



STORIES OF PROGRESS:

# CARDIOVASCULAR DISEASE

## Innovating for longer and better lives

TRANSFORMING LIVES

**PRESENT DAY...**

### AKASH'S HEART DISEASE

Akash discovers he is at high risk of heart disease and manages his condition with cholesterol-lowering and anti-hypertensive drugs, while trying to limit the lifestyle factors that raise his risk.



**FORTY YEARS AGO...**

In 1968, Akash may not have been diagnosed in time to take action. Experiencing a heart attack, he would have been resuscitated with a poor understanding of the role of blood clots, and no statins, would have been treated with painkillers and monitored for abnormal heart rhythms. He then would have taken beta blockers, with the high risk of another cardiac event remaining.

**IN THE FUTURE...**

Akash hopes that digital technologies and improved understanding of biomarkers will help him to monitor his disease more closely. If he does suffer a heart attack, he hopes his heart can be fully repaired with stem cell therapy. He hopes risk factors are more readily identified and people are empowered to choose healthy diets and lifestyles.

Cardiovascular disease (CVD) includes all the diseases of the heart and circulation including coronary heart disease, angina, heart attack, congenital heart disease and stroke.

CVD was long considered an inevitable, though unfortunate, part of getting older. In the last 50 years, understanding of the interplay of various genetic, environmental and lifestyle factors have advanced considerably along with the available range of preventive medicines. While these medicines have had tremendous success saving and extending lives, CVD remains the leading cause of death worldwide today.

## KEY MILESTONES

- **1969:** First clinical implantation of a total artificial heart.
- **1970s:** Mounting evidence of the role of the major CVD risk factors (diet and blood lipids, blood pressure, and smoking) led to intensified practical approaches to prevention.
- **1971:** Aspirin's mechanism of action in its prevention of clotting was made clear, paving the way for its use as a cornerstone in antiplatelet therapy.
- **1977:** The first angiotensin-converting-enzyme inhibitor developed for the treatment of hypertension, is discovered.
- **1982:** The WHO Expert Report on Prevention of Coronary Heart Disease attempted to reduce the antagonistic aspects and emphasized complementary roles of the medical high-risk approach and the population-public health strategy of prevention.
- **1987:** The first statin, a drug lowering cholesterol in the blood, approved.
- **1991:** The first in a new class of drugs, P2Y<sub>12</sub> receptor antagonists, is approved. P2Y<sub>12</sub> receptor antagonists are antiplatelet agents that have been shown to significantly reduce the risk of cardiovascular events.
- **1999:** Lifetime risk at age 40 years of developing coronary heart disease is found to be one in two for men and one in three for women.
- **2001:** High-normal blood pressure is found to be associated with an increased risk of CVD, emphasizing the need to determine whether lowering high-normal blood pressure can reduce the risk of CVD.
- **2004:** Serum aldosterone levels are found to predict future risk of hypertension in non-hypertensive individuals.
- **2011:** Death rate from heart disease dropped 46% since 1991, thanks in part to innovative new medicines.
- **2011:** pCMV-vegfl65 is registered by The Human Stem Cells Institute in Russia as a first-in-class gene therapy drug for treatment of peripheral artery disease, including the advanced stage of critical limb ischemia.
- **2013:** World Heart Federation board adopts the United Nations and World Health Organization targets for CVD, launching the 25 x 25 campaign to reduce premature death from CVD by 25% by 2025.
- **2015:** A new class of drugs, PCSK9 inhibitors are approved. PCSK9 inhibitors are monoclonal antibodies and have been shown to dramatically lower LDL cholesterol levels when combined with a statin.
- **2017:** There are 1,400 plus products in the global CVD pipeline, of which 320 are first-in-class products that act on a novel molecular target.

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## FROM UNDERSTANDING TO MANAGING RISK

The field of study in CVD has made use of, and in many ways pioneered, long-term epidemiological studies. Observing participants in detail over a long period led to an understanding that a healthy diet, not being overweight or obese, not smoking, and regular exercise are all important in maintaining good heart health. Indeed, one of the oldest and most successful cohort studies, the Framingham Heart Study, is the origin of the term 'risk factor'.

