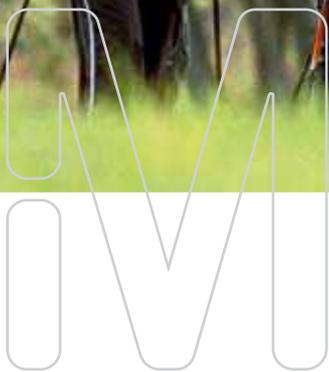
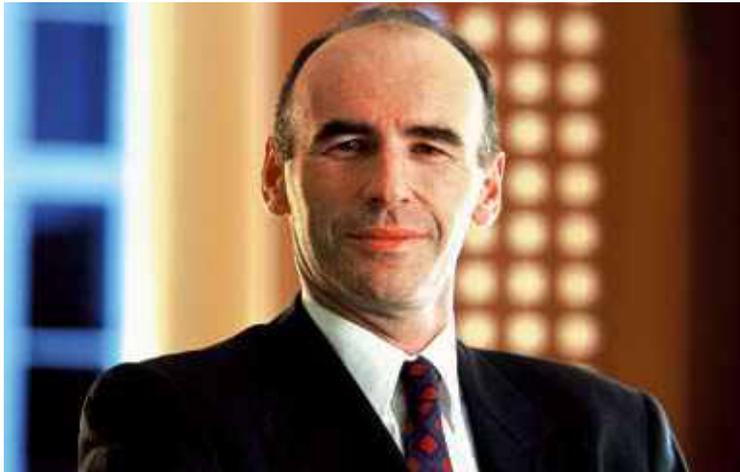


CardioMetabolic Care

Integrated management of cardiovascular and metabolic diseases



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Member of the
Executive Board of
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responsibility for the
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Dear Readers,

Health is one of the pillars of a happy life. Maintaining health and preventing disease should therefore be everyone's goal. At the same time, demographic developments and a modern lifestyle, especially in the industrialized countries, are leading to diseases of civilization such as diabetes, cardiovascular disease and thyroid disorders. The possibilities of treating these diseases, which are key therapeutic areas for Merck, are growing all the time. Innovative drugs with fewer side effects improve patient quality of life, prevent complications and increase life expectancy.

The Commercial Unit CardioMetabolic Care comprises of our range of drugs for the treatment of diabetes, cardiovascular diseases and thyroid disorders. According to the latest findings, close interrelationships exist between hypertension, lipid disorders and hyperglycemia. Physicians will be able to effectively treat these complex clinical pictures, which amount to metabolic syndrome in some patients, by adopting an integrated therapeutic approach.

As the world's oldest pharmaceutical and chemical company, Merck has a long and successful history in drug research and therapy. Our beta-blocker bisoprolol – worldwide a leading substance in its class – lowers blood pressure and reduces the strain on the heart. The results of the new CIBIS III study confirm the use of bisoprolol in a new treatment regimen for chronic heart

failure, a cardiovascular disorder that is becoming more widespread worldwide.

Metabolic disorders are affecting growing numbers of people today. They increase the risk of heart attack and stroke. Recent studies show that therapy to lower "bad" LDL cholesterol alone is not enough. In order to increase "good" HDL cholesterol, we have a nicotinic-acid-based product in our portfolio: In combination with a statin, it has been shown to halt the progression of atherosclerosis and the risk of complications.

In 2005, the International Diabetes Federation (IDF) recommended our antidiabetic agent metformin in its first ever evidence-based Global Guideline for the management of type 2 diabetes. Our drug is now the gold standard, or the "drug of choice for first-line therapy." We can look back at over one hundred years of experience with thyroid drugs. Today we rank among the top three manufacturers globally.

In our research and development work, we also apply an integrated approach that takes all aspects of a disease into account and aims for early treatment. Merck scientists work very closely with physicians, patients, research institutes and alliance partners and conduct research into the genetic origins of disease. Our integrated therapeutic approach also includes promoting healthy behaviors and strategies to prevent disease. Beyond this, we offer insights into different clinical pictures and their interrelationships as well as our therapeutic options as this brochure illustrates.

I hope you find this brochure
interesting and informative.

Elmar Schnee

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Cover photo:

Darmstadt, Germany | Walking is gentler and easier on the joints than jogging. Regular outdoor exercise has a positive impact on breathing, the cardiovascular system and physical well-being. The people depicted in this photo are members of a walking group, one of several after-work sporting activities through which Merck promotes physical fitness among its employees.

CardioMetabolic Care – an integrated approach

Physicians and patients dealing with cardiovascular diseases, diabetes and thyroid disorders have relied on Merck's products for decades. The current portfolio of products relieves disease symptoms and offers patients a better quality of life with significantly fewer complications. CardioMetabolic Care brings together Merck's arsenal of products in clinical practice around the world. In recent years, interrelationships between cardiovascular diseases, diabetes and thyroid disorders have been recognized and documented. Treating any one of these conditions in isolation is usually not adequate and a coordinated care approach in risk factor management is seen as the way forward. With its Commercial Unit CardioMetabolic Care, Merck is focusing on these disease relationships and working to leverage the expertise and competencies of its people to find better treatments in the shortest possible time. The result of such a strategy will be to advance the development of more effective therapies and innovative solutions to raise the standard of care for patients with chronic illnesses.



Rio de Janeiro, Brazil | In his free time Merck employee Celso Goncalves Bispo practices karate with his friends and his daughter Camila on Copacabana beach. Sport is part of a healthy lifestyle and promotes a general sense of well-being.

Why is an integrated approach important?

Diabetes and heart disease

Diabetes and heart disease are closely linked. Patients with diabetes are at higher risk of developing heart disease.

The frequency of heart attacks (also called myocardial infarction, or MI) is well documented in people with type 2 diabetes. Compared with non-diabetic individuals, those with diabetes are two to three times more likely to have a CV event; moreover, the proportion of people with diabetes who will die from cardiovascular causes is >70%.

OASIS, the Organization to Assess Strategies for Ischemic Syndromes, found that the risk of death for patients with diabetes and cardiovascular disease was nearly triple that for patients with neither condition.

Women with diabetes have the same risk of cardiovascular disease as men – a surprising statistic, considering that men in general have a higher incidence of cardiovascular disease than women. Diabetes cancels out this “cardiovascular gender protection” for women.

An increased risk of cardiovascular disease has also been observed in individuals who do not have overt diabetes, but who do have elevated blood glucose levels within what are considered “normal” limits – although these limits

are approaching the top end of the normal range.

Glucose tolerance has been tested in patients with no previous diagnosis of diabetes, who were admitted to hospital because of an acute heart attack. It was found that one-third of patients with heart disease had impaired glucose tolerance, or IGT, an early sign of dysglycemia, i.e. abnormal blood glucose, and a predictor of becoming diabetic.

In follow-up studies with the same group of patients, it was also shown that glucose tolerance was the primary predictor of future cardiovascular events.

Metabolic syndrome

Epidemiological studies have clearly shown that diabetes is not only associated with heart disease, but is also frequently combined with other cardiovascular risk factors, such as dyslipidemia, high blood pressure, obesity and a procoagulation state. This “clustering” of risk factors has been recognized as a predictor of diabetic or cardiovascular complications and is now referred to as metabolic syndrome. Several definitions of metabolic syndrome can currently be found in publications and clinical trials. The guidelines recommended by the USA National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) were designed for use in the standard clinical setting. An individual is diagnosed with metabolic syndrome when three or more of the following risk factors are present:

Risk factors for metabolic syndrome

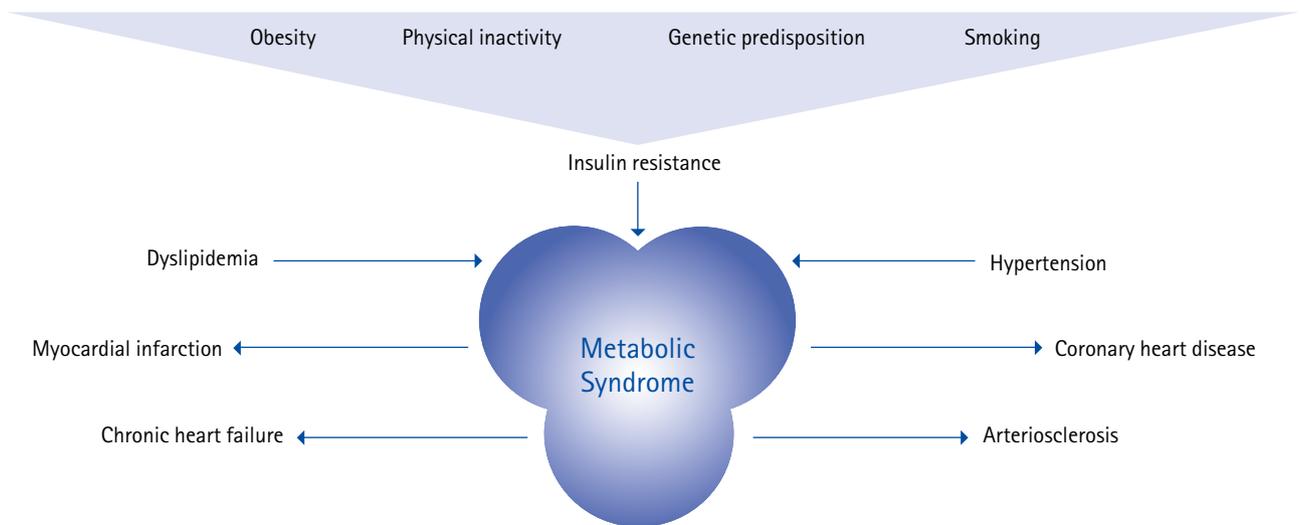
- Waist circumference exceeding 88 cm (35 ¼ inches) for women, or 102 cm (40 ¾ inches) for men.
- Triglycerides at or exceeding 1.70 mmol/L or 150 mg/dL.
- HDL cholesterol less than or equal to 1.30 mmol/L or 50 mg/dl for women, or 1.00 mmol/L or 40 mg/dL for men.
- Blood pressure at or exceeding 130/85 mm Hg.
- Fasting glucose at or exceeding 6.1 mmol/L or 110 mg/dL (recently reduced to a cutoff point of 5.6 mmol/L or 100 mg/dL by the American Diabetes Association).

