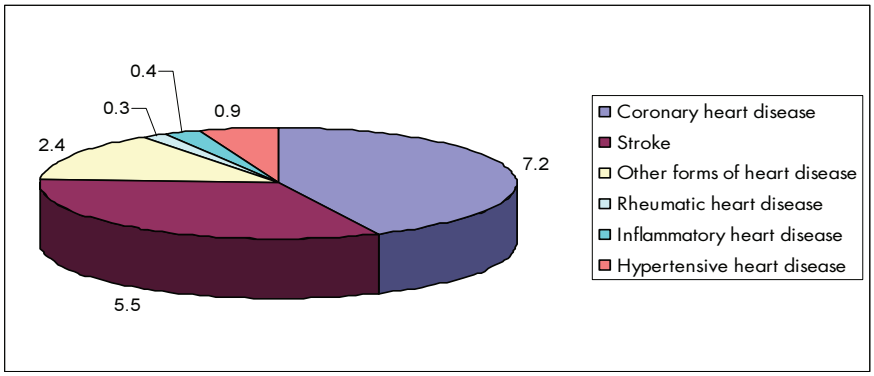

Figure 2. Global deaths in 2002 due to CVD (millions)

Source: WHO Atlas of Heart Disease and Stroke, p18

Global morbidity is expressed in terms of DALYs lost due to a disease. CVD is one of the top contributors to the total number of DALYs lost globally, along with HIV and depression (bi-polar disorders). Figure 3 shows the WHO figures on DALYs lost due to disease globally, with CVD effects split into heart disease and stroke. It also splits the figures down to differentiate between men and women, showing that for men, heart disease and stroke are the second and third largest cause of DALYs lost (the largest when combined as CVD), whereas for women they are third and fourth respectively (although again, combined as CVD they would be the largest single cause).[19]

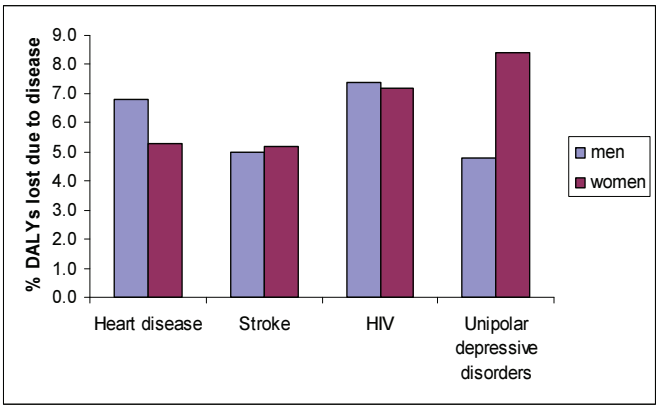

Figure 3. The top four diseases for global DALYs lost in 2002: % of global DALYs lost due to disease

Source: WHO Atlas of Heart Disease and Stroke, p46-47

[18] WHO (2004)

[19] Ibid

The amalgamation of global data is useful in understanding the importance of CVD in terms of deaths and disability. However, since there are major differences between developed and developing countries, it is important to know what the mortality and morbidity rates are in the countries being studied as part of Retrosight and in other countries. Figure 4 shows the DALYs lost per 1000 population in a number of different countries, comparing those lost in the developed world, with those lost in developing nations.

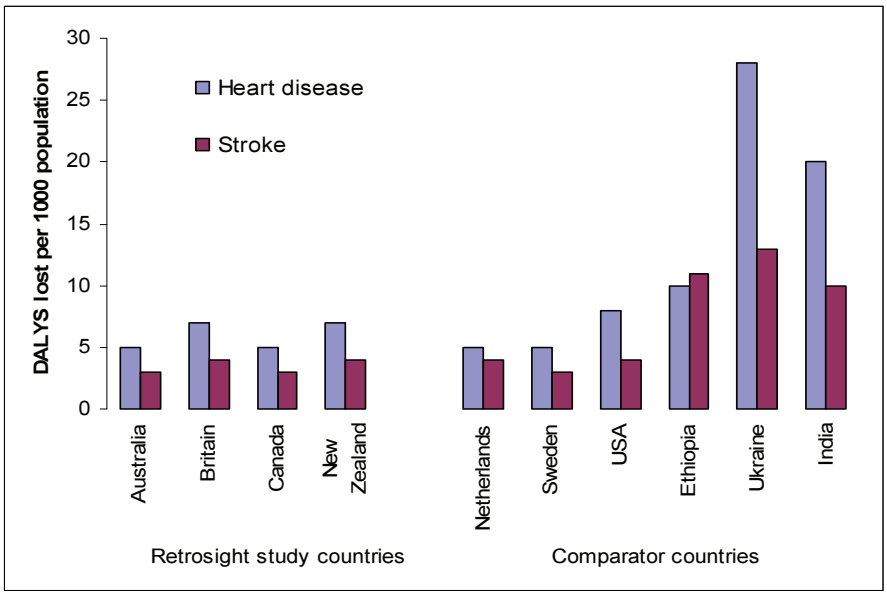

Figure 4. DALYs lost per1000 population in selected countries (2003 or nearest data)

