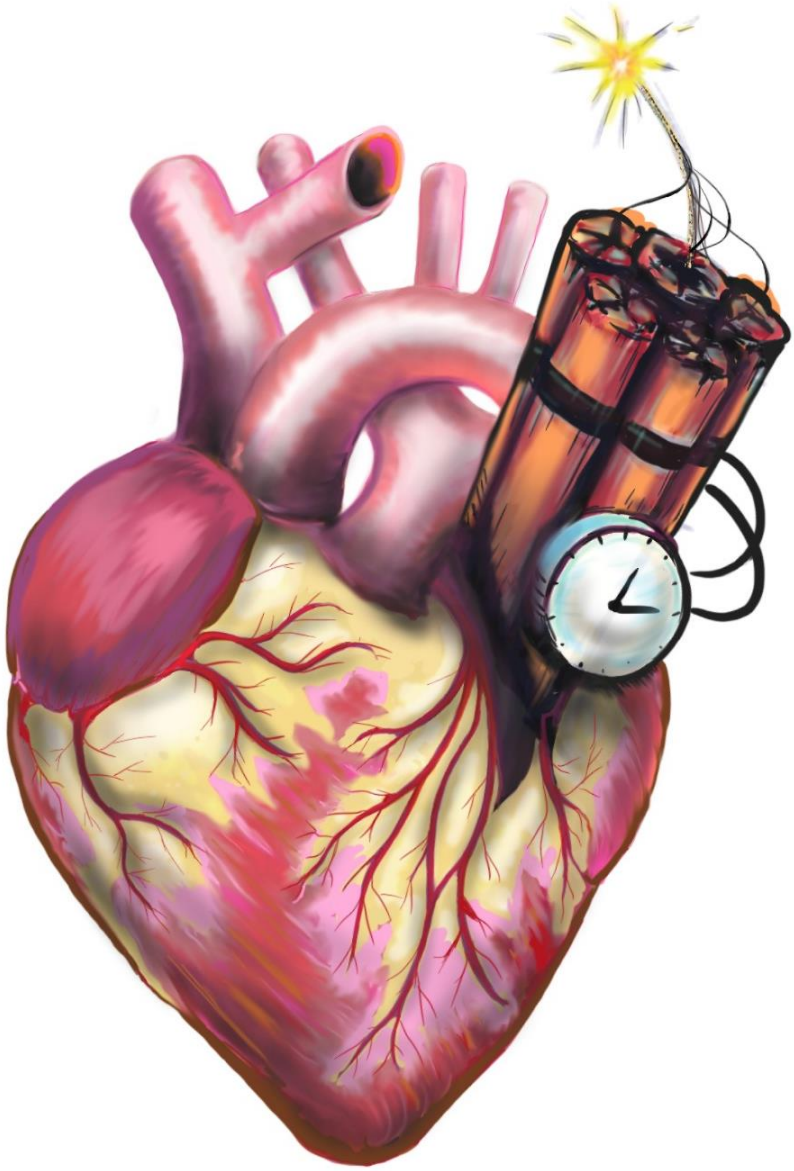
2018

50 Ways To Save Your Heart

David S. Schade

R. Philip Eaton

50 WAYS TO SAVE YOUR HEART



DAVID S. SCHADE, MD

R. PHILIP EATON, MD

White Sands National Monument, New Mexico

Acknowledgements

This book would not have been possible without the contributions of the following people, institutions, and businesses:

To Barry Ramo, MD – an outstanding cardiologist and professional medical news analyst who provided invaluable suggestions for content and structure. As a result of the many meetings with him, we gained much new insight into the clinical importance of coronary artery calcium scanning and its prediction of cardiovascular disease. He is currently overseeing the New Heart Center for Wellness, Fitness, and Cardiac Rehabilitation program in Albuquerque, New Mexico.

To Ms. Carolyn King, Unit Administrator for David S. Schade, M.D. She edited all of the chapters and corrected them for syntax and spelling.

To Ms. Janae Padilla – a student at the University of New Mexico for tirelessly organizing and proofing chapters. She constructed the book's index and section layouts.

To Ms. Christina Klauber for designing and illustrating the book's cover.

To Dr. Loren Ketai for his support in establishing the coronary artery calcium scanning techniques at the University of NM Health Sciences Center and providing coronary artery calcium figures.

To Lynda C. Shey, CNS – for giving thoughtful advice and proof reading the text.

To both Shutterstock.com and Canstock.com for providing figures to illustrate the chapters.

To all of the researchers and clinicians who have made a huge effort to understand and describe the pathophysiology of atherosclerosis and to suggest new approaches to the prevention and reversal of heart disease.

To all of our patients who provided invaluable suggestions on improving the chapters and figures for the book.

To the University of NM Health Sciences Center for their support in providing funding and encouragement for the publication and distribution of this book.

Introduction

If you want to place a winning bet, bet that heart disease will kill you. Yes, you. Why? Because heart disease kills more people in the U.S. than any other disease, including cancer. We want to reverse that bet and save your life. How? You need to read this book and follow its simple recommendations. Many people have already jumped on the bandwagon and defied the probability of dying from heart disease. This book gives you the easy tools to do just that. Prevention costs practically nothing and you don't have to give up anything. You only have to eat and be smart about saving your heart.

So why is our book different from all the books, pamphlets, notices, alerts, newspaper, magazine articles, etc., all describing heart disease in the United States?

First, in spite of all of the available therapies including bypass and stent surgery, the total number of people with heart attacks in every town, city, and state is increasing.

Second, many books fail to mention that the individual who had the heart attack incurred a hospital bill often in excess of half a million dollars and he/she may become a "cardiac cripple" requiring oxygen 24 hours/day. Needless to say, that individual's health and lifestyle has changed from "good" to "greatly impaired."

To put the seriousness of heart disease in perspective, the 600,000 individuals in the United States who have a heart attack each year equals approximately one heart attack every minute (the population of a small city). To bring these statistics closer to home, the most likely cause of your personal demise is a heart attack secondary to disease in your heart's arteries, not cancer.

The third reason that we felt compelled to write this book is that there is no rational reason for anyone to have a heart attack. The understanding and knowledge of the vessel disease that causes a heart attack and how to prevent this catastrophic event has recently been discovered and reported in the medical literature. Knowledge in the field of medicine has exploded, overwhelming many conscientious physicians from keeping up to date. This is because new knowledge has accrued from the basic sciences, animal studies, primate studies, and human studies at an astonishing rate. To assimilate this knowledge, even for specialists in the field, is a major challenge.

We believe that the answer to this dilemma is to bring new information to every individual on what that person should do to prevent heart disease in himself/herself and/or his/her family. Reading this book will provide all the knowledge that is necessary to prevent or reverse heart disease in the individual person at risk. We have purposely kept each chapter short – 2 pages, including a figure illustrating each chapter's main point. For individuals desiring more in depth information, we have included medical references at the end of each section and at the end of the book.

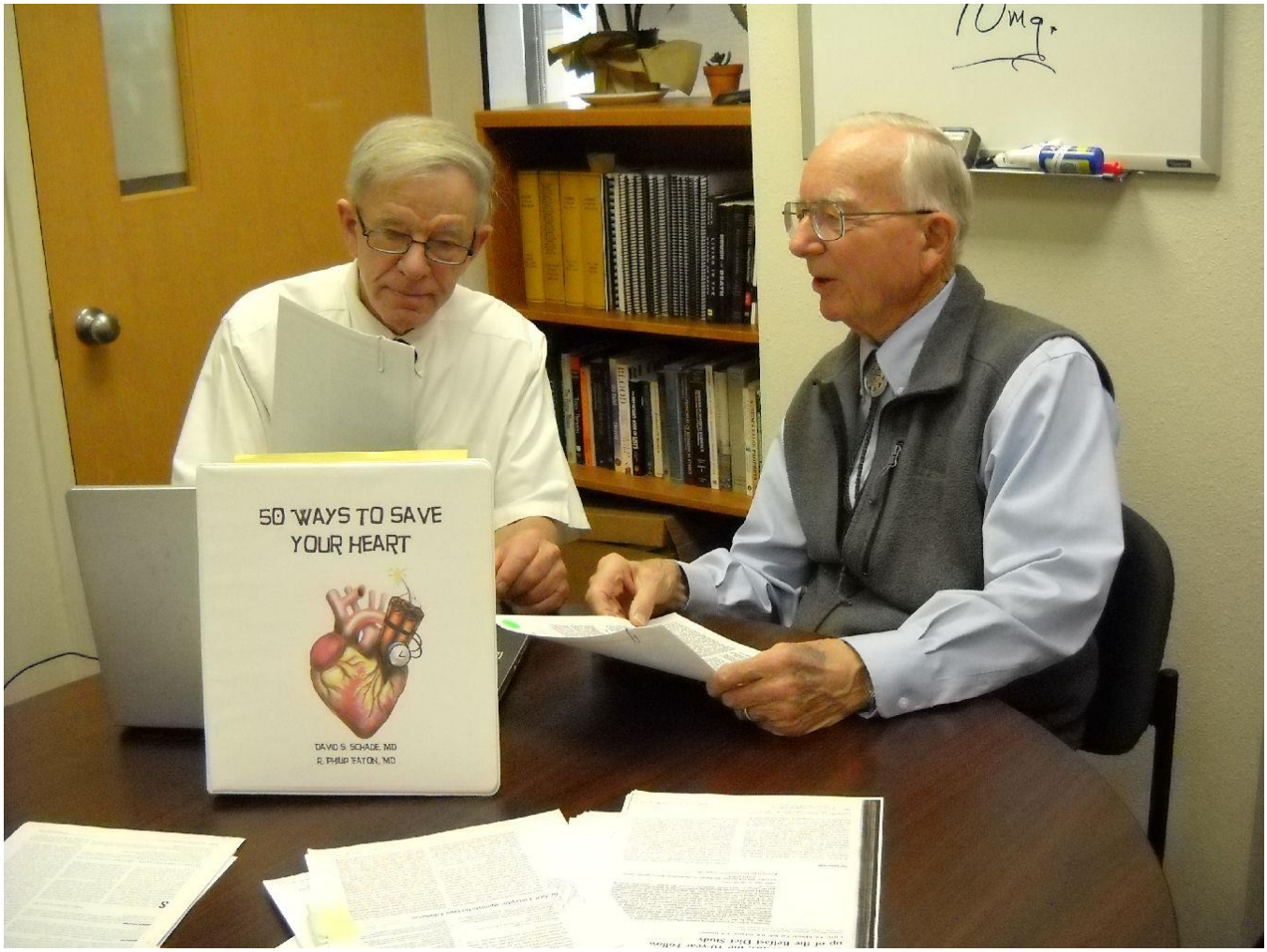


Figure legend – The authors working on chapters in the book. If you have any questions or comments after reading this book, please contact us. Our email address is HSC-endo@salud.unm.edu