Abdominal obesity is thought to play a role in triggering metabolic syndrome. Adipose tissue – fat – used to be disregarded as just an inactive form of stored energy for the body. Its effect on other systems in the body – including cardiovascular, glucose metabolism, lipid levels and blood pressure – has recently become better understood and recognized.

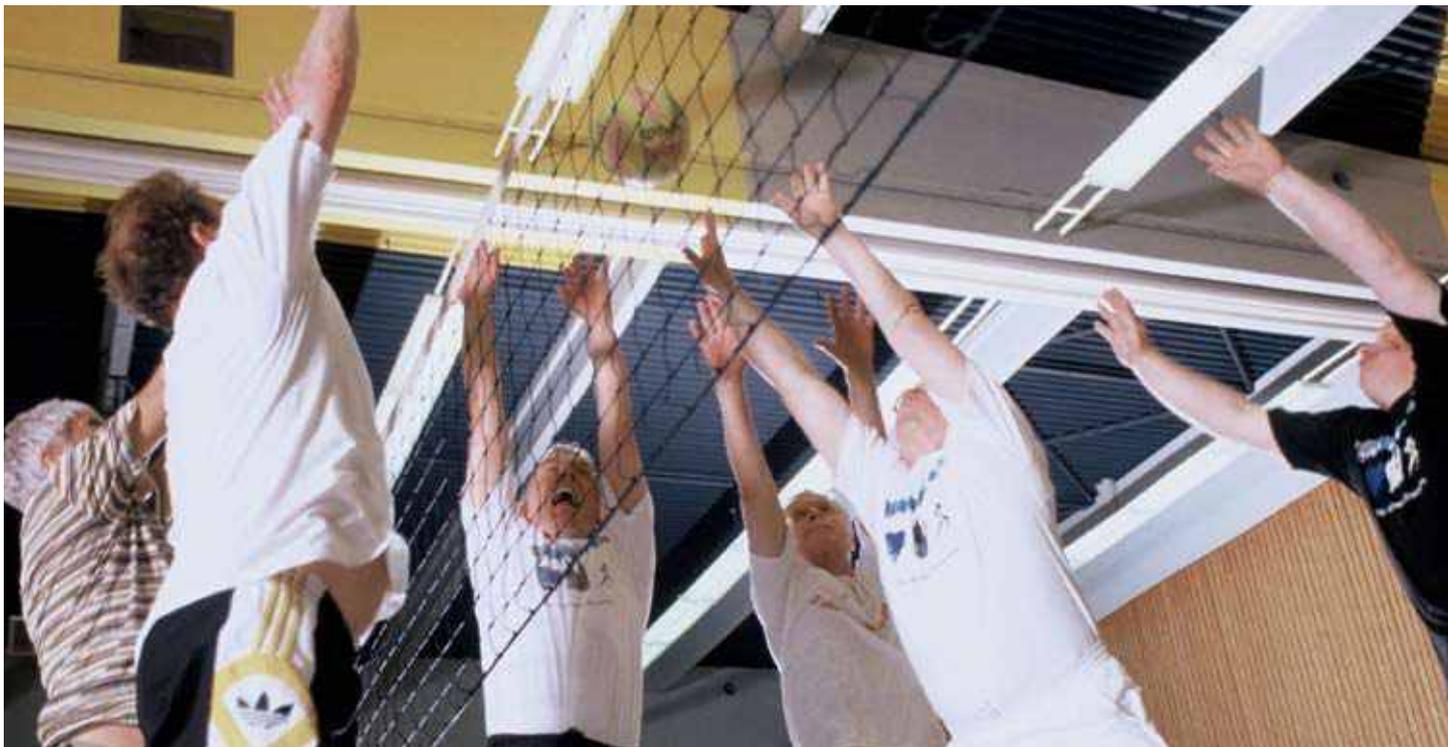
Adipose tissue, and particularly abdominal fat, releases free fatty acids (FFA) into the bloodstream. Normally, FFA release is inhibited by insulin, but the adipose tissue in the deepest part of the abdomen is less sensitive to insulin. FFA release from abdominal fat is a relatively constant metabolic process, which is why abdominal fat is considered to be metabolically active tissue. The term “metabolic syndrome” is a reference to this metabolic activity. High levels of FFA in the blood are associated with elevated blood glucose and insulin resistance.

The risk of heart attack increases with waist circumference, does as the risk of dying from heart attack.

In response to these observations, an integrated approach to correct all forms of risk is urgently needed. Intensive treatment approaches that include behavior modification and medications to control blood sugar, blood pressure and lipid profiles, along with aspirin therapy, have been shown to reduce non-fatal heart attacks, coronary artery bypass surgery, non-fatal stroke, amputation, and vascular surgery by at least 50%, compared with conventional therapy for diabetes.



Metabolic syndrome | is a clustering in one individual of three major groups of risk factors for cardiovascular disease: dyslipidemia, insulin resistance and hypertension. It is mostly triggered by a pre-diabetic state. Obesity, family history, and lack of exercise are risk factors for the disease. An integrated treatment approach considers the different factors and characteristics of metabolic syndrome.



Cologne, Germany | There is no shortage of fun at the weekly training sessions of the cardiac health sports group: The joint volleyball game is very popular among the participants.

Thyroid disorders, diabetes and cardiovascular disease

Thyroid disorders are closely associated with both diabetes and cardiovascular disease. The heart is very sensitive to circulating levels of thyroid hormones. Heart muscle cells contain receptors for thyroid hormones, so cardiac function is influenced by too many or too few thyroid hormones.

When thyroid hormone levels are deficient – hypothyroidism – the heart rate is often slowed. Although the heart may function normally for a while, prolonged or more severe deficiency in hormone levels leads to deterioration in cardiac function. In some patients with pre-existing heart disease, hypothyroidism can exacerbate the underlying heart condition, occasionally leading to shortness of breath, or rarely, congestive heart failure. In such patients, treatment with thyroid hormones may improve several parameters of cardiac function after a few weeks of treatment.

Rapid or irregular heartbeat are common complaints in patients with increased thyroid hormones – hyperthyroidism. In some older patients, hyperthyroidism can affect the sinus node, the heart's natural pacemaker, in such a way that atrial fibrillation occurs. The result is an abnormal

heart rhythm that can fluctuate between a pulse rate (heart beat) that is either too slow or too fast. It is often difficult to maintain the heart in normal rhythm until the hyperthyroidism is brought under control.

In patients with type 2 diabetes, thyroid disorders are two- to five-fold more frequent than among the general population. What are some of the underlying mechanisms that can account for this correlation?

In type 2 diabetes, tissues (particularly liver, muscle and fat) become resistant to insulin produced in the beta cells of the pancreas: As a result, glucose in the blood exceeds normal limits (hyperglycemia).

Excess thyroid hormones also cause blood sugar levels to rise, because of increased insulin resistance. Hyperthyroidism can thus mask underlying type 2 diabetes and vice versa, which complicates both diagnosis and treatment.

Type 2 diabetes is often associated with increased levels of serum triglycerides and cholesterol, particularly low-density lipoprotein (LDL). If a patient with type 2 diabetes has diminishing thyroid hormone levels, e.g. subclinical

hypothyroidism, this can lead to an increased risk of cardiovascular disease.

Correcting thyroid hormone levels in diabetic patients needs to be done cautiously and slowly. Too little or too much hormone can result in both abnormal cardiovascular function and impaired glucose metabolism. Adjustments in other medications might be necessary to ensure that all patients with disorders of the thyroid and heart, or diabetes, are appropriately managed.

As these examples illustrate, a comprehensive understanding of the underlying pathologies and interrelationships between cardiovascular disease, diabetes and thyroid disorders are critical to the development of effective therapies to raise standards of care for patients worldwide. CardioMetabolic Care brings together a team of experts, competent in related disciplines, to help advance Merck's commitment to better health for patients with chronic disabling illnesses.

CardioMetabolic Care – providing better care for patients

- by raising standards of care for people with cardiovascular disease, diabetes and thyroid disorders.
- by delivering solutions to improve the quality of life and life expectancy of patients.
- by accelerating the realization of medical innovations of the future.
- by strengthening synergies through a new strategy and structure.



Darmstadt, Germany | Wilfried H. Meyer discusses with his team proposals for communicating the concept of integrated treatment. Isabella Schmele, Mechthild Auge and Luc Duval are members of Merck's international CardioMetabolic Care team.

Widespread diseases

that affect many people

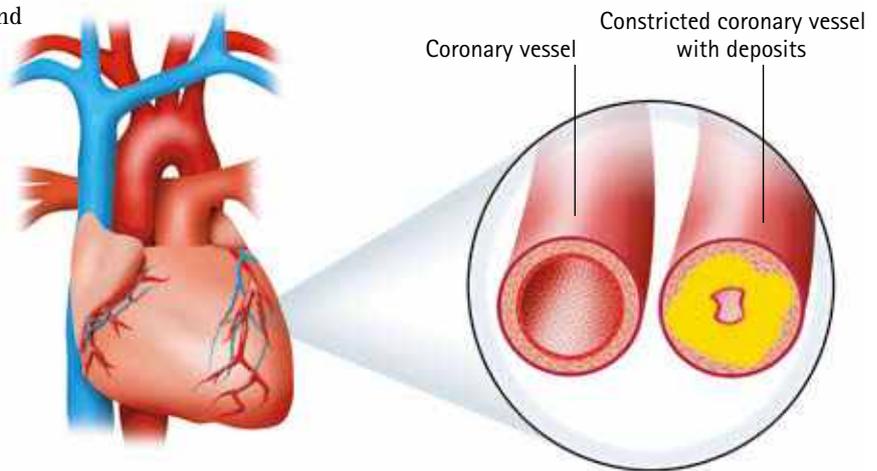
We have looked at the association between cardiovascular disease, diabetes and thyroid disorders to explain the benefits of the integrated treatment strategy behind CardioMetabolic Care. Let us now turn to the magnitude of the impact these disorders have worldwide. Later, we will look at the types of medication available to treat each disorder and how they work.