With improved understanding of the risk factors for CVD, trials could be designed to determine whether these factors are causal. Lowering cholesterol with drugs, particularly in the Lipid Research Centers Primary Prevention Trial of the 1980s and later statin trials, demonstrated its role in atherosclerosis and paved the way for lipid modification as a medical and public health prevention strategy.

In the 1970s, the first cholesterol-lowering agent was identified by a team lead by Akira Endo. While never marketed due to adverse side effects in clinical trials, it caught the attention of MSD who would go on to identify and market lovastatin in 1987. Since then, the effect of statins on lowering cholesterol and preventing CVD has been demonstrated in numerous studies. Synthetic statins were subsequently developed, including atorvastatin, at one point the world's best-selling medication. They have extended the lives of millions of people at risk of heart attack and stroke, with minimal management: one pill a day, with limited to no side effects. Statins remain the most widely prescribed class of medications today.

It was also found that anti-hypertensive drugs could reduce the risk of heart attack and stroke. This cemented the role of high blood pressure in CVD and confirmed the pursuit of hypertension control as an effective health intervention.

In parallel to the discovery and introduction of preventive statins and anti-hypertensives, effective surgical approaches have been developed and refined. Drugs that prevent clotting and stop immune systems from rejecting transplanted organs have played a major role in improving the effectiveness of these operations. Almost all patients who receive an organ transplant must take immunosuppressant drugs.

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## CARDIOVASCULAR DISEASE TODAY: IMPROVING ACCESS THROUGH PARTNERSHIPS AND GENERIC MEDICINES

There has been measurable global progress in the prevention of CVD. So why does CVD remain the number one cause of death worldwide? In part, because people live longer. Controlling for age, the CVD death rate has declined in all high-income and some middle-income countries since 1990, although this decline has now stalled for many regions of the world. At the same time, incidence and mortality due to CVD has risen steadily in the developing world. Over three-quarters of CVD deaths take place in LMICs.

Improving access to generic medications, which typically cost significantly less than their brand-name counterparts, is one strategy available for addressing unmet health needs. With increasing availability and use, generic drugs account for almost 90% of all prescriptions in the US. Generic hypertensive and cholesterol medications

**INVESTMENT IN R+D FOR NCDs IS CRUCIAL. DISEASES SUCH AS HYPERTENSION NO LONGER AFFECT ONLY DEVELOPED COUNTRIES, THEY ARE BECOMING MORE AND MORE RELEVANT IN LOW INCOME AND LOW TO MIDDLE INCOME COUNTRIES.**

Mariângela Simão,  
WHO

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saved the US health care system almost USD 60 billion in 2016. Improving access to medicines must also be balanced with the need for investment in innovation, made possible by the patent system, as the R&D-driven biopharmaceutical industry is expected to develop the drugs of the future.

Population-wide interventions such as reducing tobacco and alcohol consumption and promoting improved diets and regular exercise have been effective in many countries and can be implemented in poorer communities. These strategies have been highlighted by organizations such as the WHO as a primary means to reduce the burden of CVD. Secondary prevention involves treatments with medication, after which surgery may be required.

Finally, joint program and company-led access initiatives are helping to address access challenges. AstraZeneca's Healthy Heart Africa is designed in consultation and collaboration with non-governmental and community-based organizations, international organizations, health experts and governments to support local health systems by increasing awareness of the symptoms and risks of hypertension and by offering education, screening, treatment and control. It aims to improve access to hypertension care and sells branded AstraZeneca medicines that are part of the program in a no-profit/no-loss business model. Since its launch in 2014 in Kenya, and 2016 in Ethiopia, it has conducted 5.7 million blood pressure screenings, trained over 5,000 healthcare workers, activated 675 healthcare facilities and identified over one million people living with high blood pressure.

Pfizer also collaborates with the international non-profit Population Services International to improve the diagnosis and treatment of hypertension, a condition that can often lead to stroke and impacts one-quarter of all adults in Myanmar and Vietnam as a leading cause of mortality. Its Healthy Communities program also provides hypertension management to underserved communities by aiming to screen more than 500,000 people and train up to 400 healthcare workers in 360 private sector health facilities.