Sincerely, David S. Schade, MD and R. Philip Eaton, MD

The Authors

We thought the readers might be interested in how the authors met and why they formed a long-term partnership. In 1973, R. Philip Eaton, MD was Chief of the Endocrinology Division in the Department of Internal Medicine at the University of New Mexico School of Medicine. David S. Schade, MD had just joined the Endocrine Division as a trainee. During this two-year training period, Dr. Eaton became the mentor of Dr. Schade and provided critical information to Dr. Schade on research techniques and endocrine patient care. A solid partnership was formed, resulting in many advances in medicine that were important to the health of the New Mexico population. For example, they were the first to describe the success of a totally implantable insulin pump in diabetic patients, in collaboration with Dr. William Spencer of the Microelectronics Division of Sandia Laboratories. They were also the scientists that proved that subcutaneous insulin resistance was not the cause of poor glucose control in type one diabetes. Furthermore, they described the importance of using low dose insulin therapy in diabetic ketoacidosis, a potentially lethal condition in diabetes. More recently, they have been instrumental in efforts to prevent heart disease in New Mexico citizens, not only through multiple publications in the scientific and lay press but also at the New Mexico State legislature. Throughout these many years of partnership, their goal has always been to improve the health of the New Mexico and United States population. A short biography of each author is given below.

Figure legend – Dr. Schade (left) and Dr. Eaton (right) at the New Mexico State legislature supporting their bill to encourage medical insurance companies to reimburse patients for the cost of a calcium heart scan.

David S. Schade, M.D., Distinguished and Regents' Professor of Medicine at the University of New Mexico, is an internist (a doctor specializing in adult diseases), an endocrinologist (a doctor specializing in disease of specialized glands in the body, e.g., thyroid, adrenal, pituitary, and diabetes), and a lipidologist (a doctor specializing in the prevention and reversal of atherosclerotic heart disease). He attended Davidson College in North Carolina, Washington University in St. Louis for medical school, spent two years in the Public Health Service (National Institutes of Health), and took his internal medicine training at the University of New Mexico School of Medicine. He continued at this institution for two years for additional training in endocrinology (under the guidance of R. Philip Eaton, MD). Following this educational experience, he joined the endocrinology faculty at the University of New Mexico Medical School and spent most of his time taking care of patients, doing research in diabetes and cholesterol metabolism, and teaching medical students. He has received many awards and honors, and has over 600 publications to his credit, many coauthored with R. Philip Eaton, MD. He became Chief of the Division of Endocrinology in 1999 and is currently in that position. His primary interest is preventing and/or reversing heart disease in his patients, their families, and their friends.

R. Philip Eaton, MD is an internist (a doctor specializing in adult disease), an endocrinologist (a doctor specializing in disease of specialized glands in the body, e.g., thyroid, adrenal, pituitary, and diabetes), and a lipidologist (a doctor specializing in the prevention of atherosclerotic heart disease). He attended college at the College of Wooster, Wooster, Ohio. He attended medical school at the University of Chicago Medical School. He became a Professor of Medicine at the University of New Mexico and Chief, Division of Endocrinology and Metabolism in July 1975. His accomplishments in the Department of Medicine have been Director, Clinical Research Center; Vice-Chairman of Research; and Acting Chair, Dept of Medicine. At the Health Sciences level, Dr. Eaton has been Interim Vice President for Health Sciences, Executive Vice President for Health Sciences, and is presently Emeritus Executive Vice President for Health Sciences. His interests are in preventing and/or reversing heart disease. He has been instrumental in submitting legislation for insurance companies to include coronary artery calcium scans in their coverage.

The Development of a Heart Attack

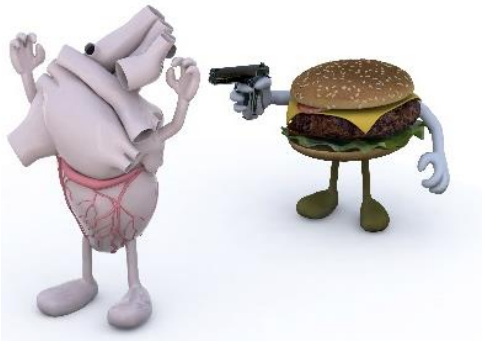
Contrary to popular belief, a heart attack doesn't just happen. In fact, it threatens to erupt for many years before the catastrophic event occurs. Knowing how it develops is the key to prevention. The figures/text below will provide you the "nuts and bolts" of how it happens so you can prevent having one. This is the number one cause of death in America today. In the United States, every minute someone has a heart attack. Do not let it be you!

When you were born, your arteries were clean, smooth, and flexible pipes, through which your blood flowed unobstructed to reach your heart and other vital organs, i.e., your brain, lungs, kidneys, as well as your legs and arms.

In this blood are red blood cells to carry oxygen, white blood cells to fight infection, and platelets to stop bleeding in case you cut yourself. The inflammation and healing of cuts and bumps like pimples can also occur in your blood vessels where they form a scab that were named "Plaques" by physicians in the 1800's.

When you eat food like dairy products that contain cholesterol (milk, eggs, cheese, etc.), your body needs a safe way to move the cholesterol and fat in these foods through your blood. In response, you developed a way of "packaging" the cholesterol in your blood into tiny particles, wrapped in protein strings called "Low Density Lipoproteins" or simply LDLc.

To keep your LDLc level in the blood normal, your body developed an ingenious solution. It constructed specific cholesterol removers called "LDL-Receptors" on the liver. These receptors catch the LDLc particles in your blood and excrete the cholesterol into your gallbladder for disposal in the stool.

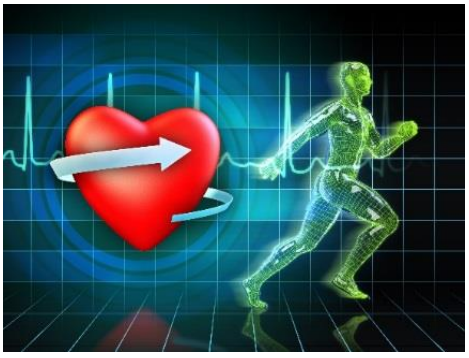


This approach worked very well until we started to eat “fast food.” We are all captives of the Western diet, which contains many foods high in cholesterol. This change caused us to eat too much cholesterol and overwhelmed the ability of the liver's removal system. When this happens, the extra LDLc becomes fuel for inflammation in the walls of our blood vessels. A high blood level of “C-Reactive Protein” (hsCRP) can mean vessel inflammation. Cholesterol plaques then develop in our arteries that our body tries to heal. This healing process sticks "flecks of calcium” around these plaques. This is lucky, since your physician can identify these calcified plaques with a CAT scan, and recognizes that they are the injured part of the artery that becomes a heart attack.

The inflammation begins when you are born, driven by LDLc alone as a natural process that accumulates each year that we live (like grey hair, i.e., a normal process of aging). However, it is aggravated by "insults" like smoking, high blood pressure, diabetes, overweight, and other risk factors.

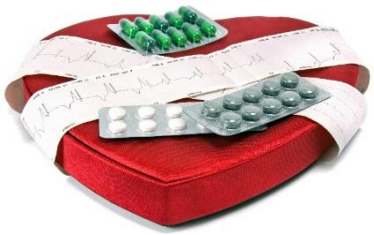
This inflammation is much like any infection in your skin, similar to a pimple containing cholesterol "pus." As it swells, it begins to push into the flow of blood within your heart blood vessels (coronary arteries). It gradually squeezes down the space in these straw-like blood vessels, which makes it hard for your heart to get oxygen from the red blood cells flowing in these vessels.

Now your heart is in a dangerous fix. These arterial plaques can suddenly explode into your coronary artery, causing an obstruction. Your body immediately responds by trying to stop the rupture by rushing plugs of platelets (similar to stopping bleeding from a cut in your skin). If the resulting blood clot totally obstructs the flow of oxygen containing blood to your heart, you develop the acute pain and crises that we know as a "Heart Attack."



Preventing a heart attack is not rocket science. It involves lowering the LDLc to the level that you were born with, and interrupting the inflammatory machine that your age, blood pressure, smoking, diabetes, etc. have been creating.