Source: WHO Atlas of Heart Disease and Stroke, World data tables, p84-91

1.2.4 Economic and socio-economic costs

The economic cost of CVD is not simply one of healthcare costs associated with the disease, but one that reflects the loss to productivity due to CVD and general care costs to the economy. With CVD so highly prevalent, this economic cost can be substantial, especially in countries that have higher morbidity due to CHD and stroke. In the USA, the cost of CVD has been estimated by the National Heart Lung and Blood Institute at over $400 billion dollars for 2006.[20] This cost is expected to rise, with the WHO predicting that the cost to the US healthcare budget for those aged 50-65 will rise from 15% in 2010 to 25% in 2030.[21]

1.2.5 Risk factors

As CVD is such a complex collection of diseases, unsurprisingly there are a number of risk factors involved. There is also the added complication that many of the risk factors for CVD interact with one another. For example, both obesity and diabetes are major risk factors for the development of CVD, but obesity is also a risk factor for type II diabetes. As such it is impossible to produce any sort of summative formula for predicting CVD based

[20] http://www.nhlbi.nih.gov/about/factbook/chapter4.htm

[21] http://www.who.int/cardiovascular_diseases/en/cvd_atlas_25_future.pdf

on risk factors, merely to say that having more than one risk factor will increase your risk of contracting one form of CVD. Below, the major risk factors associated with CVD are discussed in more detail.

Smoking

Smoking increases the risk of developing coronary heart disease is by 2–4 times. Smoking is a powerful independent risk factor for sudden cardiac death in patients with coronary heart disease; where smokers have about twice the risk of non-smokers.[22] Exposure to other people's smoke increases the risk of heart disease even for non-smokers; the British Heart Foundation estimates that regular exposure to second hand smoke can increase the risk of CHD by up to 25%.[23] Cigarette smoking interacting with other risk factors greatly increases CHD risk.

The mechanisms by which smoking increases the risk of CVD are relatively well understood. The main risk is in the increased tendency towards thrombosis seen in smokers, which can lead to myocardial infarction.[24] Other mechanisms include increased atherosclerosis, blood pressure, heart rate, cardiac output and coronary blood flow. Smoking also increases the levels of carbon monoxide in the body, which binds to haemoglobin, reducing the amount of oxygen reaching body tissues.[25]

The number of cigarettes smoked in 2000 was estimated at 5,500 billion, a number that has been rising with increasing world population. The number of daily smokers worldwide is thought to be around 1 billion men and 250 million women.[26]

Obesity

Obesity, particularly in those with excess fat around the waist, increases the chance of developing CHD even if no other risk factors are present. Excess weight increases strain on the heart, raises blood pressure and blood cholesterol and triglyceride levels, and lowers HDL cholesterol levels. All of these factors can increase the risk of atherosclerosis and thrombolytic embolism. It also increases the risk of developing type II diabetes, another risk factor for CVD. The WHO estimated that in 2005, around 1.6 billion people were overweight, with 400 million people obese.[27]

Diabetes

Diabetes is a disease that affects an individual's ability to maintain an appropriate blood glucose level. The disease has two forms, Type I and Type II diabetes. Type I diabetes is also known as insulin dependent diabetes and is caused by the body not producing any

---

[22] http://www.americanheart.org/presenter.jhtml?identifier=4726

[23] BHF Health promotion research group (2006), Op Cit

[24] Smith, Fischer and Sears (2000) "Environmental Tobacco Smoke, Cardiovascular Disease, and the Nonlinear Dose-Response Hypothesis", *Toxicological Sciences*, **54**, 462-472

[25] http://mens-health.health-cares.net/smoking-cardiovascular-disease.php

[26] WHO (2002) "The tobacco atlas", available at http://whqlibdoc.who.int/publications/2002/9241562099.pdf

[27] http://www.who.int/mediacentre/factsheets/fs311/en/index.html

insulin. Type II diabetes is the more common form of the disease, and occurs when the body either does not produce enough insulin or cells do not process the insulin properly.[28] Both of these forms can lead to an increased risk of CVD via increased cholesterol levels, hypertension and atherosclerosis.[29] Insulin resistance is also related to CHD.[30]

WHO estimates suggest that more than 180 million people worldwide have diabetes; with this number likely to more than double by 2030. In 2005, an estimated 1.1 million people died from diabetes worldwide.[31] In the USA, a survey of deaths in 1986 suggested that 60–75% of people with diabetes die from cardiovascular disease.[32]

High blood pressure

High blood pressure (hypertension) is strongly linked to both cardiac diseases and those of the vascular system. High blood pressure affects the heart by causing it to thicken and stiffen as it has to work harder to pump blood; this can lead to heart attacks. The effect on the vascular system is one of pressure on vasculature walls, leading to aneurisms and stroke.

