



XBiotech researchers manufacture a monoclonal antibody designed to reduce cardiovascular events.

work to lower pressure, we still are figuring out how low pressure can go, and how the drugs impact the peaks and the troughs of blood pressure.”

Wright says that researchers need to know whether antihypertensive drugs work by lowering the maximum blood pressure (systolic) during a heartbeat or the minimum (diastolic), or the difference between the two (pulse pressure). Whether other factors, such as the variability in blood pressure, are involved is not known. Wright is reviewing different classes of antihypertensives to assess the effects on the various forms of blood pressure. Likewise, Francois Gueyffier, a doctor at the Hospices Civils de Lyon in France, suggests a reassessment of blood pressure targets for the elderly, because blood pressure is much more variable than initially thought.

DRUG DIRECTIONS

Pharmaceutical companies are looking for ways to solve the fundamental problems. Monoclonal antibodies may be best known for treating arthritis, but they are now being applied to vascular health. XBiotech, a pharmaceutical company based in Austin, Texas, is using monoclonal antibodies to treat restenosis — a recurrence of the narrowing of a vessel after it's been opened by a stent or surgery — and vascular disease in general.

Monoclonal antibodies are a different way of dealing with that issue, says Hosam El-Sayed, a cardiovascular surgeon at the Methodist Hospital System in Houston, Texas, who has collaborated with XBiotech. In autumn 2012, XBiotech finished a phase II trial of the drug MABp1, which blocks the activity of interleukin-1 α , interrupting inflammation related to heart disease. XBiotech announced results from 42 patients showing that the group treated with MABp1 had a 58% reduction in major cardiovascular events.

Most antibodies use mouse cells to create their biologic drugs. Michael Stecher, XBiotech's medical director, says the company is cloning human antibodies instead of using mouse components, which he says makes the drugs safer and more effective.

Instead of creating new drugs, some companies are looking to combine existing medications in innovative ways. Clinical trials have started on a 'polypill' developed by the Indian pharmaceutical company Cipla, based in Mumbai, including three blood-pressure-lowering drugs and a cholesterol-lowering statin. In a 3-month trial of 84 men and women over 50 years of age at Queen Mary, University of London, the pill cut blood pressure by 12% and reduced levels of low-density lipoprotein (LDL) — the so-called 'bad cholesterol' — by 39% (ref. 1).

CHOLESTEROL MEDICATIONS

Several different types of drug can control cholesterol, but statins are the most popular.

DRUGS

Blood battles

The standard medications for hypertension and cholesterol have lingering issues, but new drugs hold promise for high-risk patients.

BY KATHARINE GAMMON

Everywhere you look in the United States, drugs for high blood pressure and high cholesterol stare back at you — from billboards and television screens to the pages of magazines. Together, these medications account for a global market worth US\$75 billion. Moreover, statins, a mere two decades after coming to market, are the best-selling drugs on the planet. Researchers have raised questions about the effectiveness of prescribing drugs to lower cholesterol and blood pressure before a person has heart disease, and nagging problems with side effects still linger. At the same time, new drugs that use novel approaches to treat the same illnesses are in development.

The World Health Organization (WHO) estimates that a third of adults worldwide have raised blood pressure, a condition that causes around half of all deaths from stroke and heart disease. Hypertension costs the US

healthcare system \$131 million each year. And it is a major cause of cardiovascular disease, the leading cause of death in the United States.

Medications can lower blood pressure in a variety of ways: diuretics squeeze salt and water out of the blood; beta-blockers reduce heart rate; angiotensin-converting enzyme (ACE) inhibitors slow the body's production of angiotensin, thereby relaxing blood vessels and reducing blood pressure; calcium-channel blockers disrupt calcium from entering the smooth muscle cells of the heart and arteries, softening heart contractions and easing the flow of blood.

Some researchers are looking to shore up our fundamental understanding of how blood pressure works in the body. "Blood pressure is a complicated system," says James Wright, a clinical pharmacologist at the University of British Columbia in Vancouver. "When drugs

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Statins inhibit the enzyme HMG-coA reductase, thereby blocking the production of cholesterol in the liver. They lower LDLs and raise the levels of 'good cholesterol', high-density lipoproteins (HDLs).

Statins undeniably help reduce deaths from heart disease in high-risk populations. One study followed about 20,000 high-risk patients for 11 years and found that patients who took a statin for 5 years had 23% fewer major vascular events than a control group². In people who have had heart attacks, those who took statins were 18–19% less likely to suffer a combination of heart problems, including strokes, heart attacks or a heart disease-related death³.

But these drugs are not without risk. Roughly 10% of people who are prescribed statins encounter serious side effects, according to recent research. These range from muscle and joint aches in 5–10% of patients, to moderately elevated blood levels of muscle enzymes in 1–2% of patients, and severe muscle injury and even kidney failure, which happens in 1 in 100,000 patients (0.001%), according to Robert Hegele, an endocrinologist who studies statins at Western University in London, Ontario. "The benefits of statins in terms of preventing heart attacks and strokes, prolonging life and keeping patients with cardiovascular disease out of the hospital dwarf these small risks, but the side effects are a barrier to treatment for some patients," says Hegele.