Other good news is that you also have a method of removing the plaque cholesterol while it is forming called "HDL Cholesterol" or "Good Cholesterol." It removes LDLc-derived cholesterol from the plaques in the wall of the artery and takes it to the liver for disposal. But it too can be overwhelmed if you don't limit your food cholesterol that you eat. That is why we say "Eat Smart and Live Long."



Finally, this story has a very exciting concluding chapter. Science today has developed medications that help the body processes lower your LDLc to a healthy level. How to do this is the focus of this book. So pick a question, read the two-page answer, and "Save Your Heart."

P.S. – a more detailed explanation of events leading to a heart attack is given in the appendix.

Contributed by: E. Duran-Valdez

Sandia Mountains at sunrise

Albuquerque, NM

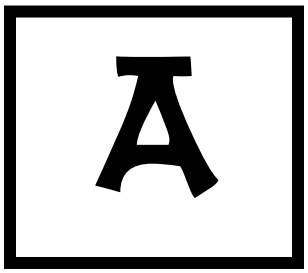
Table of Contents

Page Number

Contributed by J. Zamora

Blue Hole: An artisan-fed quarry that measures approximately 60 feet in diameter and 80 feet in depth near Santa Rosa, NM. It is very popular with divers of all types because of its crystal clear waters.

Rio Grande National Monument in winter



WHAT MAKES YOU TICK ?

Chapter A1: The history of diffuse atherosclerosis?

Clinical Vignette

Walt Eisenhoff is a 55 year old biology teacher at a local college. He is very interested in preventing heart disease but wonders whether he is seeing the big picture. At a recent public lecture on cardiovascular diseases, he asked, “Can a heart attack be considered as secondary to blood vessel disease, instead of being a disease of heart muscle? And if it can, does it mean that other blood vessels in our bodies could have atherosclerosis and cause disease in other organs?”

Comment

To rephrase Walt’s questions, “If a cholesterol-induced inflammation of vessels anywhere in the body is the fundamental disease leading to an heart attack, what other organs could also become damaged by the same process?” Historically, in 1815 the pathologist J. Hodgson first described the fatty arterial degeneration seen in arteries in man as *atheroma*, from the Greek word for porridge. Coincidently, in 1812 doctor John Warren described sudden death in patients experiencing acute chest and neck pain and called it *angina pectoris*, from the Greek words “strangling throat.” Thirty years later in 1833, the term *atherosclerosis* was first used by pathologist Johann Lobstein based upon his microscopic description of blood vessel plaque formation with fatty degeneration of cholesterol. A link between the pathologist’s description of atherosclerosis and the doctor’s description of heart attacks was suggested.

One hundred years passed with no further major medical advances in preventing heart disease. Finally, in 1945 the U.S. government initiated the Framingham Heart Study to look for connections between common illnesses and the occurrence of heart attacks. The idea was to identify any association with the proposed heart attack risks of hypertension, diabetes, blood cholesterol, aging, or gender to actual heart attacks. During the next 40 years two scientists, Doctors Brown and Goldstein asked whether families with inherited high blood cholesterol levels also experienced heart attacks. After much effort, they confirmed this link and for it received the 1985 Nobel Prize in medicine. As a result of their discovery, the search for treating high blood cholesterol immediately began. Seven years later, Dr. Akira Endo reported the beneficial effect of statins to block cholesterol production in the liver, which resulted in the reduction of the occurrence of heart attacks.

Meanwhile, the investigation of inflammation continued and in the last decade a close association of inflammation with heart attacks was established. The cardiologist, Doctor Paul Ridker, demonstrated that increased inflammation was as important as increased cholesterol for the causation of heart attacks. It is now clear that stroke occurring in the brain, abdominal aorta aneurysm, kidney failure, and vascular obstruction in legs are all diseases of atherosclerosis in blood vessels as the primary underlying disease process.

The answer to Walt's question has required over 200 years of research, from 1815 to the present. Clearly, disease of the arterial vessels providing blood to the heart is the primary cause of heart attacks. However, these diseased vessels are not restricted to just the heart. All other organs may be also damaged, resulting in strokes, aneurysms, kidney failure, and blood flow blockage to the extremities. The good news is that preventing heart disease will also prevent other organ damage by removing atherosclerotic plaques from all arterial vessels.

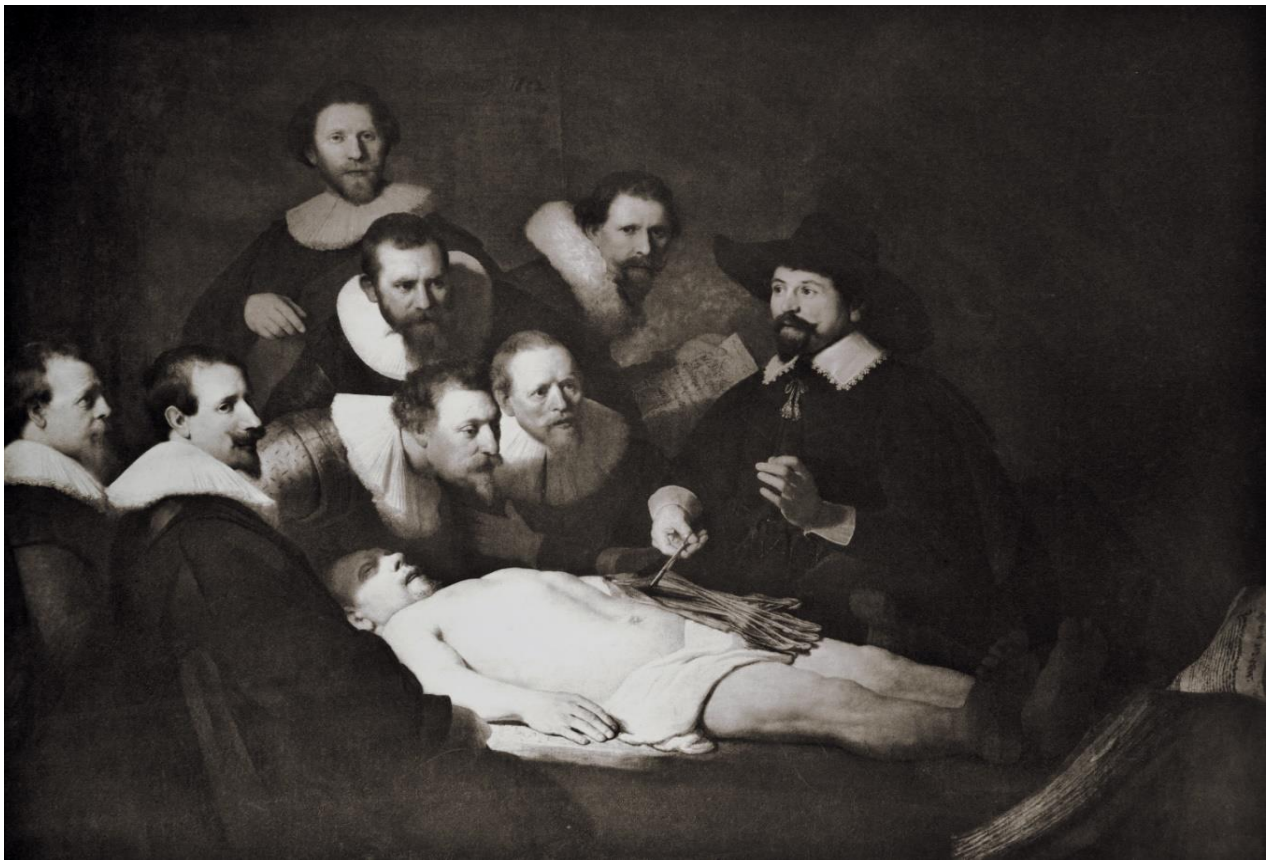


Figure legend – Diffuse atherosclerosis of the arteries can damage any organ in the body including the brain (stroke), kidney (renal failure), aorta (aneurysm), and heart (angina and myocardial infarction). Don't become a corpse in a medical textbook.

Chapter A2: A heart attack – why me?

Clinical Vignette

Jed Black is a 55 year old medically retired plumber who had a heart attack 5 years ago. He is currently taking nine different medications for his heart, his blood pressure, and his diabetes. He quit smoking ten years ago and has since gained 22 lbs., which he blames on his inability to exercise. He often gets short of breath when he lies in bed and feels better when he uses three pillows under his head. He is bitter about the fact that his friends are still working and apparently healthy. He asks, "Why did I get a heart attack – why me?"

Comment

Atherosclerosis is a progressive disease and does not stop after one heart attack. The reason that Jed had a heart attack and his friends did not is a result of many factors. Some of the factors are not under Jed's control, such as the specific genes he inherited from his parents. Genes affect many structures and functions in the body such as the size of the heart arteries and their ability to resist atherosclerosis. However, what Jed has not accepted is that there are also several factors (called risk factors) that Jed could change to prevent heart attacks. If he had taken control of these risk factors as a young adult, he would not have suffered a heart attack at middle age.

Atherosclerotic plaques in Jed's coronary arteries have been getting larger since birth. The growth of these plaques is increased by many different risk factors, and their effects add up over time. Because it is difficult to convince teenagers of their own mortality, the easiest time to improve one's lifestyle is during early adulthood. Yearly checkups that include cardiac risk factor assessment is warranted. Individuals with significant risk factors should have a coronary artery calcium scan to assess atherosclerosis in their coronary arteries. Any positive score should be aggressively treated medically and risk factor modification initiated. Heart attacks are preventable if heart disease is identified early and atherosclerosis reversal therapy is initiated.