Cardiovascular disease – the number one killer

Cardiovascular disease (CVD) is a collective name for disorders affecting the heart and blood vessels.

The most common CVD complications and life-threatening conditions are:

- **Coronary heart disease** – narrowing of the arteries that supply the heart with blood. Atherosclerosis, where plaque builds up on the inside wall of arteries, is the main cause. Coronary artery disease contributes to other cardiovascular diseases, including angina pectoris, heart attack, heart failure and stroke.
- **Heart attack** – acute interruption of blood supply to the heart muscle that occurs when one or more coronary arteries become blocked (also called myocardial infarction, or MI).
- **Stroke** – reversible or irreversible damage to nerve cells in the brain caused by lack of oxygen. Damage can occur from lack of oxygen when vessels are clogged, or from accumulation of blood from bleeding vessels.
- **Hypertension** – elevated blood pressure.
- **Peripheral vascular disease** – narrowing of the arteries leading away from the heart, usually in the legs, lower arms, or hands.
- **Chronic heart failure** – a complex clinical syndrome



Deposits | narrow the coronary vessels and inhibit the circulation of the blood. The occlusion of a vessel in the heart finally leads to myocardial infarction.

where the heart is unable to pump a sufficient amount of blood to the periphery.

- **Angina pectoris** – chest pain resulting from inadequate delivery of oxygen to the heart.
- **Arrhythmia** – any change in the normal rhythm of the heartbeat.



Darmstadt, Germany | Rainer Kohl, Tristan Allaire and Katrin Peschk work in the field of medicinal chemistry. They perform syntheses of new active ingredients quickly and efficiently in the microwave.

Cardiovascular disease (CVD) is driven by the presence of cardiovascular risk. The most important risk factors are: high blood pressure, diabetes mellitus, dyslipidemia and smoking.

Worldwide, CVD is responsible for one in every three deaths, irrespective of geographic, gender or socio-economic boundaries. By 2020, the World Health Organization (WHO) estimates that CVD deaths will rise to nearly 25 million worldwide, or almost half of all deaths.

There is a major trend toward urbanization and industrialization in developing countries. These shifts in population distribution and economic output are accompanied by lifestyle changes that increase the risk of coronary heart disease: increased tobacco use, decreased physical activity, and diets higher in carbohydrates and fats. In developed countries, these risk factors are already prevalent among lower income groups, who also have a higher incidence of CVD. As developing countries mature economically, it is predicted that the burden of CVD will also shift to lower socio-economic groups.

CVD disrupts not only the lives of individuals, but also entire families that depend on them. Clinical care of CVD is costly and prolonged and there are still some deficiencies in both diagnosis and treatment of CVD.

CVD – facts and figures:

- Approximately 17 million people around the globe die of CVD each year.
- In 2001, CVD contributed to nearly one-third of global deaths. Low- and middle-income countries accounted for 85% of CVD deaths.
- According to WHO estimates, by 2010, CVD is expected to be the leading cause of death in developing countries.
- The most rapidly growing CVD is chronic heart failure. Nearly one million new cases are diagnosed each year worldwide. Mortality associated with chronic heart failure is also high, with an overall survival rate far lower than for many forms of cancer.

Controllable risk factors

- **Obesity** – A body mass index (BMI) of 30.0 or higher increases the risk.
- **Salt intake** – Keeping salt to < 6 grams per day is recommended to avoid the risk.
- **Alcohol consumption and smoking** – To avoid risk, no more than 1-2 drinks per day should be consumed; smoking is not advisable.
- **Stress** – Hard to measure, but high stress levels contribute to high blood pressure.
- **Low physical activity** – Even moderate activities – walking, gardening, housework or climbing stairs – can be beneficial. Of course, more vigorous activities – cycling, jogging, swimming – are best for improving the fitness of the heart and lungs.

Uncontrollable risk factors

- **Heredity** – Having parents or close relatives with high blood pressure increases the risk.
- **Age and gender** – In general, the risk increases with age – for women in particular after menopause. Men are at a greater overall risk than women.

Hypertension – the silent killer

Blood pressure is used as an indicator of the movement of blood through the blood vessels to supply the vital organs with oxygen and nutrients. Blood leaves the heart through the arteries, which supply oxygen to all the organs and tissues of the body, and returns to the heart through the veins to be re-oxygenated in the lungs. Certain nerve impulses cause the arteries to dilate (become larger) or contract (become smaller). Blood pressure is lower when the arteries are dilated and higher when they contract.

Hypertension, or high blood pressure, is a condition that develops when arteries persistently remain constricted. The heart, kidney and brain are most sensitive to changes in blood pressure. Hypertension is a significant cause of stroke, heart attack and kidney failure. Adequate treatment of hypertension can prevent stroke and chronic heart failure.

The heart, brain and kidneys can continue to function normally for a long time, despite increased pressure. That is why some people live for years without any symptoms or ill effects and why high blood pressure is called “the silent killer”.

In 90 to 95% of high blood pressure cases, the cause is unknown. Even though the exact causes of most cases of high blood pressure are not really understood, there are several known factors that may contribute to high blood pressure and lead to an increased risk of heart attack and stroke.



Mumbai, India | Cardiologist Behram S. Pardiwalla from Breach Candy Hospital is one of the city's best-known doctors. At a meeting with the sales representatives Prakash D. Banavalikar and Manish D. Mukkavar, he discusses new treatment strategies.

Hypertension – facts and figures:

- The WHO estimates that 600 million people (10% of adults) with high blood pressure are at risk of heart attacks, stroke and cardiac failure.
- About 15-40% of the adult population has hypertension. In those older than 60, as many as one-half are hypertensive.
- High blood pressure is estimated to cause about 13% of deaths worldwide.
- Only half of the estimated 600 million people worldwide who have high blood pressure are diagnosed. Half of known cases remain untreated and blood pressure levels for half of those on treatment are poorly controlled.

Lipid disorders – inherited susceptibilities, worsened by modern lifestyle

Lipids are fatty substances in food that are delivered to the body via the bloodstream. Forms of lipids in the blood are cholesterol, triglycerides, and lipoproteins (molecules of fat and cholesterol linked to protein). Lipoproteins fall into two major categories: low-density lipoproteins (LDL) and high-density lipoproteins (HDL).

Lipids are ingested as food, but the body also produces them. Most people have elevated levels of total cholesterol and LDL because of genetic factors they inherited (on the right), but imbalances can be exacerbated by lifestyle factors: high-fat/high-cholesterol diet, lack of physical activity, minimal intake of fruit and vegetables. Excessive alcohol consumption and stress can also raise lipid levels. The composition of lipids in the bloodstream is also affected by age and gender. More than 182 million people in Europe and about 106 million in the United States suffer from lipid disorders.

Apart from elevated levels of total cholesterol and “bad” LDL, more and more patients also have insufficient levels of “good” HDL, which often remains unrecognized. A recent pan-European study involving more than 8,500 patients from 11 countries revealed that 33% of the men and 40% of the women had insufficient HDL levels (see

Inherited disorder	Lipid(s) affected
Familial hypertriglyceridemia [1 in 300]	▲ VLDL ▲ Triglycerides
Polygenic hypercholesterolemia [1 in 300]	▲ VLDL and LDL ▼ HDL
Familial dysbetalipoproteinemia [1 in 500]	▲ Large particles of cholesterol and triglycerides
Familial hypercholesterolemia [1 in 500]	▲ LDL ▲ Cholesterol
Familial combined hyperlipidemia [1-2%]	▲ VLDL and LDL ▼ HDL
Familial hypoalphalipoproteinemia [very rare]	▼ HDL ▼ Cholesterol transport to liver

Type of lipid	Normal role in the body	Normal level (US/EU)	Complications resulting from abnormal levels
Cholesterol	Formation of cell membranes, building block of hormones	< 200 mg/dL or < 5.2 mmol/L	<ul style="list-style-type: none"> • Coronary artery disease • Peripheral vascular disease • Stroke
Triglycerides	Energy forming much of the fat stored by the body	< 150 mg/dL or < 1.7 mmol/L	
LDL	Carries cholesterol from the liver to cells in the body	< 100 mg/dL or < 2.6 mmol/L	
HDL	Transports cholesterol away from peripheral tissue and back to the liver	> 40 mg/dL or > 1.0 mmol/L 	
Lp(a)	LDL with protein apo(a) which accelerates angiogenesis	> 50 mg/dL or > 1.3 mmol/L  < 30 mg/dL	

table on page 12 for normal levels), although these patients had been treated by their doctors for lipid disorders.

Lipid disorders are usually detected during the course of diagnosing or treating other medical conditions, such as heart attack, stroke, coronary heart disease, diabetes, underactive thyroid, overactive pituitary, liver disease or kidney failure.

High cholesterol is strongly associated with coronary heart disease. According to the British Heart Foundation, 46% of people under the age of 75 who die from coronary heart disease have high blood cholesterol. In 2004, the INTERHEART case-control study estimated that 45% of heart attacks in western Europe and 35% of heart attacks in central and eastern Europe are due to abnormal blood

lipids, and that those with abnormal lipids are at over three times the risk of a heart attack compared those with normal lipids. It is estimated that 18% of men and 16% of women have blood cholesterol levels that put them at high risk for coronary heart disease.

Lipid disorders are a major underlying factor for cardiovascular diseases and are frequently associated with other “at risk” conditions (i.e. diabetes and thyroid disorders). The best way to ensure an optimum balance of lipids is to eat a well-balanced diet and limit the intake of saturated fats. Regular exercise helps to elevate HDL and lower LDL levels. However, genetic predisposition can make medication necessary in addition to diet and exercise therapy to achieve normal lipid levels.