High blood pressure is a very common problem in developed countries, with one in four adults in the USA diagnosed with hypertension, although this represents a drop in the numbers since the 1980s when prevalence was around one in two.[33] It is expected that global hypertension rates will rise in the next 20 years, reaching 1.5 billion adults globally, up to $^{1}/_{3}$ from ¼ of the world population.[34]

High LDL cholesterol

The basic method by which LDL cholesterol (low density lipoprotein cholesterol) increases the risk of CVD is by increasing the fatty deposits in blood vessels, leading to atherosclerosis. Recently, research has suggested that this is more of an active process than previously thought, with LDL cholesterol actually activates endothelial cells to express adhesion molecules that speed the process of atherosclerosis.[35]

A WHO analysis in 2004 looked at the prevalence of high cholesterol levels in a number of countries and estimated that a total of 4.4 million deaths worldwide and over 40 million DALYs were due to "non-optimal cholesterol". [36] These account for around 8% of deaths,

---

[28] See the website of the American Diabetes Association, http://www.diabetes.org/about-diabetes.jsp

[29] http://diabetes.niddk.nih.gov/dm/pubs/stroke/#connection

[30] Press release from NIH, http://www.nhlbi.nih.gov/new/press/sep01-99.htm

[31] http://www.who.int/mediacentre/factsheets/fs312/en/index.html

[32] http://www.clinicalevidence.com/ceweb/conditions/dia/0601/0601_background.jsp

[33] http://www.fauxpress.com/kimball/med/heart/h2/bloodpres.htm

[34] Kearney, Whelton, Reynolds, Muntner, Whelton and He (2005) Global burden of hypertension: analysis of worldwide data, *The Lancet*, **365:9455**, 217-223

[35] Ganjia, Kamannaa and Kashyap (2003) Niacin and cholesterol: role in cardiovascular disease (review), *The Journal of Nutritional Biochemistry*, **14:6** , 298-305

[36] Ezzati, Lopez, Rodgers and Murray (2004) Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attribution to Selected Major Risk Factors, World Health Organisation, Chapter 7. Available at: http://www.who.int/publications/cra/chapters/volume1/0391-0496.pdf

and 3% of DALYs worldwide. Cholesterol levels have on the whole been rising globally[37] and are expected to continue rising in predictions up to 2030 (although interestingly, North America and Western Europe are expected to have a drop in cholesterol levels).[38]

Socio-economic risks

CVD deaths are associated with low socio-economic standing. For example, in developing countries such as Ukraine and India, the levels of CVD are up to 6 times higher than developed countries such as Canada, Australia and Britain (see Figure 4). This risk is inextricably tied in with several other risk factors such as diet, physical activity and levels of obesity. Even smoking is correlated with lower socio-economic status in south Asian populations in the UK.[39]

Other risk factors

Several other risk factors are important in the onset of CVD. For example, physical inactivity is seen as a large risk factor. Physical activity can reduce cholesterol levels, decrease obesity and cause the heart and muscles to work harder in pumping blood around the body. Alcohol intake is also a risk factor, and one that is complex since low levels of alcohol can reduce the risk of heart disease (through antioxidant polyphenols inhibiting the oxidation of LDL cholesterol) but high levels of alcohol intake actually increase the risk of CHD and stroke (by increasing blood pressure). Another key risk factor often cited is nutrition, with poor diet having a direct effect on fat concentrations in the body (increasing the risk of high cholesterol and obesity), sugar levels in the blood (increasing the risk of developing type II diabetes) and salt levels in the blood (increasing blood pressure and the risk of stroke).

1.3 Future of disease

The WHO has produced projections of the future of CVD up to 2030, based on current trends and analysis of relevant data.[40] Their predictions for mortality show a rise in global annual CVD deaths to 18.1 million in 2010, 20.5 million in 2020 and up to 24.2 million by 2030. These represent 30.8%, 31.5% and 32.5% of all global deaths respectively.

For male deaths due to CHD, there is a predicted rise from 13.1% of all male deaths in 2010, to 14.9% in 2030. Interestingly, the same statistic for women predicts a drop in deaths due to CHD, from 13.6% in 2010 to 13.1% in 2030. Stroke deaths are predicted to rise for both men and women (from 9.2% to 10.4% for men, and from 11.5% to 11.8% for women).

Morbidity predictions (all in DALYs) suggest that there is a strong upward trend in both the number of DALYs and the % of all DALYs represented by CVD (see Table 1). By 2020, stroke is expected to become the 4th largest contributor to DALYs lost globally.

---

[37] Ezzati, Lopez, Rodgers and Murray (2004) p444

[38] Ibid, p446, Table 7.18

[39] http://www.bhf.org.uk/news/index.asp?secID=16&secondlevel=241&thirdlevel=1875&artID=8138

[40] WHO (2004) "Atlas of Heart Disease and Stroke", chapter 25

Table 1. Future predictions of global morbidity due to CVD

	By 2010	By 2020	By 2030
CVD DALYs (millions)	153	169	187
Burden of CVD (% of all DALYs)	10.4	11.0	11.6
CVD Rankings globally	3rd CHD	3rd CHD	3rd CHD
	5th Stroke	4th Stroke	4th Stroke

Major risk factors for CVD are also projected to 2030, with the number of smokers predicted to rise over the next 34 years. The number of cases of diabetes is also likely to increase dramatically over the same timescale. Although both of these statistics are tempered by a predicted rise in world population, there is still a real increase in smokers and diabetes cases predicted to 2030 (Table 2).