Heart disease risk factors all come together to accelerate the atherosclerotic process. This involves the movement of LDL cholesterol particles from the blood into the walls of the coronary arteries (and all other arteries also). Movement of LDL cholesterol is accelerated by

inflammation throughout the body, which can be increased by obesity, diabetes, smoking, high LDL cholesterol and many other risk factors. Once inside the artery wall, the LDL particles are engulfed by macrophages, which merge to form fatty streaks and atherosclerotic plaques. These plaques eventually rupture into the artery and cause a blockage which prevents blood from delivering oxygen and nutrients to the heart muscle. This causes pain in the chest, neck, and arm which is historically called “angina”.

Jed needs to remember that it is not too late to reduce his risk factors. Otherwise, he will likely have another heart attack that may kill him. Atherosclerosis is a progressive disease and does not stop with one heart attack. He needs to acknowledge that his previous lifestyle contributed to his current heart condition and make a serious effort to take charge of his health. A cardiac rehabilitation program would be a good place for Jed to start. Setting goals of an LDLc of <50 mg/dl and an hsCRP <1.0 mg/L is critical.

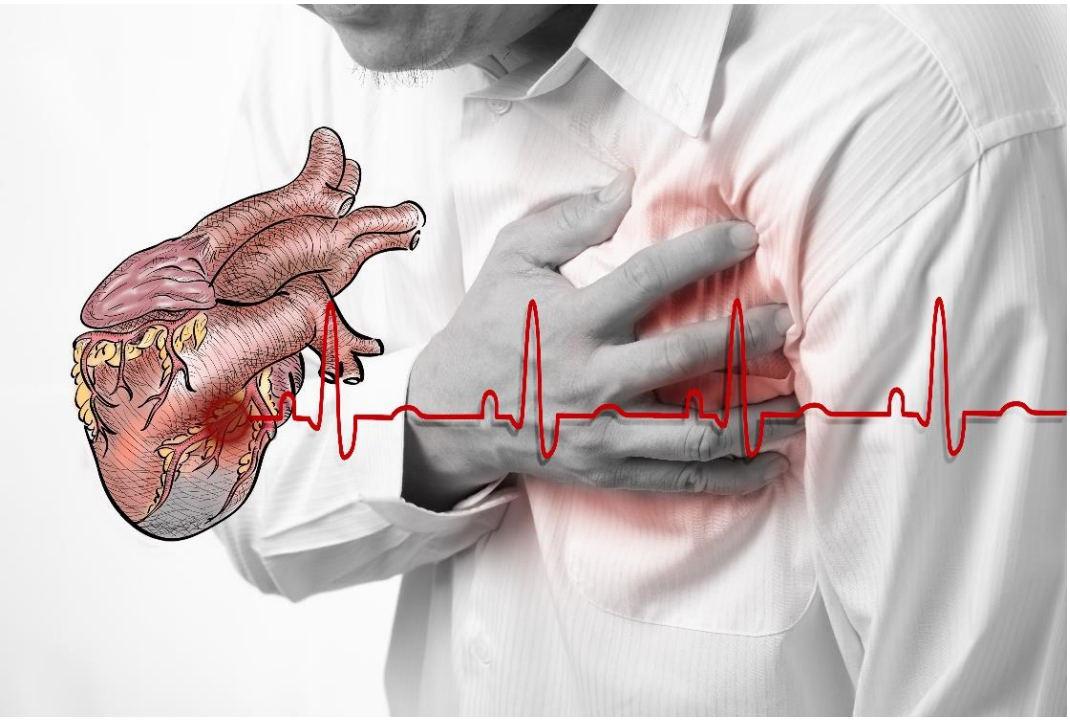


Figure legend – A heart attack occurs when LDL cholesterol builds up (as a plaque) in an artery wall and it ruptures into the lumen. This rupture than causes a blood clot to form over the rupture that then blocks the artery. Preventing or reversing the LDL cholesterol build up will prevent a heart attack and result in a long life span.

Chapter A3: What is Inflammation and is it harmful?

Clinical Vignette

Fred Hersey is a 33 year old male who has severe pains in his hands and feet that his doctor identified as rheumatoid arthritis. His joints become swollen and warm to the touch. It is difficult for him to write a letter because of the pain in his hands. His doctor put him on a medicine which is supposed to reduce the inflammation. He was told that his C-reactive protein (CRP) was very high and that it was a good measure of inflammation. Although his LDL cholesterol is "on the low side," he is worried about heart disease because his father and one uncle both had a heart attack at an early age. He has heard that inflammation is a major risk factor for heart disease and wants to know what it is and what he can do about it.

Comment

Inflammation is a term that is used to describe the activity of the body against harmful invaders. This can take many forms and sometimes we don't know who the invaders are. However, we recognize the body's defenses by the pain, swelling, redness, and warmth that inflammation causes. Inflammation is caused by the secretion of chemicals from circulating white blood cells. These chemicals destroy invading bacteria and viruses. The chemicals also attract more white blood cells (macrophages) which also have the ability to take up cholesterol particles (LDL cholesterol) and form fatty streaks that eventually turn into atherosclerotic plaques. These plaques can rupture and cause a heart attack or stroke. Many chronic diseases such as diabetes, hypertension, arthritis, etc., cause a general (throughout the body) inflammatory state. In the presence of a chronic inflammatory disease like arthritis, the heart vessels are vulnerable to damage. This puts the person at risk for heart disease, even though his/her chronic disease has nothing to do with the heart. Measuring your hsCRP is a good way to determine if you are at risk because of inflammation. You should try to get your hsCRP below 1.0 mg/L. Many medicines will reduce inflammation but some have serious side effects. Relative to preventing heart disease, both statins and ezetimibe reduce inflammation. In addition, a small dose of aspirin also reduces inflammation. Keep this in mind if your coronary heart calcium scan is positive.

Figure legend– Everyone has experienced inflammation. It can occur anywhere in the body, including the heart. The cause may be an infection, trauma, obesity, genetics, or other unknown factors. In the heart, it causes LDL cholesterol to form atherosclerotic plaques (hardening of the arteries). One goal of treatment is to reduce the inflammation. One measure of inflammation in your body is the blood level of C-reactive protein (hsCRP). A calcium heart scan will suggest whether inflammation has affected your heart and caused the formation of dangerous atherosclerotic plaques that have calcified.

A.

WHAT MAKES YOU TICK?

Citations

1. Aliev G, Burnstock G. Watanabe rabbits with heritable hypercholesterolemia: a model of atherosclerosis. Histol Histopathol.1998(3):797-817.

2. Fuchs VR, Milstein A. The $640 billion question – Why does cost-effective care diffuse so slowly? N Engl J Med 2011; 364(21):1985-1987.

3. Fuster V. The CVD paradox: mortality vs. prevalence. Nature Reviews Cardiology. 2009; 6:669 doi:10.1038/nrcardio.2009.187

4. Havel RJ, Yarnada N, Shames DM. Watanabe heritable hyperlipidemic rabbit: animal model for familial hypercholesterolemia. Arteriosclerosis Supplement I (1989; 9:1-33 – I 38.

5. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol. 2013; 62(19):1748-1758. doi: 10.1016/j.jacc.2013.05.071.

6. Libby P, Theroux P. Pathophysiology of Coronary Artery Disease. Circulation 2005; 111:3481-3488.

7. Libby P. Atherosclerosis: The new view. Sci Am 2002 May; 286(5):46-55.

8. Libby P. Inflammation in atherosclerosis. Nature 2002; 420:868-874.

9. Morris ZS Wooding S, Grant J. The answer is 17 years, what is the question: Understanding time lags in translational research. J R Soc Med 2011; 104:510-520.

10. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 2012; 366:54-63.

11. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D et al. From vulnerable plaque to vulnerable patient – Part III: Executive summary of the screening for Heart Attack Prevention and Education (SHAPE) Task Force Report. AM J Cardiol. 2006 Jul 17; 98(2A):2H-15H.

12. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study. J Am Coll Cardiol. 2008; 52(7):523-527.

13. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017; 377(12):1119-1131. doi: 10.1056/NEJMoa1707914. Epub 2017 Aug 27.

14. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S et al. for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, Pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation 1998; 98:839-844.

15. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999; 340(2):115-126.

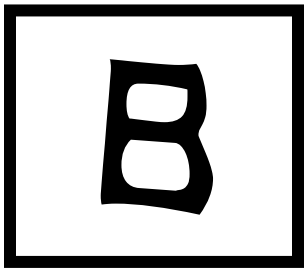
16. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011; 364(3):226-35.

17. van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994; 89(1):36-44.

18. Yonetsu T, Kakuta T, Lee T, et al. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. European Heart Journal 2011; 32:1251–1259. doi: http://dx.doi.org/10.1093/eurheartj/ehq518 1251-1259 First published online: 27 January 2011

Contributed by: S. Murphy

San Felipe de Neri Church in Old Town,
Albuquerque, NM



MY FIRST STEP

Chapter B1: How do I get started reversing my heart disease?

Clinical Vignette

Sarah and Tony Brown are a married couple in their 40's. They both have a strong parental family history of heart attacks and strokes. They have read this book and are convinced that they do not have to repeat their parents' fate and die of cardiovascular disease. They realize that atherosclerosis is a progressive disease which begins at birth and sooner or later, they will suffer the same fate as their parents unless they make some changes. However, they are confused about how they should get started since the concept of reversing atherosclerosis is new to them. Any suggestions?

Comment

It is understandable that Sarah and Tony are a little overwhelmed with their new information. However, we can assure them that reversing atherosclerosis is not rocket science. It is actually very easy if they approach it step by step. They have already taken the *first step,* i.e., to acknowledge that no one should die of cardiovascular disease. This acknowledgement will result in a lifelong commitment to avoid behaviors that put them at risk.