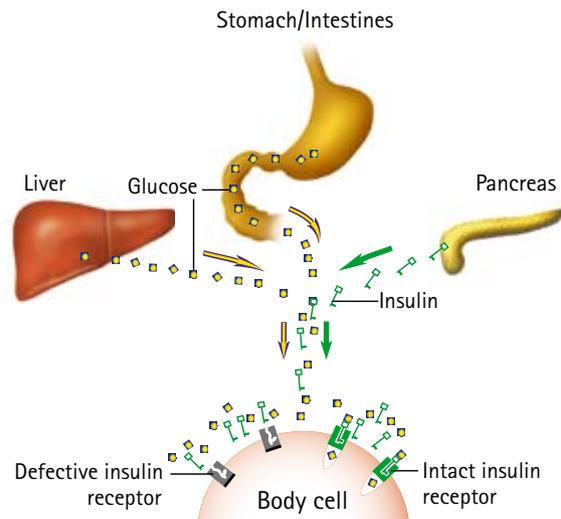
London, United Kingdom | Dr. Verander Winayak with Angie Searer in his practice: She is presenting Merck's nicotinic acid-based HDL raiser to him. A growing number of people suffer from lipid disorders and only a fraction of them receive adequate treatment. As a result, the risk of cardiovascular diseases is on the rise.

Type 2 diabetes – a global problem

Type 2 diabetes (previously called non-insulin-dependent diabetes, adult-onset diabetes, or maturity-onset diabetes) is a condition where the pancreas is deficient in producing insulin and the body cannot effectively use the insulin it produces.

When the body is unable to use insulin, the result is higher levels of glucose in the blood. As the ability to use insulin declines (resistance to insulin increases), a pre-diabetic condition known as impaired glucose tolerance (IGT) develops. About one-third of people with IGT go on to develop type 2 diabetes. The International Diabetes Federation's estimate that only 50% of people with diabetes are aware of their condition is alarming. In some countries, this figure may rise to 80%. The percentages are even higher for IGT. However, individuals diagnosed with IGT who increase their physical activity and improve their diet can prevent or significantly delay the progression to diabetes. Therefore, improved detection of IGT, followed by lifestyle modifications and/or medication, has the potential to significantly lower the incidence of type 2 diabetes. Some pharmacotherapies, such as metformin and acarbose, have shown potential to delay the onset of diabetes.

The incidence of diabetes increases with age; however the disease now affects younger and younger age groups. There is a direct correlation between obesity and the incidence of type 2 diabetes in young people. Obesity among children is on the rise worldwide and so, too, is type 2 diabetes. Obesity is now the most common nutritional disorder in children in the United States, and other countries are following suit. Diets worldwide are changing from natural ingredients like cereals, fruit and vegetables, toward processed and fast food. Physical exercise is also decreasing. Diabetes and its complications, including cardiovascular disease, eye complications, non-traumatic



Type 2 diabetes | Insulin is produced by the beta cells of the pancreas. Its main function is to transport glucose into body cells. Like a key and lock, insulin fits into its receptor and opens the way for glucose to enter the cell. Patients with type 2 diabetes have defective insulin receptors, so glucose is not absorbed into cells.

amputation and kidney failure, are a major burden on healthcare systems. The economic burden of diabetes is significant: Direct costs in 2002 were estimated at U.S.\$ 225 billion worldwide. The EU and the United States spent U.S.\$ 70 billion and U.S.\$ 82 billion respectively – approximately 12% of their healthcare budgets.

Diabetes – facts and figures:

- According to the International Diabetes Federation, there are currently more than 230 million people with diabetes worldwide. The IDF estimates that this number will increase to 350 million by 2025 if nothing is done to slow the epidemic.
- In 2003, the five countries with the largest numbers of diabetes sufferers were India (35 million), China (23 million), the United States (16 million), Russia (10 million) and Japan (7 million). According to data published more recently, China now tops the list with 39 million people who have diabetes.
- According to estimates, the prevalence of diabetes in developing countries is expected to increase at a much faster rate than in developed countries.

Hypothyroidism – an under-recognized disease

Hypothyroidism refers to any state in which thyroid hormone production is below normal. Thyroid hormones affect growth, development and many cellular processes, thus insufficient thyroid hormones have widespread consequences for the body.

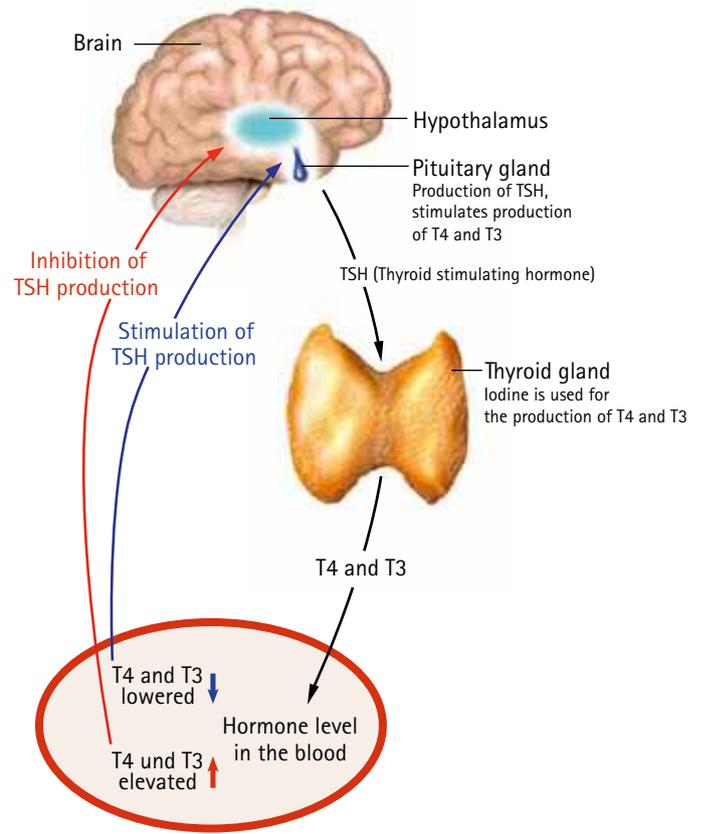
Iodine (mostly available from the diet in foods such as seafood, bread and iodized salt) is used to produce thyroid hormones. The two most important hormones are thyroxine (T4) and triiodothyronine (T3). T3 is produced from T4 as needed.

The thyroid is regulated by the pituitary gland, which steers thyroid hormone production like a sensor via a feedback control mechanism. If too few thyroid hormones are produced (hypothyroidism), the pituitary stimulates production. If too many thyroid hormones are in the bloodstream (hyperthyroidism), the pituitary shuts down production by decreasing TSH (thyroid stimulating hormone).

Hypothyroidism is a very common condition. Estimates are that 3 to 5% of the general population has some form of hypothyroidism. It is more common in women than men and increases with age. Hypothyroidism is observed in conjunction with other disorders, such as cholesterol imbalance, diabetes, and heart disease.

Subclinical hypothyroidism, i.e. the state in which patients do not exhibit the symptoms of hypothyroidism, is receiving increased attention and focus from the medical community. However, the role of subclinical hypothyroidism in abnormal lipid profiles and cardiovascular disease is a subject of much debate.

The symptoms of hypothyroidism are subtle. They are not specific (which means they can mimic the symptoms of many other conditions) and are often attributed to “normal” aging. The majority of patient complaints are related to a slowing of the body’s metabolism. Once diagnosed, treatment requires hormone replacement therapy – usually life-long.



Thyroid hormones are produced by the thyroid gland using iodine. The hormones are thyroxine (T4) and triiodothyronine (T3). T3, as the active hormone, affects the metabolism of cells, while T4 is the circulating “pool” that is converted to T3 as needed. The pituitary gland, located in the brain, regulates thyroid hormone circulation.

CardioMetabolic Care – putting it all together

Merck is recognized for its expertise in cardiovascular disease, diabetes, lipid and thyroid disorders. By bringing together the individual indications in the Commercial Unit CardioMetabolic Care, Merck is pursuing a strategy that will benefit our customers, physicians and patients alike. The integration of our activities, from research to ultimately making the product available to the patient, will help to sharpen the focus on patients in various disease states.

The team working in CardioMetabolic Care sees its challenge and purpose in improving the quality of life of patients with chronic illnesses. This is a long-term goal and one that we are proud of.

Treatment strategies

We have looked at the causes and worldwide impact of cardiovascular disease, hypertension, diabetes, lipid and thyroid disorders. Now, our focus will switch to the treatment strategies available to protect the health and quality of life of patients with one or more of these conditions.

Managing cardiovascular disease

Cardiac output, peripheral resistance and blood volume – a triad of cardiovascular function

The heart's job is to circulate blood and supply oxygen to cells throughout the body. Three major systems function together to successfully keep the body supplied with oxygen:

- **The heart** – measured as the quantity of blood pumped, or cardiac output.
- **The elasticity of blood vessels** (opening and closing) – measured as blood pressure, or peripheral resistance.
- **The kidneys** – measured as blood volume and electrolyte balance of the bloodstream.

A change in any one of these systems has an effect on the others. To illustrate this, we will look at one pathway important for controlling blood pressure – the sympathetic nervous system.

Sympathetic nerves communicate by releasing transmitters, small proteins that travel across the space between two nerve cells and bind to a receptor, a type of “docking” station for the transmitter. When a transmitter binds to a receptor, it triggers its activity, just like a light switch turns on a light.

One very important transmitter/receptor system consists of the transmitters noradrenaline and adrenaline and receptors called adrenoceptors, of which there are two major types: α and β . When α -adrenoceptors are turned on, they cause blood vessels to narrow, increasing the peripheral resistance, which causes a rise in blood pressure. When β -adrenoceptors are turned on, cardiac output is

increased (also increasing blood pressure).