Table 2. Projection of major risk factors for CVD

		By 2010	By 2020	By 2030
Smokers	Number (upper estimate)	1.4 billion	1.6 billion	1.8 billion
	% World population	20.6	21.3	22.2
Diabetes	Number (>20 years old)	221 million	300 million	366 million
	% World population	3.3	4.0	4.5
World population[41]	Number (billions)	6.79	7.50	8.11

Obesity is the other major issue associated with CVD that is growing to epidemic proportions.[42] As mentioned in the risk factors section, obesity is already a huge problem in the developed world, however it is also becoming a problem in the developing world too.[43] Children are becoming increasingly vulnerable to overweight and obesity around the world. At least 155 million school-age children worldwide are overweight or obese, according to the latest estimates from the "International Obesity TaskForce". Around 30-45 million within that figure are classified as obese - accounting for 2-3% of the world's children aged 5-17. A further 22 million younger children are also affected according to previous IOTF global estimates based on WHO data for under-fives.[44] Indeed, the WHO predicts that by 2015, 2.3 billion adults will be overweight and over 700 people will be obese.[45] This is worrying data, since the morbidity due to CVD is increasing in developed countries. It is also worrying since childhood obesity is linked to diabetes development,

[41] World population estimates taken from Population division, Department of Economic and Social Affairs, (1999) "World at 6 billion", United Nations Secretariat, USA, Part 1, page 5 (available at http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf)

[42] The WHO even responded to the threat of a worldwide epidemic of obesity in 2000 by publishing a Technical Report entitled "Obesity: Preventing and managing the global epidemic" (available at http://whqlibdoc.who.int/trs/WHO_TRS_894.pdf)

[43] WHO obesity and overweight factsheet: http://www.who.int/mediacentre/factsheets/fs311/en/index.html

[44] See the IOTF website - http://www.iotf.org/childhoodobesity.asp

[45] WHO obesity and overweight factsheet

another CVD risk factor, and the WHO prediction that diabetes deaths will grow by 50% in the next 10 years.

CHAPTER 2 Cardiovascular research overview

The importance of CVD as a worldwide disease is reflected in a global research effort that aims to reduce both the death rate (mortality) due to CVD and the prevalence (morbidity) of the disease. The research into CVD covers a wide range of topics, from preventative population measures such as campaigns to reduce smoking or obesity levels, through to invasive surgical procedures such as key-hole heart surgery.

2.1 History and timeline of research

The field of cardiovascular research goes back as far as China in 26th Century BC, when the Emperor *Huang Ti* concluded that blood flowed in a circulatory system in the body that was controlled by the heart.[46] Advances have arrived steadily over the years, including Leonardo Da Vinci describing atherosclerosis (although not coining that term) in the 15th Century.[47] Research into the cardiovascular system really took off in the 19th Century when cholesterol was discovered, atherosclerotic plaques were described and the electrical pulse associated with the heartbeat discovered.[48]

In modern times, the major discoveries of the 20th Century in cardiology are the ones upon which modern clinical cardiology is based.[49] One key discovery was of the importance of electrics in cardiology, both in terms of the electrical activity of the heart per se, and the implantation of electrical devices as pacemakers. Along with the electric monitoring of heart activity was the imaging of heart activity, initially through echocardiography[50] and then through MRI, CT and MRA techniques. The development of the lipid hypothesis of atherosclerosis in Russia in the early 1900s provided the basis for research into cholesterol and the clinical relief of atherosclerosis through angioplasty (including catheterisation with balloons, and stents). Other surgical advances that have been key to CVD treatment include open heart surgery and keyhole surgery – both of which have advanced greatly

[46] WHO (2004) "Atlas of Heart Disease and Stroke", chapter 26

[47] Ibid

[48] Ibid

[49] Taken from: Mehta and Khan (2002) "Cardiology's 10 greatest discoveries of the 20th Century", *Texas Heart Institute Journal*, **29**(3), 164-171

[50] Interestingly one of the original developers of echocardiography (Hellmuth Hertz) also invented the inkjet printer which facilitated the development of colour Doppler echocardiography.

since the 1950's when the first open heart surgery was performed. Drug treatments have developed rapidly over the 20th Century, in particular the use of aspirin to prevent heart attacks and stroke in the 1970s, and the continuing advance of thrombolytic therapeutic drugs such as streptokinase (discovered in 1945).

Perhaps the most talked about research of the 20th Century that is associated with CVD is the Framingham study. This was initiated in 1949 as a large cohort study, based in Massachusetts, to try and understand the causes of CVD in the population. The first results were published in 1961,[51] and identified high blood pressure, smoking and high cholesterol as risk factors for developing CVD – the first time the concept of risk factors had been suggested. The Framingham study has continued for over 50 years, and reports continue to be published that highlight new associated risk factors for CVD (recent examples include the fact that high HDL cholesterol levels can reduce the risk of death from CVD).

Figure 5 and Figure 6 show the timeline of major events in CVD research and treatment, although as mentioned above, it is almost impossible to provide a comprehensive timeline of major research since CVD is such a wide are to research and has such a long history of achievement.