The *second step* is to review whether they have any of the major risk factors that contribute to atherosclerosis (hypertension, smoking, diabetes, obesity, and high LDL and/or inflammation). Getting these risk factors under control is extremely important for lowering the risk (and progression) of atherosclerosis. This book contains a chapter describing these risk factors and how to control them.

The *third step* is for Sarah and Sam to assess their own current status of atherosclerosis in their heart (and presumably elsewhere, including their brain). This can easily be done with a coronary artery calcium scan. This inexpensive, noninvasive test will directly measure any substantial plaque buildup in their heart. The magnitude of the calcium score will accurately predict their chance of a cardiovascular event in the future.

The *fourth step* is to measure their risk as related to their blood lipid profile (especially the LDL level) and their blood level of inflammation as measured by a high sensitivity C- reactive protein (hsCRP). Their goal should be an LDL below 50 mg/dl and an hsCRP below 1.0 mg/L.

It is likely that this goal will require the addition of two inexpensive medications at low dosages: rosuvastatin 10 mg/day and ezetimibe 10 mg/day.

The *fifth step* is to change their diet and "Eat Smart." Eating smart does not mean giving up anything that they like. It means eating a diet that will not cause weight gain or raise their LDL level. Chapters throughout the book discuss this approach in more detail. Of course, Sarah and Sam should discuss these changes with their physician. In our experience, primary care physicians always support an improved lifestyle and a reduction in atherosclerotic risk.

Figure legend – Many risk factors for heart disease and stroke can be corrected, including reducing cholesterol in your diet. Some risk factors will require medication from your doctor and some will necessitate an improvement in your lifestyle. However, having a heart attack or stroke is much worse than any change you need to make in correcting these risk factors. Skeptical? Just ask anyone who has had a heart attack or stroke – if they are still alive.

Chapter B2: Should I monitor heart disease risk factors in my teenage children?

Clinical Vignette

Shirley Blackstone is a 51 year old mother of three healthy teenage boys, ages 12, 15, and 17 years. Their father died last year at age 53 of a heart attack. Their grandfather also had heart disease and died at age 58 years. Shirley does not want the same fate to befall her children. Her physician told her that they were probably too young to worry about testing for heart disease. However, the boys' pediatrician recommends screening for blood fat disorders. Shirley wants to know what she should do.

Comment

The answer to Shirley's dilemma is very important to the long-term health of her children. In order to make the right decision, she needs to know about the medical condition called familial hypercholesterolemia. This medical term relates to a gene which carries an inherited form of high blood cholesterol. Familial hypercholesterolemia is inherited as a gene from one or both parents. If it is inherited from both parents so that one gene came from each parent, it is called familial homozygous hypercholesterolemia (a real mouthful). If it comes only from one parent, it is called familial heterozygous hypercholesterolemia (another big mouthful). Why is this condition important to Shirley? The reason is that her children may have inherited the gene from the father or grandfather. What can she do about it?

Familiar hypercholesterolemia is important because it is the number one genetic cause of heart attacks in the U.S. population. It was discovered by two investigators who received the Nobel Prize in 1985 for their discovery. In the homozygous form of the disease, children may die of a heart attack by the age of twenty years if not treated. Thankfully, this form of the disease is rare. In the general population, the incidence of the heterozygous form is one in 250 people but it is much more common in people with a family history of heart attacks at an early age (like Shirley's). It is easily recognized with a blood test because it is characterized by an increase in the blood concentration of LDL cholesterol.

The American Academy of Pediatrics recommends that all children be screened for this condition by the age of 12 years with a blood lipid profile. Treatment should always involve improved lifestyle including diet and exercise and if necessary, low dose statin therapy.

The recommendation of early screening is based on the fact that many young people who have died suddenly in automobile accidents have been shown to already have cholesterol plaques in their heart's arteries (premature heart disease). Since atherosclerosis starts in an individual before birth, is there any reason to wait for adulthood before starting to attack this lethal disease? The answer to Shirley's question is for her to have all of her teenage children screened for familial hypercholesterolemia as soon as possible.

Figure legend - A positive family history of heart disease or stroke is a good indication that there may be a genetic predisposition to a high blood cholesterol. The best protection against this deadly disease is early detection, screening, and treatment of all teenage adolescents with a routine lipid profile blood test. Early treatment will prevent major heart problems later in life.

Chapter B3: How do I know if my pills are working?

Clinical Vignette

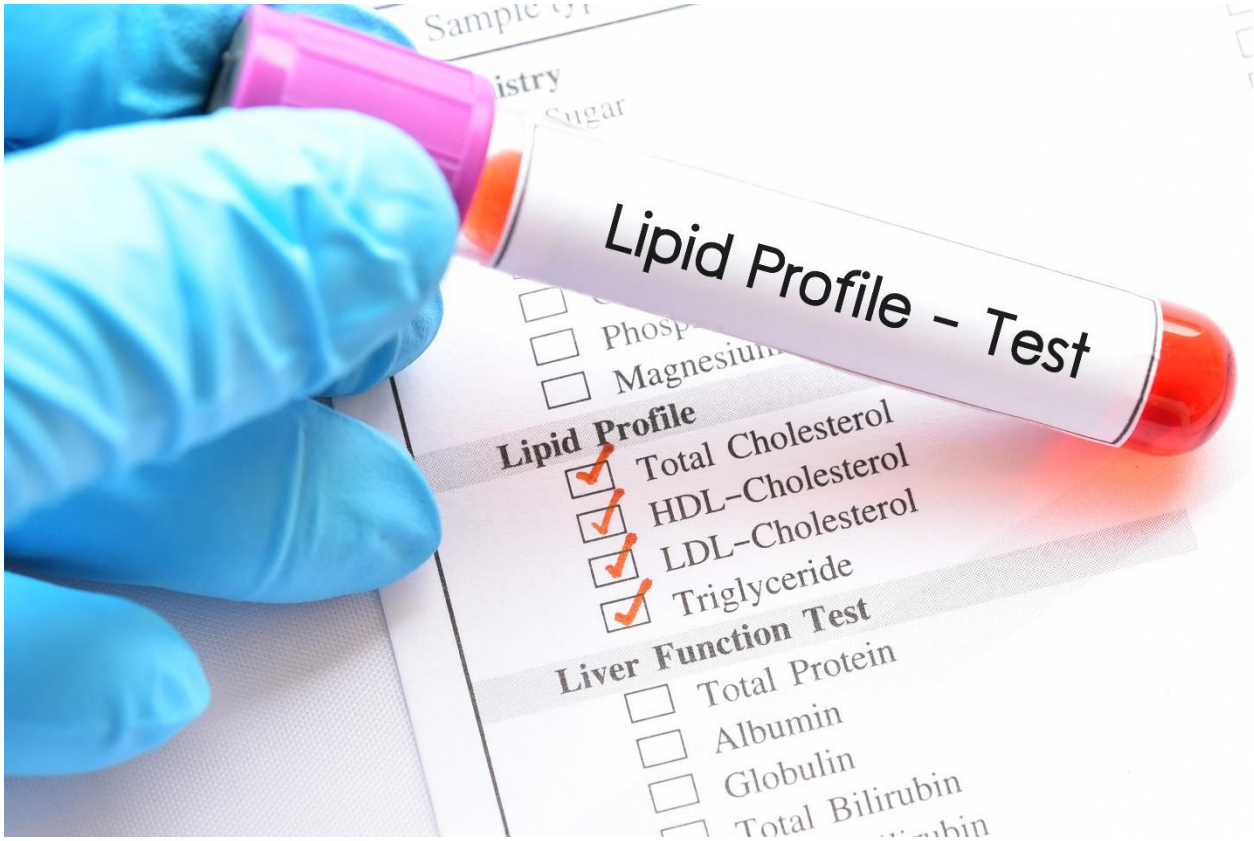
Fred Herman is a 61 year old farmer who has been working on a dairy farm his whole life. His diet is high in butter, cheese, eggs, and meat. His LDL cholesterol is 145 mg/dl. He smokes two packs of cigarettes per day and has recently developed type 2 diabetes. He doesn't like doctors or the medicines that they prescribe for his hypertension. They make him feel light-headed. However, he does follow their advice, so he had a calcium heart scan two weeks ago and his score was 1,230. His doctor immediately put him on triple therapy (rosuvastatin 10 mg/day, ezetimibe 10 mg/day, aspirin 81 mg/day) because of his high heart attack risk. He asks his doctor "How do I know these pills are working?"

Comment

Fred asks a question that most people ask who take triple therapy because the medications cause no changes in his body that he can feel. Studies that have actually monitored the reversal of atherosclerotic plaques in the coronary heart arteries have used sound waves (i.e., ultrasound) to visualize the changes in plaque volume with medication. What they have found is that when the LDL cholesterol goes below 65 mg/dl, that some plaque regression can be seen. However, the volunteers in these studies usually do not have all the risk factors for heart disease that Fred has. To account for the added danger of Fred's risk factors, we recommend that Fred reduce his LDL cholesterol to below 50 mg/dl. If he does, Fred can be 99% sure that he is reversing his atherosclerotic plaques.