The angiotensin converting enzyme (ACE) leads to an increased formation of angiotensin II in the bloodstream. Angiotensin II is very effective at contracting blood vessels, which increases peripheral resistance and causes the kidneys to retain salt in the body. These effects of angiotensin II increase blood volume. Increased peripheral resistance and increased blood volume both lead to increased blood pressure.

In a healthy person, these effects are temporary and blood pressure reverts to normal levels on its own. However, in people with chronic hypertension, something prevents this “vicious cycle” from returning blood pressure levels to normal without assistance, either from lifestyle changes, medication, or both.

Different treatment strategies

Cardiovascular medications that are used alone or in combination with other medications target these three major systems: Beta-blockers “block” the β -adrenoceptors so noradrenaline and adrenaline cannot exert their effects; ACE inhibitors decrease the production of angiotensin II; diuretics work to decrease the overall level of fluid and salt in the body and thus reduce the blood volume. A reduction in fluid is also linked to a decrease in cardiac output. The widely used calcium antagonists mainly lead to the dilatation of blood vessels. Each type of medication targets a component in order to keep the overall function of the cardiovascular triad in balance.

Bisoprolol – targeting β_1 -adrenoceptors

Cardiovascular disease often begins years before its symptoms emerge. Beta-blockers are a core component for treat-



ing a wide range of cardiovascular disorders. The benefits of administering beta-blockers to patients with chronic heart failure have also been proven.

Bisoprolol has been administered for cardiovascular disorders (e.g. high blood pressure and angina pectoris) for several decades. Alone, or in combination with other drugs, bisoprolol has proven effective for relieving various symptoms (e.g. it improves blood flow to the heart muscle by reducing heartbeat rate and can thus also help to relieve related chest pain) and for treating high blood pressure. It has improved quality of life for thousands of patients and continues to be a mainstay of treatment strategies.

Bisoprolol's mechanism of action is quite specific to the β_1 -adrenoreceptor. This has several advantages for hypertensive patients and angina patients, especially those with

concomitant diseases such as diabetes and lipid disorders. In addition, bisoprolol has effects beyond that of simply controlling blood pressure. Other positive benefits of bisoprolol include:

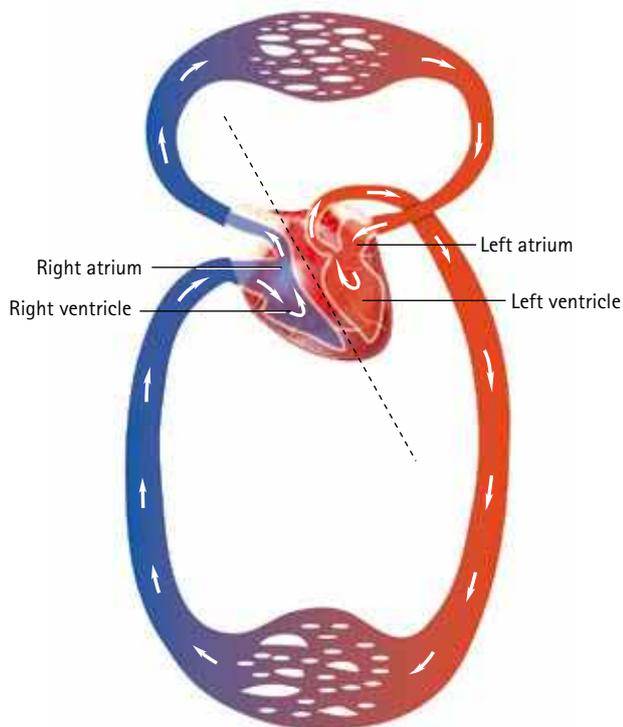
- Maintaining better oxygen levels in cardiac and other tissues
- Cardioprotective effects
- Reducing heart enlargement
- Slowing the heart rate and increasing pumping/antiischemic efficacy
- Survival benefits in chronic heart failure patients.

Let us look at some of the ways bisoprolol is used to benefit patients with various cardiovascular disorders.

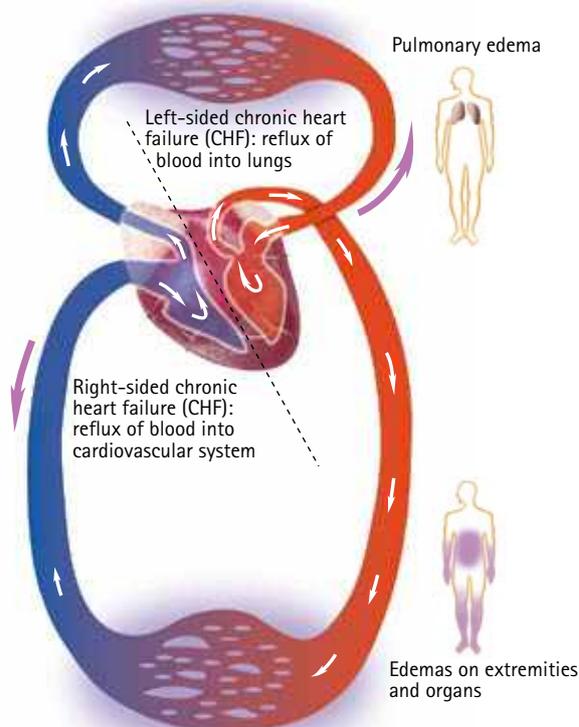


Darmstadt, Germany | Sandro Monteleone and Ugur Aytac inspect a packing machine: Our beta-blocker bisoprolol is put into in blister packs here.

Cardiovascular system of a healthy heart



Cardiovascular system of a weak heart



Chronic heart failure | can occur on one or both sides of the heart. If the left side fails, fluid accumulates in the lungs. If the right side fails, fluid accumulates in the body, usually in the lower legs and abdominal area, the liver being the organ most often affected.

Treating coronary artery disease, angina pectoris and heart attack

Coronary artery disease (CAD) results when the internal diameter of the blood vessels is narrowed, most commonly from atherosclerosis buildup (plaques containing cholesterol that stick to the inside wall of blood vessels). Patients with CAD are at high risk of heart attack and angina pectoris.

Patients with coronary artery disease can experience uncomfortable pressure, fullness, squeezing or pain in the center of the chest. Discomfort may also be felt in the neck, jaw, shoulder, back or arm. These symptoms of coronary artery disease are called angina pectoris and occur when the heart muscle becomes starved of oxygen (ischemia). Taken on a regular basis, beta-blockers such as bisoprolol reduce the heart's workload, and thus the oxygen demand, preventing chest pain. As a result, the frequency of angina pectoris attacks decreases and patients can tolerate a greater amount of physical activity. Beta-blockers can

be used alone (as monotherapy), but are also appropriate for combination therapy in conjunction with other agents, such as calcium antagonists or nitrates.

Patients with coronary artery disease can also have pain-free incidents, where the heart becomes temporarily starved of oxygen ("silent ischemia"). However, this condition is associated with a high risk of myocardial infarction or death. To be effective, a beta-blocker should reduce the total ischemic burden – the total period of time the heart muscle is starved of oxygen. Bisoprolol reduces the total ischemic burden in patients with coronary artery disease, and also markedly reduces the number of ischemic incidents (with or without pain).

Bisoprolol also plays an important role for patients who have suffered a heart attack (also called myocardial infarction, or MI). These patients are at high risk of suffering another heart attack, heart failure or sudden death due

to fatal arrhythmias. The use of beta-blockers in post-MI patients, regardless of whether they have hypertension, reduces mortality by about 25%. Current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines recommend that beta-blockers be used long term in all patients after MI, providing they have no contraindications to therapy.

Chronic heart failure – combining beta-blocker with ACE inhibitor and diuretic

The story of bisoprolol in chronic heart failure (CHF) is also the story of a revolution in modern cardiology. In the past, beta-blockers were contraindicated in CHF. The think-

Bisoprolol: Benefiting patients with CHF

Cardiac Insufficiency Bisoprolol Studies (CIBIS)

CIBIS

First study of 641 patients with chronic heart failure who not only received an ACE inhibitor and diuretic, but also the beta-blocker bisoprolol (320 patients).

- Trend toward lower overall mortality
- Significant mortality reduction in specific subgroups

The conclusion was that patients did benefit from the addition of beta-blockers and these results helped to get CIBIS II started.

CIBIS II

Study demonstrating that the addition of bisoprolol to standard therapy for chronic heart failure reduced:

- Mortality by 34%
- Sudden death by 44%
- All-cause hospital admission by 20%
- Hospitalization due to worsening CHF by 36%.

Economic analysis showed that, by reducing hospitalization costs, bisoprolol reduced the costs of care by 5-10%.

CIBIS III

This study compared the efficacy and safety of two treatment regimens. Treatment was started either with bisoprolol or an ACE inhibitor, followed by a combination of both.

Mortality and the frequency of hospitalizations were comparable in both treatment groups. In addition, there was a higher reduction in mortality among those patients who were treated first with bisoprolol in the first treatment year, which was probably due to a reduction in the number of cases of sudden cardiac death.

At present, guidelines indicate that treatment of patients with heart failure already stabilized on diuretics should be started with an ACE inhibitor followed by the addition of a beta-blocker. However, this order is determined only by the "history" of the studies conducted in CHF and is now being re-evaluated in light of the results of CIBIS III.

ing was that their mechanism of action (reducing cardiac output and lowering blood pressure) would exaggerate the symptoms of heart failure. At that time, standard treatments (diuretics and glycosides) alleviated the symptoms of CHF, but provided no benefit in terms of survival. Today, however, beta-blockers are recommended as standard treatment for CHF after several large-scale studies (e.g. CIBIS II/III) demonstrated reductions in mortality. Adding beta-blockers such as bisoprolol to combination therapies (ACE inhibitors and diuretics) has been one of the most important advances in CHF treatment in recent years.