[51] Kannel, Dawber, Kagan, Revotskie and Stokes (1961) "Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study", *Annals of Internal Medicine*, **55**, 33-50

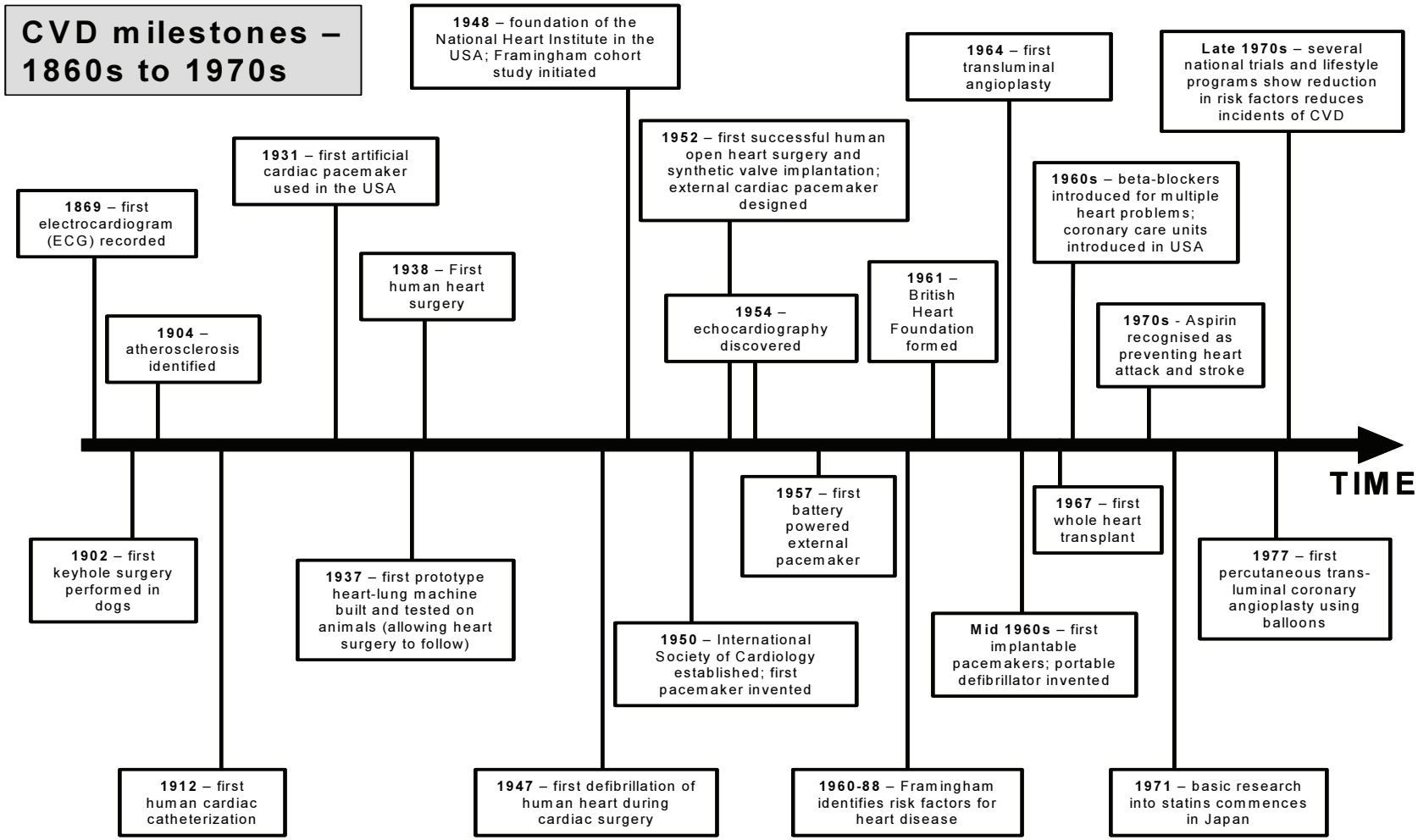

Figure 5. Timeline of CVD research: 1860s to 1970s

Sources: WHO (2004) "Atlas of Heart Disease and Stroke"; Mehta and Khan (2002); and American Heart Association website