Although not studied in the same way as LDL cholesterol, inflammation induced by major risk factors has been shown to be a critical factor in the rupture of atherosclerotic heart plaques. The stability of the plaque is dependent on the amount of inflammation around the edges of the plaque's cap. Therefore, Fred should also monitor the amount of inflammation in his body by reducing his C-reactive protein (CRP) to less than 1.0 mg/L. His triple therapy will help him do this as well as getting his diabetes under control and attaining normal body weight. It is also very important that Fred stop smoking to reduce his inflammation. In other words, controlling his risk factors and taking his medication is Fred's best chance to avoid a heart attack. He should monitor his LDL cholesterol and C-reactive protein every three months for the first year,

then every six months as long as he is close to the target goal described above. If he does, Fred can be assured that he reversing his plaques and saving his heart.



.

Figure legend – The best way to tell if your rosuvastatin and ezetimibe pills are working is to obtain a lipid profile. Compare your LDL cholesterol value with the value you had before starting the pills. You should wait at least two months after starting your pills before getting another lipid profile because it takes that long for the pills to reach maximum effectiveness. Remember that the diet also affects the LDL cholesterol level so be sure to follow the dietary recommendations in this book.

B.
MY FIRST STEP

Citations

1. Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT, et al. Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years. J Am Coll Cardiol. 2016; 67(9):1013-1022.

2. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. BMJ. 2002; 324(7353):1570-1576.

3. Leening MJG, Berry JD, Allen NB. Lifetime perspectives on primary prevention of atherosclerotic cardiovascular disease. JAMA 2016; 315(4):1449-1450.

4. Leibowitz M, Karpati T, Cohen-Stavi CJ, Feldman BS, Hoshen M, Bitterman H, et al. Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment. JAMA Intern Med. 2016; 176(8):1105-1113.

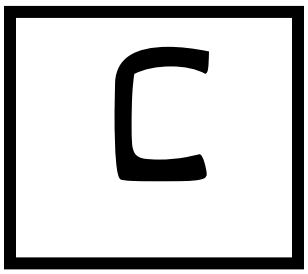
5. Mamudu HM, Paul TK, Veeranki SP, Budoff M. The effects of coronary artery calcium screening on behavioral modification, risk perception, and medication adherence among asymptomatic adults: a systematic review. Atherosclerosis. 2014; 236(2):338-350.

6. O'Keefe JH, Jr., Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: Lower is better and physiologically normal. J Am Coll Cardiol 2004; 43(11):2142-2146 doi: 10.1016/j.jacc.2004.03.046.

7. Ohman EM, Chronic stable angina. N Engl J Med 2016; 374:1167-1176.

8. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: A meta-analysis. JAMA Cardiol. Doi:10.1001/jamacardio.2018.2258

9. Steinberg D. Earlier Intervention in the Management of Hypercholesterolemia. JACC. 2010;56(8):627-629.



CALCIUM IN MY HEART

Chapter C1: What is a coronary artery calcium scan?

Clinical Vignette

John Whitcome is a 46 year old male with a family history concerning for atherosclerotic heart disease. His 49 year old brother was recently admitted to the hospital for acute, severe chest pain and his father died suddenly at the age of 51of an unknown cause. He has mild hypertension and borderline high cholesterol. He was recently laid off at his work place and lost his health insurance. His wife is currently working so he is just able to pay his bills. He wants to know if he has heart disease and his doctor recommends a coronary artery calcium scan. He wants to know what that test is.

Comment

The coronary artery calcium scan is arguably the best, cost-effective, noninvasive heart test that has become popular in the last decade. It is based on the observation that the body walls off foreign bodies with calcium when it can't readily remove them. When tuberculosis was very common in the US population, it was often recognized on chest x-rays by the small calcium deposits in the lungs. The body takes a similar approach to atherosclerotic plaques in your coronary arteries and deposits calcium in and around the plaque. This can be seen on a chest CT scan, which takes picture slices through the heart. The test takes about ten minutes and is noninvasive and painless. The small amount of radiation that you receive is equal to living in Denver for 3 months. Think of it as a virtual biopsy of the health of your heart.

Besides being noninvasive, the coronary artery calcium scan has several advantages over other screening tests for heart disease:

1) It's relatively inexpensive ($50 to $200) in most U.S. cities. Some medical insurance policies cover at least part of the cost. Check with your insurance carrier.

2) It's very specific for heart disease – if your score is above zero, heart disease is present.

3) If the score is zero, the chance of having a heart attack in the next ten years is very, very small.

4) The higher the score, the greater the risk for heart disease.

In summary, this is a great test for anyone who wants to know what their risk is of having a future heart attack. This test will also suggest the urgency of medical treatment. If you are an adult, then you are never too young or too old to have this test, especially if you have any major risk factors for heart disease (diabetes, hypertension, obesity, smoking, and/or elevated blood LDL cholesterol). It will encourage you to improve your lifestyle and reduce your risk of heart disease. We highly recommend it.

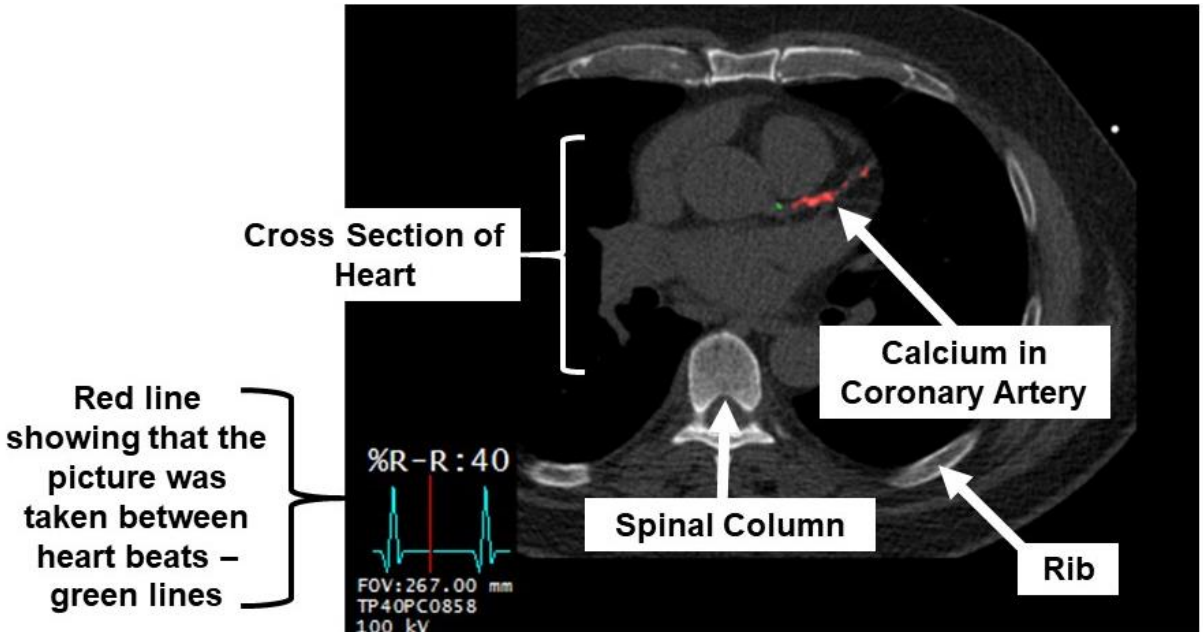


Figure legend - This figure of a coronary artery calcium scan demonstrates calcium deposits in a heart vessel (normally white but colored red in this figure for emphasis). Parts of the ribs in the chest wall are also seen. The person with this scan would have an elevated coronary artery calcium score. However, only the calcium in the four main coronary arteries is counted when calculating the total score. Pictures of multiple slices of the heart and blood vessels are taken between heart beats. This is one slice.

Chapter C2: Why should I have a calcium heart scan?

Clinical Vignette

Michael Neff, a 45 year old male, is a professor at a university. He complains of tightening in his chest when sitting at home in the evening preparing for the next day's lectures. He admits that he gets nervous when preparing and giving lectures to very large classes. He gets no chest pain at any other time. His father had a heart attack at age 51. His wife is worried that he is about to have a heart attack and asks him to see a doctor. His cholesterol is in the average range and he has no other risk factors for a heart attack except for mild obesity and his father's history. He decides to have a calcium heart scan which shows no calcium in any heart blood vessels. He is greatly relieved with this test result since the incidence of a heart attack is very low in people with a coronary artery calcium score of zero. However, to be on the safe side, he decides to increase his exercise program, eat healthier foods, and to lose ten pounds. He agrees to repeat the calcium heart scan in five years.

Comment

A calcium heart scan can be very reassuring to people worried about their heart, and may motivate their changing to a healthier lifestyle. If calcium is present in the heart arteries, it always means that these vessels have a dangerous buildup of cholesterol plaque. These plaques can rupture, resulting in a blood clot in the heart arteries, causing a heart attack. This is the reason that a calcium heart scan with a positive score should immediately be treated (as discussed in other chapters). However, when the scan shows no calcium, then immediate medical treatment is not necessary. Because plaque buildup can occur as people get older and calcification of these plaques will eventually occur, a repeat calcium heart scan is a good way to monitor your risk for a future heart attack. We recommend a repeat calcium heart scan at least every five years as a good preventative test. Other preventative tests are done on a periodic basis (such as a colonoscopy or mammogram), so why not also check for heart disease? Since heart disease is reversible when identified early, this test can save your life.

Compared to other diagnostic tests, a calcium heart scan is very inexpensive and noninvasive. It takes about 10 minutes to complete and the only preparation by the patient that is needed is to avoid coffee the morning of the test (caffeine increases your heart rate, which makes it difficult for the CAT scan to take pictures of your heart between heart beats). We have

included a copy of the brochure in the Appendix that we give our patients before their coronary heart scan. We think that you will agree that this is the most pleasant diagnostic test that you have ever taken.