The challenge today is to communicate the results of these large-scale studies and to ensure that patients with CHF are receiving the benefits that beta-blockers can bring. The Commercial Unit CardioMetabolic Care is committed to supporting both research and communication in these areas.

Hypertension treatment – combining beta-blocker and diuretic to lower blood pressure

Diuretics and beta-receptor blocking drugs have been a favored first-line treatment for patients with high blood pressure when lifestyle changes have proven to be ineffective.

Diuretics and beta-blockers are an excellent combination for treating hypertension, because together they can lower blood pressure more effectively than when either drug is used alone. Diuretics mainly affect blood volume; it is not completely understood how beta-blockers work to lower blood pressure. However, the effectiveness of combining a beta-blocker – such as bisoprolol – with a diuretic in lowering blood pressure is well established.



Billerica (MA), United States | Healthy eating, regular exercise and weight loss reduce the risk of diabetes and cardiovascular diseases. Patients on drug therapy are well advised to follow these lifestyle rules..

We have seen how bisoprolol fits into a comprehensive regimen for treating a variety of cardiovascular diseases and hypertension. Now we will look at other medications in the CardioMetabolic Care cardiovascular product line.

Nicorandil – improving angina outcomes

Angina pectoris is usually a symptom of coronary artery disease. In stable angina, chest pains are predictable, such as during exercise or stress, and relief is achieved via rest or medication. Unstable angina is unpredictable – often

occurring during rest – and represents an acute cardiac emergency with an increased risk of heart attack, arrhythmia, or sudden cardiac death.

Since its launch in Japan (1984) and Europe (1994), nicorandil has significantly improved the outcome for patients with chronic stable angina. One study (IONA) involving more than 5,000 patients showed that nicorandil improved prognosis and significantly reduced angina symptoms, chronic heart disease deaths, non-fatal MI and unplanned hospitalization due to chest pain.

Naftidrofuryl – improving quality of life in peripheral vascular disease

Peripheral vascular disease (PVD) occurs when circulation in blood vessels outside the heart and brain is slowed by constriction. Intermittent claudication, or cramping in the legs (usually calves), is the most common symptom of PVD. It is usually brought on by walking and relieved by rest. Blocked arteries deliver less oxygen and nutrients to muscles and are less effective at removing waste products from muscles. Pain from intermittent claudication can reduce functional independence and lower quality of life. PVD also increases the risk of heart attack or stroke from blood clots breaking free from the inside of damaged arteries.

Naftidrofuryl provides relief from the pain of intermittent claudication by decreasing the constriction of damaged arteries and reducing the build-up of waste products in muscles during exertion. With naftidrofuryl, PVD patients can walk farther without pain (NCIS study) and their quality of life is enhanced (NIQOL study).

Managing dyslipidemia

Statins – lowering LDL, the primary target

Lowering high levels of “bad” cholesterol (LDL-C) is the primary target of lipid management. In this regard, statins (e.g. lovastatin, atorvastatin, simvastatin), which can decrease LDL-C by about 50% and reduce the risk of cardiovascular events by 25–30%, are the cornerstone of lipid-modifying therapy. Statins work by lowering the body’s own production of cholesterol. Less cholesterol means less LDL in the bloodstream.

Nicotinic acid – protecting patients by raising HDL

As effective as statins are, reducing LDL-C is not the only consideration when managing dyslipidemia. Low levels of

“good” high-density lipoprotein (HDL-C) are an independent risk factor for coronary heart disease, irrespective of LDL-C levels. Two-thirds of men with coronary heart disease have low HDL levels. Also among patients who had already been treated for lipid disorders, 33% of the men and 40% of the women had insufficient HDL levels.

Clinical trial evidence suggests that raising HDL significantly reduces the risk of coronary heart disease, providing additional benefits beyond LDL reduction. Simultaneously lowering LDL and raising HDL seems to achieve the greatest benefits.

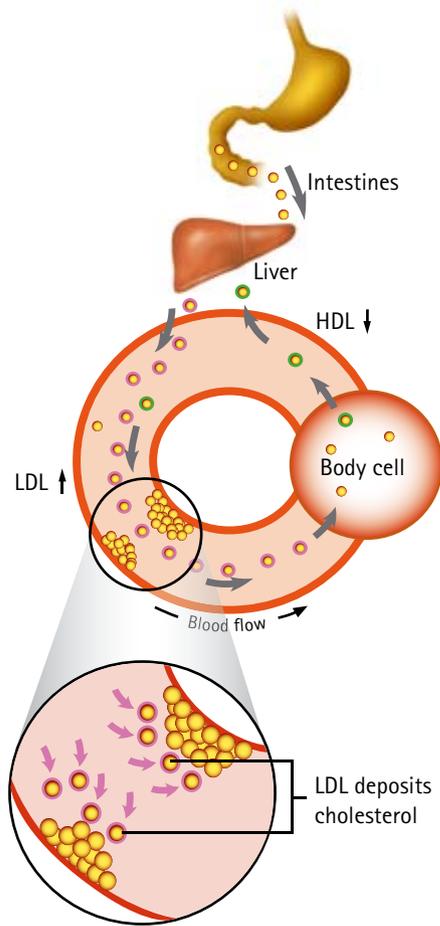
Statins have little beneficial effect on HDL. Among the lipid-modifying drugs available today, niacin or nicotinic acid is the most potent HDL raiser. Besides significantly increasing HDL, nicotinic acid improves other lipid parameters, including LDL-C and triglycerides, and it is the only lipid-modifying drug that can reduce Lp(a) significantly.

The Coronary Drug Project, a long-term study on the connection between myocardial infarction and lipid disorders, demonstrated that nicotinic acid monotherapy can significantly reduce the risk of recurrent non-fatal heart attack over five years. Moreover, nine years after the end of the trial, it was revealed that the number of fatal heart attacks also declined. Many patients with dyslipidemia benefit from combined treatment with a statin (to lower LDL) and nicotinic acid (to raise HDL and strengthen the lipid-lowering effect of statin on LDL-C and triglycerides)

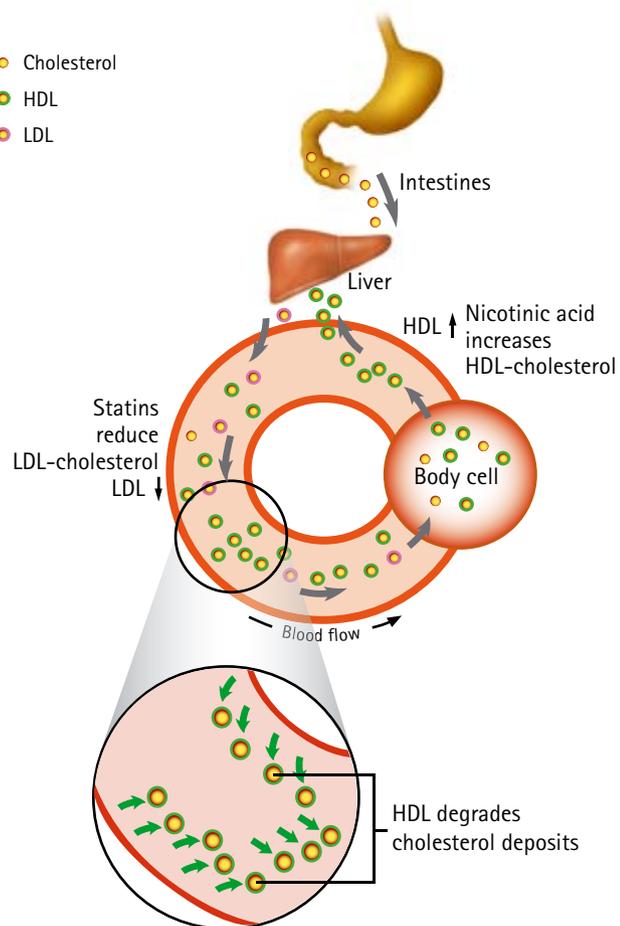
The ARBITER 3 study showed that the progression of atherosclerosis can be halted. After two years of treatment with a combination of a delayed action nicotinic acid and a statin, intima media thickness (IMT), a marker of atherosclerosis measured on the jugular veins, decreased significantly.

A paper published by the European Consensus Panel on HDL reported on the importance of elevating HDL-C to reduce cardiovascular risk and recommended nicotinic acid. A prolonged-release formulation of nicotinic acid was launched by Merck in 2003.

Abnormal lipid metabolism



Lipid metabolism in treated patients



Dyslipidemia | An elevated level of LDL causes lipid plaques in the vessels. Dyslipidemia can be treated with statins, which lower the concentration of LDL in the blood. Additionally, therapy with nicotinic acid raises the level of the "good cholesterol" HDL. HDL carries cholesterol to the liver, where it is catabolized.

This new formulation was designed to reduce a troublesome side effect of immediate-release nicotinic acid: flushing, or hot flashes, which are the result of blood vessels opening wide. The new prolonged-release form of nicotinic acid reduces flushing.

Recent studies suggest that combination therapy with lovastatin and

prolonged-release nicotinic acid may be an effective combination for patients who require correction of multiple abnormalities in their lipid profile.

Diabetic patients are at higher risk for cardiovascular disease and managing dyslipidemia is an important component of comprehensive care for diabetics. Nicotinic acid, both alone and in combination with statin therapy, is effective at balancing lipid profiles in diabetic patients and has no significant effect on their glycemic control regimen.

Managing diabetes

Lowering blood sugar – a multi-faceted approach

The main goal of diabetes treatment is to lower blood sugar to normal levels. The types of treatment employed to achieve this goal in type 2 diabetes patients include:

- Biguanides decrease glucose production by the liver.
- Thiazolidinediones (TZDs) address the problem of insulin resistance.
- Sulfonylureas lower blood sugar by causing the pancreas to release more insulin.
- Alpha-glucosidase inhibitors slow the breakdown of food into glucose, slowing the entry of glucose into the bloodstream.