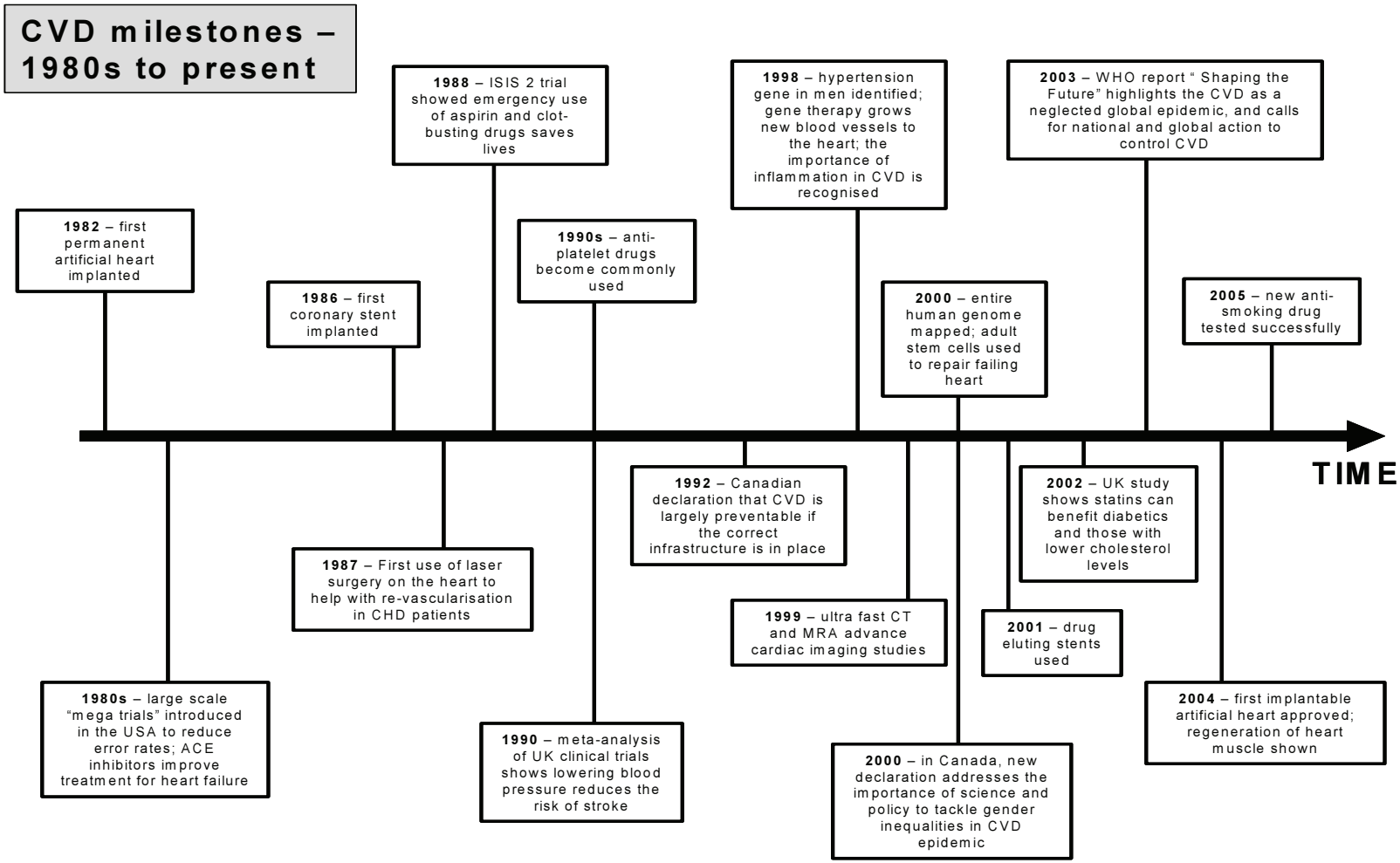

Figure 6. Timeline of CVD research: 1980s to present

Sources: WHO (2004) "Atlas of Heart Disease and Stroke"; Mehta and Khan (2002); and American Heart Association website

2.2 Typology of research

Since we can see that cardiovascular disease encompasses a range of clinical conditions, unsurprisingly there are a large number of distinct research fields that address clinical needs for CVD. In this chapter we split the research on CVD into four main groups (electrics, surgery, mechanics, other research areas) in order to try to cover the main strands of research that are affecting clinical practice today. [52]

CVD is a convenient grouping for a large number of disparate clinical conditions; this means that research necessarily covers a wide range of clinical and biomedical interventions. Aligned with this, the nature of clinical research to pursue multiple cures or treatments for any one condition creates an even wider variety of research topics and areas that can be aligned with CVD. In this section we have classified areas of CVD research not by the condition affected but by method of research. For example, surgery is an area of research that affects many different aspects of CVD from arterial vascularisation to congenital heart defects. Since many advances in surgery are applicable across these types of procedures it is sensible to group surgical advances together.

Described below are four areas in which CVD research has advanced in the last 20-30 years. The areas are:

- Electrics – pacemakers, defibrillators, etc.
- Surgery – open heart surgery, keyhole surgery, transplantation etc.
- Mechanics – stents, balloons, etc.
- Other advances – these include drugs to prevent rejection of transplanted tissue, lifestyle research for causes of CVD, prevention research, screening techniques, etc.

For each of these areas we will discuss the types of research that fall into them, with some advances used as illustrative examples. We will also discuss how the areas overlap and are not necessarily distinct. For example, advances in drug therapy to prevent rejection of transplanted tissue are an obvious area where surgery cannot advance without advances in areas such as the quality of drug therapy or effective genotyping of transplant donors.

2.2.1 Electrics

The first major breakthrough in electrics came with the invention of the pacemaker in the 1950s. Electrics research now comprises projects looking at a variety of problems in cardiology that can be treated with electrical devices. One such area is the miniaturisation of implantable pacemakers, so that they do not need unwieldy battery packs. Another would be the use of implanted defibrillators to both monitor and restart the heart rhythm in any case of fibrillation. Advances in cardiology electrics are now very much dependent on developments in electrical engineering and computing technology.

[52] This typology is based upon an interview with a BHF professor of cardiovascular sciences, who recommended grouping research by research area rather than disease area.