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## **EMERGING SOLUTIONS: FROM LENGTH OF LIFE TO QUALITY OF LIFE**

Although accounting for more than 30% of global deaths, CVD research has stalled. The R&D of new cardiovascular medicines represents less than 10% of global R&D spending. There are many reasons for this, among them, the high regulatory bar, which demands 'hard' endpoints like reducing death and heart attack. The successes in the history of innovation in CVD also makes it hard to demonstrate a meaningful benefit over existing medicines. But there are promising signs this may be about to change.

Companies are looking to the successes in other areas of medicine, such as oncology, which has improved patient outcomes through precision medicine. Precision medicine allows doctors and researchers to predict more accurately which treatment and prevention strategies will work in which patients, considering their genes, environment, and lifestyle. The first hypertension gene was discovered in 1998, and while the role of genes in CVD is not well understood, it is a very promising area of



research. A precision medicine approach also means looking at biomarkers – the naturally occurring molecules, genes, or characteristics that signal particular diseases and specific pathological or physiological processes. Tracking these in a patient means that treatment can be adjusted according to their real-time development.

Improved rates of CVD survival bring new challenges. The number of people surviving a heart attack, or two or three heart attacks, has increased and there are many more people now living with very badly damaged hearts. These people are living with heart failure, which occurs when the heart is weakened and cannot pump enough blood to meet the body's needs. Despite available drugs which improve the lives of people with heart failure, it remains a debilitating condition, often significantly reducing quality of life. But recent advances have shown that certain cells in the heart play a role in its repair, so-called progenitor cells. This opens up possibilities to help damaged hearts repair themselves to restore full function.

**THE NEXT BIG PHASE OF GENETICS WILL BE INFORMATICS, BRINGING TOGETHER MASSES OF DATA AND TRYING TO UNDERSTAND HOW HUNDREDS OF SMALL GENETIC DIFFERENCES COMBINE TO PUT PEOPLE AT RISK OF A PARTICULAR DISEASE.**

**Peter Weissberg,**  
former Medical Director,  
British Heart Foundation

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CVD patients are considered an at-risk population for developing serious complications from the flu, and studies have shown that influenza is associated with an increase of heart attacks and stroke. This means that those with heart disease or who have had a stroke need to take steps to fight the flu, and as recommended by the Centers for Disease Control and Prevention (CDC), should get a flu vaccine.

Irregular heart beat (atrial fibrillation) is the most common cardiac arrhythmia. The majority of patients have non-valvular atrial fibrillation (NVAf) and the risk of stroke is five times higher in this patient population. For decades, the standard of care for NVAf required routine blood testing and frequent dose adjustments. While a risk of bleeding is associated with all oral anticoagulants, novel versions that now exist offer potential advantages over previous treatments, including fewer drug interactions and fixed doses, without the need for routine blood testing.

Researchers are targeting inflammatory pathways to prevent cardiovascular events where there is a sudden drop in blood flow to the heart. An anti-inflammatory medicine in development inhibits certain enzymes associated with the inflammation that occurs in the blood vessels during and immediately following an acute coronary syndrome event.

CVD research stands to benefit from sophisticated data-led advances that can bring to light insights from large-outcome trials that would otherwise remain hidden. Take, for example, the Novartis CANTOS trial which observed 10,000 patients over six years, showing that targeting inflammation in heart attack survivors reduces CVD risk. Similar approaches are being explored in genetics, combining huge amounts of data to uncover how small genetic differences combine to put people at risk of a particular disease. By linking population outcomes to specific genes, Amgen's deCODE discovered a gene associated with a 34% lower risk of coronary artery disease.

The establishment of large, quality patient registries has fueled large-scale real-world evidence generation, helping inform clinical debate as well as payer and regulatory decision-making. CVD-REAL is a recent example, a study of more than 700,000 patients with type-2 diabetes from registries spanning North America, Europe, Asia Pacific, and the Middle East, looking at the use of diabetes drugs and their impact on critical cardiovascular outcomes. This research reflects a growing understanding of links between cardiovascular disease and conditions such as kidney disease and diabetes, and their common underlying mechanisms.

And finally, there is huge potential for digital technologies to revolutionize prevention and care. Companies are collaborating with payers and other stakeholders to develop algorithms that can predict risk and drive early intervention. Big data, sensors and artificial intelligence open up the possibility of precise, real-time monitoring of patients – a whole new world for CVD.