CardioMetabolic Care focuses its activities on management strategies for patients with type 2 diabetes. In this growing epidemic, early detection and adequate treatment are essential for offering patients freedom from complications due to their high glucose levels (thirst, dehydration) and long-term complications, such as heart attack and blindness.

A primary objective of type 2 diabetes treatments is to correct the dual defects of tissue unresponsiveness to insulin (insulin resistance) and insulin deficiency arising from impaired functioning of the beta cells in the pancreas that make insulin.

Metformin – a long-standing foundation of diabetes care

Metformin belongs to the biguanide class of molecules and is a first-line treatment for type 2 diabetes. In 2005, the International Diabetes Federation recommended metformin as such in its global guideline. It corrects insulin resistance by making tissues, such as the liver and muscle, responsive to insulin. This way we get less “in-house” glucose production in the liver and better glucose uptake into muscle, where it is stored as glycogen or burnt off to produce energy. The net result is restoration of normal glucose levels in the blood.

There are some 5,600 articles about metformin that have been published in the scientific literature since 1957, the year of its introduction into clinical practice. A recent landmark study, the United Kingdom Prospective Diabetes Study (UKPDS), has shown metformin to be unique in being the only antidiabetic agent that lowers blood glucose without weight gain, while reducing the risk of long-term



Chilly-Mazarin, France | Christine Charon performs in vitro experiments at our research center. She tests substances identified as hits in high-throughput screening performed in Darmstadt.

complications, such as heart attacks or stroke. Furthermore, clinical outcomes for UKPDS confirm that metformin is effective in reducing death rates from all causes, as well as from cardiovascular disease.

There is growing recognition that metformin has a pharmacological profile that lowers the risk of atherosclerosis and thrombosis. In particular, clinical studies have confirmed a modest but significant reduction in plasma triglycerides and cholesterol, and an improved stimulus for dissolving blood clots, both in the diabetic and non-diabetic states.

Combination therapy – metformin and glibenclamide

Treatment strategies today call for physicians to aggressively treat elevated blood glucose levels and restore them to near normal. Single treatments have limitations over time in achieving normal glucose levels because of the progressive nature of type 2 diabetes. In response to this, Merck has developed a combination of metformin with glibenclamide, a sulphonylurea, which targets the pancreas and helps stimulate insulin release, complementing metformin's effect of reducing insulin resistance.

Thyroid care

Deficiency of the thyroid hormones T3 and T4 may result in symptoms such as general “slowing down”, depression, weight gain, and (in women) menstrual irregularities and infertility. The effects of hypothyroidism go beyond such symptoms, however. Recent studies indicate that even mild hypothyroidism can raise LDL levels, increase the risk of heart attack, and impair cardiac function.

Prompt diagnosis and treatment of hypothyroidism with levothyroxine can improve patient well-being, as well as reduce LDL levels, improve cardiac function, and reduce cardiovascular risk.

Levothyroxine from Merck is available in more than 60 countries. Nearly seven million people worldwide are treated with Merck’s brand of levothyroxine every year for a wide variety of thyroid disorders, including:

- Hypothyroidism in adults and children
- Euthyroid goiter, a condition where the thyroid is enlarged, often as a result of iodine deficiency
- In hyperthyroidism in combination with anti-thyroid drug treatment – to ensure that thyroid hormone levels do not fall too low thus triggering thyroid growth
- Thyroid cancer after surgery

Merck conducts and supports thyroid research worldwide, including large epidemiological studies in collaboration with the WHO and national thyroid associations, financial grants for thyroid researchers, and clinical trials in the thyroid field. Merck also sponsors internationally renowned awards for thyroid research.



Wiesbaden, Germany | At his practice in Wiesbaden Municipal Hospital, Professor Jörg Spitz uses a gamma camera to examine Andreas Schmidt's thyroid gland. Diagnostics play an important role in making drug therapy decisions.

The future – promising research for treating metabolic syndrome

The unique strategy underlying the Commercial Unit CardioMetabolic Care at Merck focuses on finding solutions to the challenges posed by metabolic syndrome.

Before discussing the development of new treatments for metabolic syndrome, we need to look at how different regulatory systems in the body communicate via messenger molecules, and how deregulation of one system can affect other systems. The bloodstream is very important: Not only does it carry oxygen to cells, but other agents, whose job is to trigger specific actions, are also delivered to their destinations via the blood. Much like a letter reaching its destination via the postal service, these molecules deliver their message by binding to receptor proteins located on the surface of certain cells. Binding to a receptor triggers a response inside the cell.

Several of these receptors interact with kinases, an important class of proteins inside cells, whose job it is to communicate the received messages. Kinases modify other proteins in order to activate or deactivate them. A message received by the receptor via the bloodstream is amplified by kinases, which act in a cascade effect to turn other kinases on and off.

SGK-1 is a kinase that “sits” in the middle of one such cascade. Activated SGK-1 causes:

- Increased glucose absorption from the gut
- Extracellular matrix build-up in organs including the kidney, heart and liver
- Increased salt absorption in the kidney
- Increased production of proteins that in turn cause blood clots to form on the inside wall of blood vessels.

These factors contribute to obesity, diabetic kidney disease, arterial thrombosis (blood clot formation), and high blood pressure. A vicious cycle exists in diabetes and the metabolic syndrome, whereby molecules transported by the blood increase the expression and activation of SGK-1 and thus further aggravate the disease and its complications, and vice versa.

Genetic studies on SGK-1 have shown that about 5% of people have a particular variation of the gene where SGK-1 is consistently more active than normal. These same people have a higher body mass index and higher

New compounds in clinical development at Merck

Our projects in phase I of clinical development include EMD 387008, a compound in a new class of antidiabetic agents. The ability of this compound to control blood glucose levels matches that of standard treatments, e.g. metformin. Yet it has shown a superior safety and tolerability profile. In preclinical studies, our researchers have determined that treatment poses no risk of hypoglycemia. To date, there have been no instances of lactic acidosis, edema or weight gain. Gastrointestinal side effects have been minimal.

Merck is developing a direct and selective Factor Xa inhibitor which, as a new class of orally active anticoagulants, differs from current treatments by its mechanism of action. Also, no routine coagulation monitoring is needed. It is being developed as an efficacious and safe treatment for “prevention of arterial and venous thromboembolism” and “stroke prevention in patients with atrial fibrillation”. There is a high unmet medical need for safe, effective and convenient oral anticoagulant drugs without coagulation monitoring. Anticoagulants are used for the primary and secondary prevention of thrombotic events, for instance thrombosis after total hip replacement surgery or deep vein thrombosis.

blood pressure than those who do not have this form of the SGK-1 gene. This puts them at higher risk.

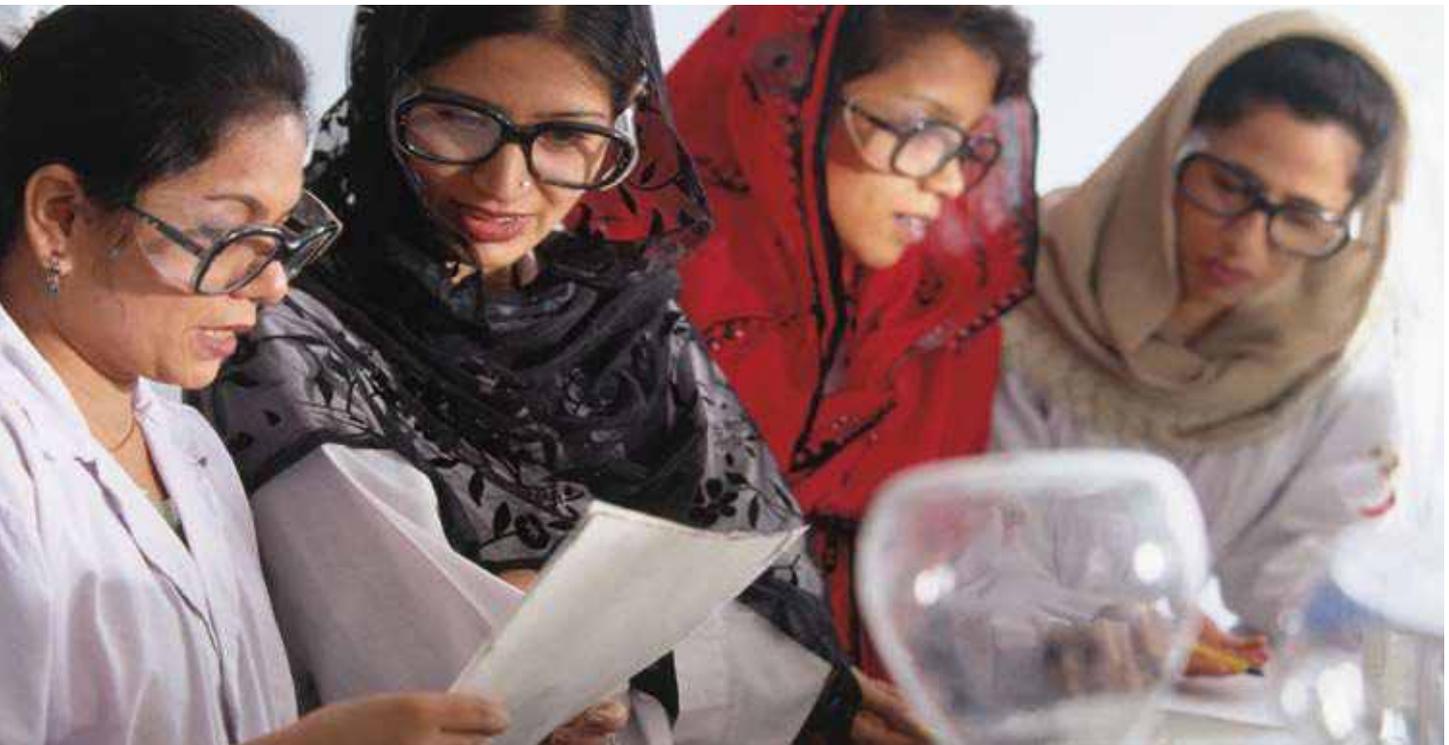
One strategy being pursued by scientists in Cardio-Metabolic Research is to identify inhibitors of SGK-1 and actively look for treatments to target SGK-1 to benefit patients with type 2 diabetes or metabolic syndrome. To accelerate progress in this area, we have established collaborations with academic scientists who are leading the SGK-1 field at major universities. This promising new treatment option epitomizes CardioMetabolic Care’s commitment to improving the lives and health of patients.