2.2.2 Surgery

Heart surgery is the best known surgery technique associated with CVD, and open heart surgery was made easier by the invention of the *Heart-Lung Bypass* machine in the 1960s.[53] These days, research into surgery techniques runs along two main lines. Firstly, research continues into heart surgery, concentrating on heart valve replacements and work on beating hearts. Secondly, research on surgery to other parts of the cardiovascular system is a major area of research. These include breakthroughs in angioplasty[54] and implantation of electrical devices during surgical procedures.

2.2.3 Mechanics (Stents, balloons, catheterisation)

Although biomechanics in a cardiovascular science context often refers to the fluid mechanics of the cardiovascular system, the use of the phrase "mechanics" is slightly different in the clinical arena. In this document we use mechanics to mean those interventions that mechanically alter the cardiovascular system. For example, stents are wire mesh tubes that are used to physically hold open the arteries. This allows blood to flow more easily to organs around the body. Stents are often used to keep arteries open after angioplasty so that the artery can heal without contracting and reducing blood flow. Stents are now also able to be covered in slow release drug coatings that inhibit closure (sclerosis) of the artery after surgery. These are called "drug eluting stents" and are becoming the common choice of cardiovascular surgeons.

In order to insert stents, either surgery or catheterisation is required. If using a catheter, then it is often necessary to have a stent that is initially smaller in diameter than the artery it is designed to hold open (in order to allow the stent to be put in place. This is done using a technique known as "balloon angioplasty". In this technique, the catheter has a deflated balloon on the end. This balloon is surrounded by the mesh stent. When in position in the artery, the balloon is inflated, increasing the diameter of the stent and pushing the stent into position. Once open and holding the artery, the balloon is deflated and removed with the catheter, leaving the stent in place.

More complex forms of catheterisation can remove atherosclerotic plaques; this is the process of atherectomy. There are a number of atherectomy methods that include shaving the plaque, sucking away parts of the plaque, using a rotational device that wears down the plaque (as a rotational sander would), and even laser atherectomy using adapted catheters.

2.2.4 Other fields of CVD research

The fields described above are near the clinical end of the CVD research spectrum. Those that are more towards the basic science end include research into atherosclerosis and the science behind plaque formation; drug research into reducing symptoms of CVD (such as statins research and thrombolytic research); imaging techniques that allow more accurate understanding of the actions of the heart in vivo; genetics research into the underlying mechanisms of CVD; and stem cell research into regenerating damaged cardiac tissue. There is also a wealth of research into screening techniques for CVD (including

[53] See the BHF website for more details, http://www.bhf.org.uk/about/index.asp?SecID=17&secondlevel=62

[54] Angioplasty is surgery to repair damaged arteries.

phenotypic and genotypic screening); risk factor identification and prevention of CVD; service delivery research; and policy research to reduce CVD.

Cardiovascular disease is a huge field in which to locate research and often, basic science research that is relevant to CVD is actually from other fields. A particularly good example of this is the mapping of the human genome. The American Heart Association publishes a "Top 10 Research Advances in CVD" every year[55] and in 2000, the top advance was the human genome, despite not being CVD research at all. This goes to show that it is very difficult to define what CVD research is, and that the examples given above are merely a taster of the areas in which CVD research occurs.

2.3 High profile research

One way to identify what is high-profile scientific research is to analyse publications and citations arising from those publications. This has been criticised in the past as it biases against applied clinical research, since clinical researchers have different citation patterns to basic researchers. As part of the initial work in Project Retrosight, there will be a bibliometric analysis of the cardiovascular research field, identifying research from the case study countries in particular. The remaining information in this section gives a flavour for the sorts of numbers involved in bibliometric analysis of CVD research in previous years, but the current bibliometric research will provide a more detailed analysis.

Work by the Wellcome Trust in 1998 looked at publications in biomedical science and their distributions.[56] This included looking at distribution of papers in the Science Citation Index (SCI) across different research areas, countries and funders. Overall, cardiology papers represented 11% of all papers in biomedical research. Of these cardiology papers, the majority came from researchers based in the USA. The UK accounted for 9% of the total, Canada 5% and Australia 2% (figures for New Zealand are not included in the Wellcome study). According to WHO data,[57] there are more trials into CVD subjects than any other, even if only looking at clinical trials on coronary heart disease (Figure 7).

In 2005, "The Scientist" magazine published a bibliometric analysis of the top papers (based on citations) published in all science over three periods – 2003-2005; 1995-2005; and all time.[58] In the recent two year window, CVD research was represented by two papers;[59] in the ten year window by two papers;[60] however it was not represented in the all time list (although the majority of papers in the all time list were methodological).