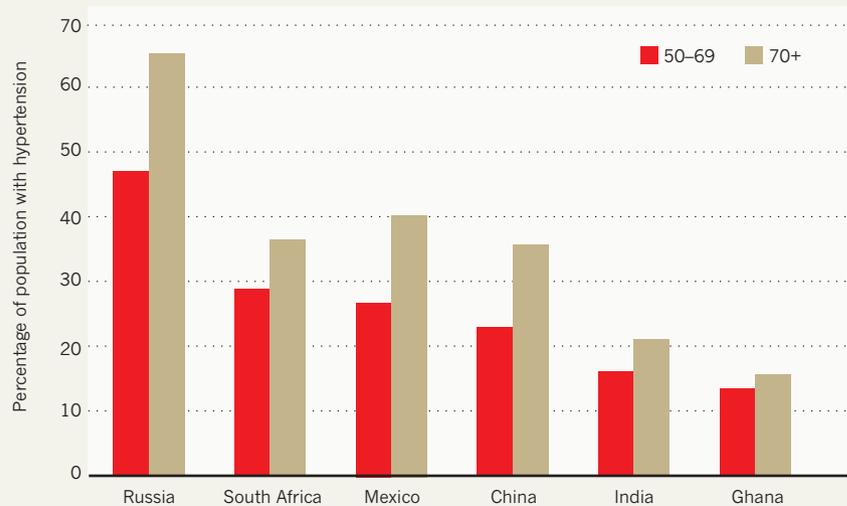
Hegele says that although statins have made an impact since the 1980s, there is still an unmet need for a way to lower cholesterol. "Some patients fail to reach their targets even with various drug combinations, and patients who cannot tolerate a statin represent yet another group for whom new therapies are needed," he says.

Statins have an undisputed place in treating people with unhealthy levels of cholesterol — generally starting at total cholesterol of 240 milligrams per decilitre (mg dl⁻¹), or an LDL level of 130 mg dl⁻¹. But the medical community has long debated whether statins should be used as a prophylactic. Cardiologist Rita Redberg at the University of California, San Francisco, sees no evidence that statins help healthy people⁴. "Statins are widely used in primary prevention, but the benefits are not clear," says Redberg. "So you're talking about prescribing a drug that doesn't benefit quality of life or living longer." The most optimistic projections suggest that for every 100 healthy people who take statins for 5 years, one or two will avoid a heart attack — but one person will also develop diabetes, says Redberg.

The need to figure out why statins don't work for everyone is motivating some researchers to study what cholesterol does in the body. Cholesterol is an essential part of the human cell; it is involved in everything from the brain to hormones. "Cholesterol is what distinguishes animals from plants. It gives us a

HIGH LEVELS OF HYPERTENSION

For people who are 50–69 years old (red), one-quarter or more suffer hypertension in many countries, and for people who are 70 or more years old (brown) the percentages surpass one-third in many countries, reaching roughly two-thirds in Russia.



nervous system and a brain," says Stephanie Seneff, an artificial-intelligence researcher at the Massachusetts Institute of Technology in Cambridge, who has recently turned her attention to statins.

Seneff says that some of the other side effects of statins, such as muscle weakness and memory loss, are easily put down to the effects of ageing, and might not be recognized as consequences of taking the drug. "Many people are feeling like they're getting old, and they don't realize that the statin drugs are making it worse," says Seneff.

REPLACING STATINS

With the widespread prescription of statins, researchers are looking to find alternatives. There are several types of treatment under development to lower LDL cholesterol that work differently to statins.

One of those drugs is a monoclonal antibody that works against an enzyme called PCSK9, which destroys a receptor for LDLs. The drug, called AMG 145, was tested in a recent controlled study in 631 patients aged 18–80 years⁵. In patients who received the shot each month, the drug reduced LDL cholesterol by 42–50% at the end of 12 weeks compared to placebo.

"The idea is: the enemy of your enemy is your friend," says Robert Giugliano, study author and cardiologist at Brigham and Women's Hospital in Boston, Massachusetts. Amgen, the drug's developer, is planning a large phase III study in 20,000 patients.

Another cholesterol-lowering class of drugs in development acts by blocking the action of molecules in the liver that shuttle cholesterol. Four such cholesterylester transfer protein (CETP) inhibitors are in the pipeline;

the one furthest along is a pill from Merck called Anacetrapib. Merck is now recruiting 30,000 high-risk patients in Europe, China and the United States for a 4-year trial of anacetrapib called the Randomized Evaluation of the Effects of Anacetrapib through Lipid Modification (REVEAL) trial. The drug will be given in conjunction with a statin to further lower LDL. Anacetrapib has been shown in previous studies to raise HDL by 140% and reduce LDL by 25–40%, says Martin Landray a clinical investigator at Oxford University, UK, who is also involved in REVEAL.

Giugliano stresses that most of the new drugs are for high-risk patients or those who have had a heart attack, and that most people with high blood pressure or high cholesterol should still start their path to wellbeing with a healthy lifestyle. "We're doing better with smoking and hypertension, but weight and exercise is going in the wrong direction. That's the foundation, and the next step will be extra help for people who need help with lowering cholesterol."

Despite the growing list of powerful pharmaceuticals to treat high blood pressure and cholesterol problems, and the ubiquitous adverts proclaiming their success, the most effective treatment might not be found in a pill, but in a pair of running shoes and a salad. ■

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