Products and services

The drugs marketed by the Commercial Unit CardioMetabolic Care include some of Merck's most successful products. CardioMetabolic Care intends to build on this portfolio of products. By bringing together experts from multiple disciplines, we intend to advance the development and delivery of products to the market for the benefit of the patient and the company alike.

Product profile

- The various brands in the bisoprolol product family are among the top beta-blockers in most countries (number two in Europe), making the bisoprolol product family Merck's strongest selling range.
- Merck is a global market leader in oral antidiabetic agents. Some six million patients in over 100 countries around the globe currently benefit from various metformin products.
- Merck is number one in Europe and Latin America for thyroid treatments and number three worldwide. The market for Merck's thyroid products is growing, mainly due to the increasing numbers of patients with newly diagnosed thyroid disorders.



Quetta, Pakistan | In an analytical laboratory for quality control Ziviqar, Zartaj Awan, Charlotte Faria and Shazia Dilwar examine raw materials for use in drug production.



The CardioMetabolic Care portfolio – major products

<i>Drug type</i>	<i>Indications*</i>
Bisoprolol Cardioselective beta-blocker	Hypertension Coronary artery disease
Bisoprolol Cardioselective beta-blocker in lower-dose tablets for flexibility in chronic heart failure	Chronic heart failure
Bisoprolol / hydrochlorothiazide Low-dose combination of a beta-blocker and a diuretic	Hypertension, first-line treatment
Bisoprolol / hydrochlorothiazide Combination of a beta-blocker and a diuretic in standard doses	Hypertension, if monotherapy is ineffective
Nicorandil Anti-anginal drug with a unique mode of action	Angina pectoris
Digitoxin Cardiac glycoside	Heart failure, arrhythmias
Naftidrofuryl Vasoactive drug	Peripheral arterial disease
Nitroglycerine Vasodilator, sublingual spray	Acute episodes of angina
Nicotinic acid	Dyslipidemia, characterized by elevated levels of LDL cholesterol, triglycerides, and low HDL cholesterol
Metformin Biguanide antihyperglycemic agent	Type 2 diabetes
Metformin / glibenclamide Biguanide antihyperglycemic agent/sulphonylurea	Type 2 diabetes
Levothyroxine Thyroid hormone T4	Hypothyroidism, goiter

*Please consult local prescribing information for indications and trademarks in your country.

CardioMetabolic Care: Merck milestones

1894	First Merck thyroid product derived from sheep thyroids	1999	DECREASE study shows bisoprolol reduces mortality in high-risk patients undergoing non-cardiac surgery
1949	Introduction of digitoxin for cardiac diseases	2002	IONA study demonstrates a cardioprotective effect for nicorandil
1957	Introduction of antidiabetic agent metformin in France (1973 in Germany, 1995 in the United States)	2002	CIBIS III trial begins
1973	Introduction of levothyroxine tablets for thyroid diseases	2002	DPP shows metformin can help prevent the onset of type 2 diabetes in people with IGT
1986	Introduction of beta-blocker bisoprolol for hypertension and coronary artery disease (angina pectoris)	2002	Merck received the license for nicotinic acid
1994	CIBIS results indicate a trend in CHF mortality reduction	2004	Launch of nicotinic acid in Europe and worldwide
1995	TIBBS study shows bisoprolol more effective than nifedipine in reducing total ischemic burden in angina	2005	Results of the successful CIBIS III study confirm a new treatment regimen for chronic heart failure
1998	UKPDS shows monotherapy with metformin reduces cardiovascular complications of diabetes and improves survival	2005	The International Diabetes Federation recommends metformin as the "drug of choice" in first-line therapy of type 2 diabetes
1999	CIBIS II shows bisoprolol reduces mortality in CHF		

Online information for patients and doctors

Merck's Commercial Unit CardioMetabolic Care provides a wide range of support services and materials for patients and health professionals.

Information for patients:

www.cardiovascular.merck.de	Gives a short overview on cardiovascular disorders, such as hypertension, coronary artery disease, chronic heart failure and the treatment options that Merck offers.
www.dyslipidemia.merck.de	Gives a short overview on lipid disorders and the treatment options that Merck offers.
www.diabetes.merck.de	Gives an overview on type 2 diabetes, its prevalence, its development and its therapy, including the history of metformin. The development is explained via a series of diagrams to click through.
www.thyrolink.com	Provides an overview of Merck's products and activities in the thyroid area and facilitates access to thyroid-related information on the Internet.
www.thyroid.merck.de	Gives insight to thyroid diseases, causes, symptoms and treatment options.



Middlesex, United Kingdom |

Alison Hannah, David Garmon-Jones and Bernadette Lang are responsible for various products in the CardioMetabolic Care range. They are discussing integrated therapy options.

Information for doctors:

www.cme-heartfailure.net

Is a one-stop site for heart failure, supported by an unrestricted educational grant from Merck KGaA. It gives doctors immediate access to up-to-the minute news, research, publications and education on heart failure. At the heart of the site lies a huge digital library of information on the pathology, diagnostics and treatment of heart failure, saving endless hours of searching through books and journals. Physicians are alerted to the latest news on heart failure via Reuter's health news, updated daily. www.cme-heart-failure.net also allows physicians to undertake CME courses in heart failure, accredited by the European Board for Accreditation in Cardiology (EBAC).

www.cibis3.info

General information and results of the CIBIS III study

www.bisoprolol.com

www.bisoprolol-slides.info

Offers immediate access to information on bisoprolol, and on its use in hypertension, coronary heart disease, chronic heart failure and non-cardiac surgery. The site provides details of all the key clinical studies on bisoprolol, including CIBIS and CIBIS II, TIBBS and DECREASE. Physicians can also access information on pharmacoeconomic studies to further facilitate informed treatment decisions.

www.lodoz.com

Offers physicians a searchable database of information on the low-dose combination, including product information and details of clinical and pharmacoeconomic studies.

www.niaspan.info

Provides information on dyslipidemia and nicotinic acid.

www.diabetes-source.com

Is an information resource available exclusively to members of the CardioMetabolic Education Forum, an organization sponsored by Merck to provide information and education on diabetes to physicians worldwide. www.diabetes-source.com provides regular updates on new developments in diabetes management, and a comprehensive slide library on diabetes and its management.

www.thyrolink.com

Provides an overview of Merck's products and activities in the thyroid area and facilitates access to thyroid-related information on the Internet.

Merck KGaA – company profile

The Merck Group is a global pharmaceutical and chemical enterprise. In 2005, Merck Group sales totaled € 5.9 billion.

We are pursuing a strategy of “focused diversification” with the three divisions of our Pharmaceuticals business sector and the two divisions of our Chemicals business sector.

Our Pharmaceuticals business sector comprises our prescription branded drugs, e.g. for the treatment of cancer, metabolic disorders and cardiovascular diseases, as well as generics for cost-efficient basic health care, and over-the-counter products. Our pharmaceutical research and development activities center on Oncology and CardioMetabolic Care, with a research focus on type 2 diabetes. Around 850 employees work in pharmaceutical research in Darmstadt alone; other major pharmaceutical competence centers are located in Chilly-Mazarin (France), Mollet de Vallès, near Barcelona (Spain), and Billerica, near Boston, Massachusetts (United States). In 2005, Merck invested € 579 million in pharmaceutical research.

The Chemicals business sector offers chemicals for high-tech applications: liquid crystals for displays; effect pigments for industry and cosmetics; analytical reagents and test kits, as well as products and services along the entire process chain of the pharmaceutical and biotech industry.

Merck is the world’s oldest pharmaceutical and chemical company, with roots dating back to 1668. From the start of industrial production in 1827 to the discovery of liquid crystals more than 100 years ago up to our entry into targeted cancer therapy with the launch of Erbitux® in 2003, many milestones in our history provide strong evidence of the pioneering spirit of the people at Merck. Today, more than 29,000 committed employees are helping to continue the company’s 338-year-old tradition.

Since going public in 1995, Merck’s operating activities are under the umbrella of Merck KGaA. Today, around 27% of the total capital of Merck KGaA is publicly traded, while the Merck family owns a 73% interest via the general partner E. Merck OHG.



Darmstadt, Germany | Merck KGaA, the oldest pharmaceutical and chemical company in the world, steers its global operations from corporate headquarters in Darmstadt.

Further information & publication contributors

Our publication series TopTopics deals with subjects of interest concerning health and chemical products, as well as Merck's research:

- **TopTopics Liquid Crystals – Merck Makes Bits and Bytes Visible**
- **TopTopics Oncology – Merck Breaks New Ground in Cancer Therapy**

If you are interested or have questions, feel free to contact Corporate Communications via:
TopTopics@merck.de

More information about Merck can be found on the Web at www.merck.de and in the following brochures, which you can read (www.publications.merck.de) or order online (available in German and English):

- **Merck transparent** (Company portrait; also available in French and Spanish)
- **Responsibility for Employees, the Environment and the Community** Report 2005
- **A Strong Site** A Global Player Rooted in Darmstadt
- **"Was der Mensch thun kann..."** History of Merck –
The World's Oldest Pharmaceutical and Chemical Company
- **The History of the Future** 100 Years of Liquid Crystals at Merck
- **Special-Effect Pigments** A New Colour Dimension
- **Chemistry with a Future** A Glimpse of Research at Merck
- **Research for life** Promoting health through active ingredients from Merck

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