---

[55] American Heart Association, available at: http://www.americanheart.org/presenter.jhtml?identifier=220

[56] Dawson, Lucocq, Cottrell and Lewison (1998) "Mapping the landscape: National biomedical research outputs 1988-1995", Public Report No. 9, Wellcome Trust

[57] WHO (2004) chapter 18

[58] "Top 10 Papers Published...", *The Scientist* (2005), **19**(20), p26

[59] Manica *et al* (2003) "2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension", *Journal of Hypertension*, **21**, 1011-1053; and Moses *et al* (2003) "Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery", *New England Journal of Medicine,* **349**, 1315-1323

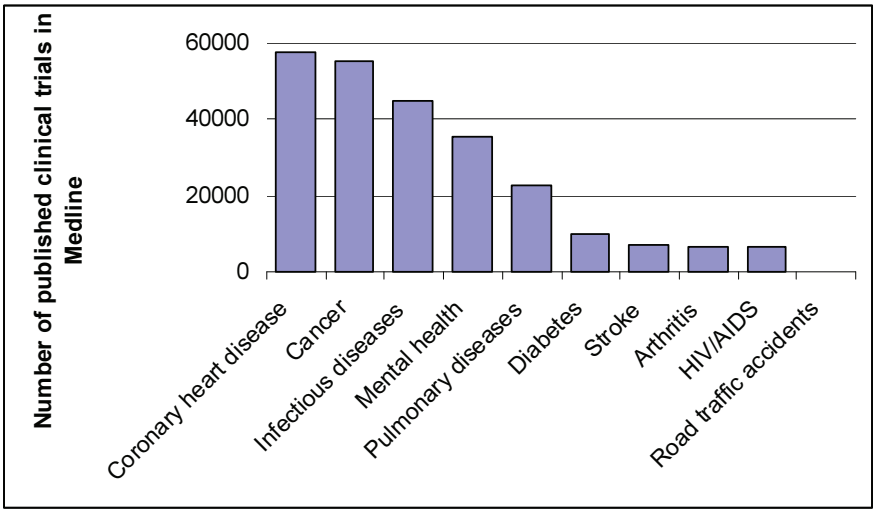

Figure 7. Number of global clinical trials published in Medline in selected biomedical subjects

2.4 Future research agenda

The future of CVD research is one that is often discussed amongst scientists. In particular, around the turn of the millennium saw a selection of editorials and lectures concerning the direction that CVD research would take. In 1997, the Shattuck Lecture discussed cardiology at the turn of the millennium, and identified opportunities for further research breakthroughs in: identifying new risk factors (such as oestrogen deficiency in post-menopausal women); advancing cardiac imaging; understanding the molecular basis of CVD; transgenic experimentation for CVD research; and gene transfer.[61]

In an editorial in Circulation Research in 2001,[62] Claude Lenfant – a former Director of the National Heart, Lung and Blood Institute in the US – described some of the basic biological technological advances that will benefit cardiovascular research (in particular heart disease) in the future. Unsurprisingly, genetics, molecular biology and genomics feature as potentially key to the future of CVD research. However, Lenfant suggests that it is the follow up to decoding the human genome, identifying the make up of the human proteome that is going to be key in understanding pathological processes at the cellular level.[63] He also described how advances in cell biology (for example in terms of cell transplantation within a CVD sufferer) and immunobiology can benefit transplantation therapies by decreasing the chance of rejection by the host's immune system. At it's extreme this could even mean organogenesis. Imaging is also mentioned, but in a more

[60] Ross (1999) "Atherosclerosis - An inflammatory disease", *New England Journal of Medicine*, **340**(2), 115-126; *and* Shepherd *et al* (1995) "Prevention of coronary heart-disease with pravastatin in men with Hypercholesterolemia", *New England Journal of Medicine*, **333**(20), 1301-1307

[61] Braunwald (1997) "Shattuck Lecture – Cardiovascular medicine at the turn of the Millennium: Triumphs, concerns and opportunities", *New England Journal of Medicine*, **337**(19), 1360-1369

[62] Lenfant (2001) "Cardiovascular research: A look into tomorrow", *Circulation Research*, **88**, 253-255

[63] The human proteome is the protein equivalent of the human genome, i.e. a full map of every protein in the human body (through analysis of protein coding regions of the genome).

speculative fashion. Lenfant refers to the prospect of molecular imaging, specifically in terms of PET imaging to identify gene activation in cardiac cells.

These research themes are echoed in Lefkowitz and Willerson's 2001 "Prospects for Cardiovascular Research".[64] They identify risk factors as the first issue to deal with, arguing that current known risk factors account for only around half of all cases of cardiovascular disease. Their identification of future areas of CVD research are more clinical than those of Lenfant, and often use the basic biology advances Lenfant determines. An example of this is the use of molecular biology advances to understand the molecular basis of plaque formation in atherosclerosis. However, these research agendas are very much researcher led, rather than disease led. As the majority of CVD actually occurs in developing countries, it will become increasingly important to tailor research agendas to address problems encountered in those countries.[65]

Perhaps the most intriguing view of the future for CVD research is that espoused by the WHO as part of their Atlas of Cardiovascular Disease.[66] In it, the WHO identify potential advancements in R&D and treatment (which will rely on R&D advances). For example, they predict that by 2020, a vaccine may have been developed which switches of nicotine receptors (cutting the physical addictiveness of cigarettes). They also predict that by 2020 screening for heart disease will use an array of genetic markers; that xenotransplantation (transplantation of animal organs into humans) will be possible due to improved understanding of tissue rejection; and that nano-technology will allow intra-artery repair of atherosclerosis.

[64] Lefkowitz and Willerson (2001) "Prospects for Cardiovascular Research", *Journal of the American Medical Association*, **285**(5), 581-587

[65] For an example see: Commerford and Mayosi (2006) "An appropriate research agenda for heart disease in Africa", *The Lancet*, **367**, 1884-1885

[66] WHO (2004) Chapter 25