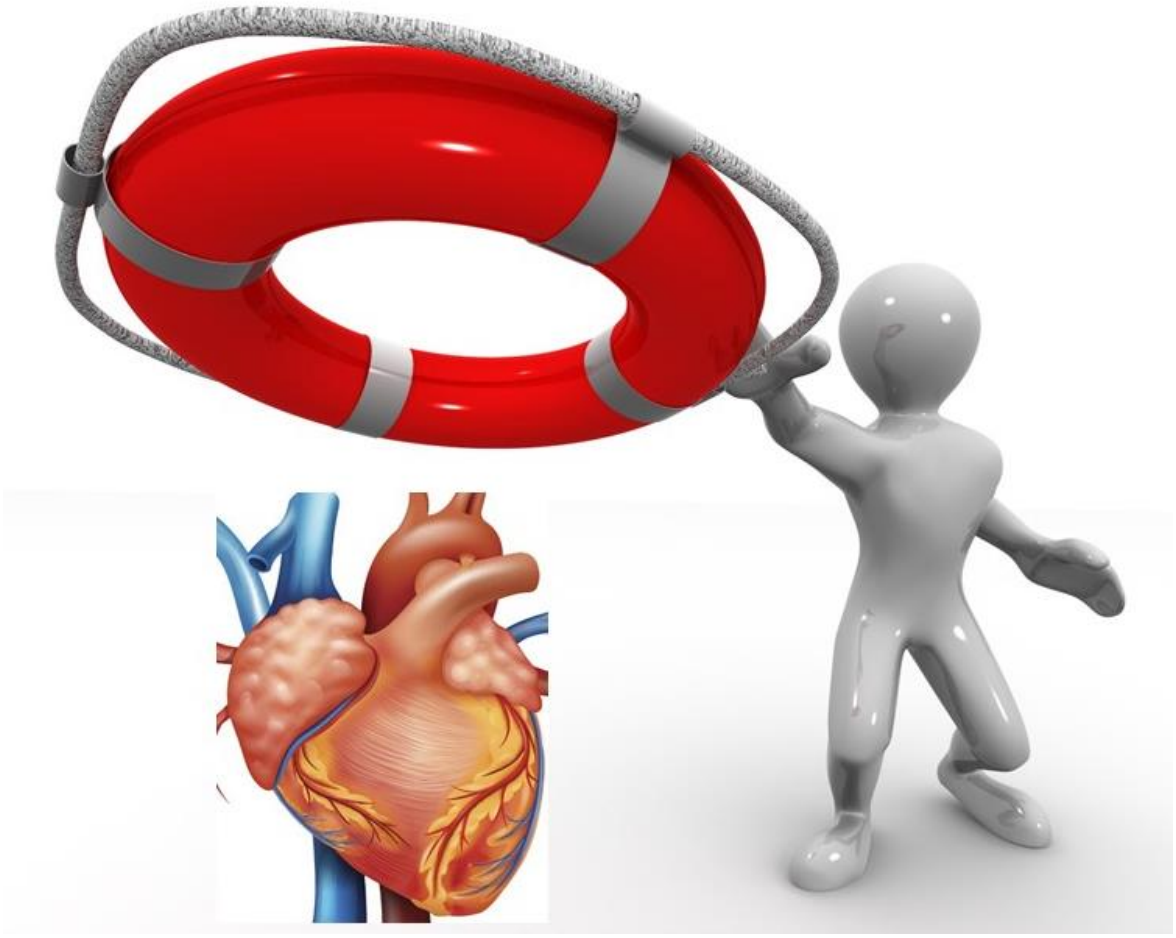


Figure legend – A coronary calcium heart scan is a noninvasive test that requires10 minutes and takes multiple pictures of your heart arteries. The amount of calcium in your heart arteries predicts your chance of a heart attack in the future. It is similar to throwing a life preserver to a drowning person. It is the best way to tell you about your heart and whether or not it needs help.

Chapter C3: Where can I get a calcium heart scan?

Clinical Vignette

Rebecca Vigil is a 51 year old postal worker who has three major risk factors for atherosclerotic heart disease. She lives in a small, rural town outside of Kansas City, Missouri. She read a magazine article on the benefits of a calcium heart scan and decides both she and her husband should obtain one. Her local physician is not familiar with this test and does not know where she can have one done. How should she solve this dilemma?

Comment

Rebecca asks a good question – actually three good questions: 1) Where can I get a calcium heart scan? 2) How much will it cost?, and 3) Do I need a doctor's prescription? Let's answer each question in turn. To our knowledge, there is no country-wide database that lists all of the locations doing calcium heart scans in the U.S. However, all institutions that do CT (computed tomography) scans are technically able to do calcium heart scans because they already have the necessary equipment. However, they do need to have a trained technician and an administrative setup to handle the paperwork. The easiest approach to finding a facility near your location is to go to the internet and then to the website of the nearest hospital or radiological group in your town. At their website, go to their radiology department and see if calcium heart scans are listed as procedures that they offer. If nothing is listed, call their radiology department and ask specifically whether they perform coronary artery calcium heart scans? Alternatively, you can go to your telephone book's yellow pages and look up the number of a radiology facility near you and call them to ask the same questions. With a little perseverance, you will find a facility doing calcium heart scans.

The second question you should ask is the cost of the calcium heart scan. The cost should range between $50 and $200. Don't ask us why there is a fourfold difference in cost – it's known as a profit margin. If it exceeds this cost, we suggest finding another location for your scan. In addition, some insurance companies will reimburse you for the cost of the scan. You will need to check with your insurance company because reimbursement varies from state to state. For example, in some parts of the southwest U.S., Medicare will reimburse you $94 toward the cost of the scan.

The third question is whether you need a doctor's prescription or order to obtain a calcium heart scan. This is variable – some facilities do require an order from your doctor and some do not. You need to ask the facility that you are planning to go to for your scan. We strongly recommend that whether you get a doctor's order or not, that you have a physician to discuss the results with you before having the scan. Getting a calcium heart scan will do nothing toward saving your life if you don't get appropriate medical treatment if the scan is positive.

Figure legend – A calcium heart scan takes about ten minutes. It's a simple test requiring no injections, no pills, no intravenous fluid lines, and very little preparation. All facilities with a CT scanner can do this test but may not be administratively set up to process the data and billings. All cities and most large towns will have facilities to do a calcium scan. Contact your local radiological CT facilities or hospital and inquire about calcium heart scanning.

C.

CALCIUM IN MY HEART

Citations

1. Agarwal S, Cox AJ, Herrington DM, Jorgensen NW, Xu J, Freedman BI, et al. Coronary calcium score predicts cardiovascular mortality in diabetes: diabetes heart study. Diabetes Care. 2013; 36(4):972-977.

2. Alexopoulos N, Raggi P. Calcifaction in atherosclerosis. Nat Rev Cardiol. 2009;6(11):681-688.

3. Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, et al. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging. 2009; 2(6):692-700.

4. Blaha MJ, Blumenthal RS, Budoff MJ, Nasir K. Understanding the utility of zero coronary calcium as a prognostic test: a Bayesian approach. Circ Cardiovasc Qual Outcomes 2011; 4:253-256.

5. Blaha MJ, Budoff MJ, DeFilipppis AP, Blankstein R, Rivera JJ, Agatston A, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011; 378:684-692.

6. Budoff MJ, McClelland RL, Nasir K, Greenland P, Kronmal RA, Kondos GT, Shea S, Lima JA, Blumenthal RS. Cardiovascular events with absent or minimal coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2009; 158:554-561.

7. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010; 3:1229 –36.

8. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, Shea S, Szklo M, Post W, Lima J, Bertoni A, Wong ND. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-ethnic study of atherosclerosis). J Am Coll Cardiol 2013; 61:1231-1239

9. Budoff MJ, Young R, Burke G, Carr JJ, Detrano RC, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: The multi-ethnic study of atherosclerosis (MESA). Eur Heart J. 2018; 0, 1-10. Doi:10.1093/eurheartj/ehy217.

10. Budoff MJ, Yu D, Nasir K, Mehrotra R, Chen L, Takasu J, Agrawal N, Liu ST, Blumenthal RS. Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 2005; 149:695-700.

11. Burge MR, Eaton RP, Comerci G, Cavanaugh B, Ramo B, Schade DS. Management of asymptomatic patients with positive coronary artery calcium scans. J Endo Society 2017; 1(6):588-599. Doi: 10.1210/js.2016-1080

12. Burge MR, Eaton RP, Schade DS. The role of a coronary artery calcium scan in type 1 diabetes. Diabetes Technol Ther 2016; 18(9):594-603.

13. Carr JJ, Jacobs DR, Jr, Terry JG, Shay CM, Sidney S, Liu K, et al. Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death. JAMA Cardiol. 2016; doi:10.1001/jamacardio.2016.5493 Published online February 8, 2017.

14. Chaikriangkrai K, Velankar P, Schutt R, Alchalabi S, Nabi F, Mahmarian J, et al. Additive prognostic value of coronary artery calcium score over coronary computed tomographic angiography stenosis assessment in symptomatic patients without known coronary artery disease. Am J Cardiol. 2015; 115(6):738-744.

15. Cheng VY, Lepor NE, Madyoon H, Eshaghian S, Naraghi AL, Shah PK. Presence and Severity of Noncalcified Coronary Plaque on 64-Slice Computed Tomographic Coronary Angiography in Patients With Zero and Low Coronary Artery Calcium. Am J Cardiol 2007; 99:1183-1186.

16. Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, Backlund J-Y C, Zinman B, Jacobson A, Sun W, Lachin JM, Nathan DM for the DCCT/EDIC Research Group. The Effect of intensive glycemic treatment on coronary artery calcification in type diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) Study. Diabetes 2006; 55:3556-3565.

17. Eaton RP, Burge MR, Comerci G, Cavanaugh B, Ramo B, Schade DS. Abnormal coronary artery calcium scans in asymptomatic patients Am J Med 2016; http://dx.doi.org/10.1016/j.amjmed.2016.10.006

18. Greenland P, Blaha M, Budoff M, Erbel R, Watson K: Coronary Calcium Score and Cardiovascular Risk. J Am Coll Cardiol. 2018 Jul 24;72(4):434-447. doi: 10.1016/j.jacc.2018.05.027.

19. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004; 14; 291(2):210-215.

20. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr. 2017; 11(2):157-168.

21. Hecht HS, Narula J. Coronary artery calcium scanning in asymptomatic patients with diabetes mellitus: a paradigm shift. J Diabetes 2012; 4:342-50.

22. Hecht HS. Coronary artery calcium scanning: past, present, and future. JACC Cardiovasc Imaging 2015 May; 8(5):579-596 doi: 10.1016/j.jcmg.2015.02.006.

23. Kalia NK, Miller LG, Nasir K, et al. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis 2006; 185(2):394-399. Epub 2005 Jul 26 PMID: 16051253

24. Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi A-A, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: A meta-analysis. JAMA 2016; 316(20):2126-2134. Doi:10.1001/

25. Keelan PC et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation 2001; 104:412-417.

26. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: What does it really mean? JACC Cardiovasc Imaging. 2018; 11(1):127-142. doi: 10.1016/j.jcmg.2017.10.012.

27. Nakanishi R, Li D, Blaha MJ, Whelton SP, Matsumoto S, Alani A, et al. The relationship between coronary artery calcium score and the long-term mortality among patients with minimal or absent coronary artery risk factors. International Journal of Cardiology 2015; 185:275–281. Doi: 10.1016/j.ijcard.2015.03.146

28. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, Krumholz HM. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines. J Am Coll Cardiol 2015; 66:1657-1668.

29. Nasir K, Rubin J, Blaha MJ, Shaw LJ, Blankstein R, Rivera JJ, Khan AN, Berman D, Raggi P, Callister T, Rumberger JA, Min J, Jones SR, Blumenthal RS, Budoff MJ. Interplay of coronary artery calcification and traditional risk factors for the prediction of all-cause mortality in asymptomatic individuals. Circ Cardiovasc Imaging 2012; 5:467-473.

30. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with Type 1 diabetes: A stronger correlate of clinical coronary artery disease in men than in women. Diabetes 2000; 49:1571-1578.

31. Redberg RF. What is the prognostic value of a zero calcium score? Am Coll Cardiol 2010; 55(7):635-636.

32. Roberts ET, Horne A, Martin SS, Blaha MJ, Blankstein R, Budoff MJ, et al. Cost-Effectiveness of Coronary Artery Calcium Testing for Coronary Heart and Cardiovascular Disease Risk Prediction to Guide Statin Allocation: The Multi-Ethnic Study of Atherosclerosis (MESA). PLoS ONE 2015; 10(3):e0116377. Doi:10.1371/journal.pone.0116377

33. Rodrigues TC, Veyna AM, Haarhues MD, Kinney GL, Rewers M, Snell-Bergeon JK. Obesity and coronary artery calcium in diabetes: The coronary artery calcification in type 1 diabetes (CACTI) Study. Diabetes Technol Ther 2011; 13(10):991-996. Doi:10.1089/dia.2011.0046

34. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol Jan 1998; 31(1):126-33.

35. Shaw L, Giambrone AE, Blaha MJ, Knapper JT, Berman DS, Bellam N, Quyyumi A, Budoff MJ, Callister TQ, Min JK. Long-term prognosis after coronary artery calcification testing. Ann Intern Med 2015; 163:14-21 doi: 10.7326/M14-0612

36. Shaw LJ, Min JK, Budoff M, Gransar H, Rozanski A, Hayes SW, et al. Induced cardiovascular procedural costs and resource consumption patterns after coronary artery calcium screening: results from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study. J Am Coll Cardiol. 2009; 54(14):1258-1267.

37. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Michael Brazaitis M, O'Malley PG. Coronary Calcium Independently Predicts Incident Premature Coronary Heart Disease Over Measured Cardiovascular Risk Factors Mean Three-Year Outcomes in the Prospective Army Coronary Calcium (PACC) Project. J Am Coll Cardiol 2005; 46:807-814.

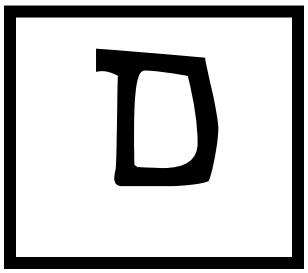
38. Tota-Maharaj R, Blaha MJ, McEvoy JW, Blumenthal RS, Muse ED, Budoff MJ, et al. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. Eur Heart J 2012; 33:2955-2962.

39. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcifction improves cardiovascular risk prediction in the elderly. Circulation. 2005;112(4):572-577.

40. Whelton SP, Silverman MG, McEvoy JVV, Budoff MJ, Blankstein R, Engl J, et al. Predictors of long-term healthy arterial aging: Coronary artery calcium non development in the MESA study. J Am Coll Cardiol Img 2015 Dec; 8(12):1393-1400. doi: 10.1016/j.jcmg.2015.06.019 Epub 2015 Nov 11.

41. Yano Y, O'Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, et al. Association of Coronary Artery Calcium Score vs Age With Cardiovascular Risk in Older Adults: An Analysis of Pooled Population-Based Studies. JAMA Cardiol. 2017. doi: 10.1001/jamacardio.2017.2498.

42. Yoon H-C, Emerick AM, Hill JA, Gjertson DW, Goldin JG. Calcium begets calcium: Progression of coronary artery calcification in asymptomatic subjects. Radiology 2002; 224:236-241. Doi: 10.1148/radiol.2241011191



DO I HAVE HEART DISEASE ?

Chapter D1: What kind of Doctor should advise me about my heart?

Clinical Vignette

Robert Gatsby is a 51 year old accountant for a local publishing firm. He asked "Who should I see about my heart?" He wants advice about keeping his heart healthy because one of his close friends just died of a heart attack. This scared him because his friend was younger than he and had no symptoms of chest pain or other warning signs before collapsing while walking his dog.

Comment

This is a very common question. Many people believe that the answer to Robert's question would be a cardiologist because this medical specialty deals directly with heart disease. The problem with arranging a consultation with a cardiologist is that it is often very difficult to schedule an appointment, and cardiologists usually treat already established heart disease or signs and symptoms of serious heart disease. Alternatively, your primary care giver is very competent to identify if you have heart disease. He/she will perform a history and physical exam including listening to your heart and ordering the appropriate laboratory and radiographic tests. It is very important that you make a list of the testing you should obtain to be certain that your primary care giver does not omit important information.

The first goal is to identify any risk factors for heart disease that you might have. Smoking, obesity, and high blood pressure will be identified by history and physical. Laboratory blood tests will identify diabetes (by hemoglobin A1C), abnormal blood fats (by a lipid profile for high LDL cholesterol), and high inflammation (by a high sensitivity CRP). An electrocardiogram will demonstrate if the electrical conduction through your heart is normal. Most importantly, a coronary artery calcium scan will tell you directly if any calcified plaques are present in your heart vessels. You should discuss the results of each of these tests with your primary care giver before deciding on therapy. If all of the above tests are normal (or negative), we recommend repeating them at least at five year intervals.

Much more likely, however, is that some of the tests will be abnormal. Your primary care giver can give you guidance and suggestions for improvement.

Of all the above tests, the coronary artery calcium score is the most important relative to the health of your heart. In summary, it represents all of the potential insults that may have occurred in the past that would damage your heart. If the scan is positive, then you definitely need preventive therapy. Several chapters in this book discuss our recommendations for this therapy, particularly improvement in lifestyle and reduction of LDL cholesterol to less than 50 mg/dl. To return to Robert's question of what type of physician he should see for his heart, we recommend his primary care giver, with the caveat that Robert should bring a list of tests (listed above) with him to his caregiver's visit so that all of the necessary information about his heart will be obtained.

Figure legend – Robert needs to consult with his primary care giver to find out about the health of his heart. All the tests that he needs are noninvasive and will tell him what his next step should be. We recommend taking a copy of this book chapter to his medical visit to be certain that all the necessary tests will be done.

Chapter D2: Do I need a stress test?

Clinical Vignette

George Akins is a 44 year old surveyor with a positive family history of heart disease (in his father and brother). Recently, while out surveying a property, he became short of breath. He attributed this episode to his being overweight and smoking for 20 years (he recently quit). His electrocardiogram (heart tracing) was normal but his physician recommended a cardiac stress test. George's medical insurance covers only 50% of the $545 that the test costs. George asks, "What is a stress test and what will it tell me about my heart?"

Comment

George is smart to ask this question. The answer may surprise him. A stress test is a commonly ordered test to assess a person's heart function if limited blood flow to the heart is suspected. There are several ways to perform this test, but in its simplest form the patient is first connected to an electrocardiogram with wire leads attached to different parts of the chest. The individual then walks on a raised treadmill to increase his/her heart rate. When the heart rate reaches a maximum rate, the technician examines the electrocardiogram tracing to see if there are any changes in electrical activity to suggest limited blood flow to the heart (this is called "ischemia"). This test is usually safe, although fatalities from heart attacks during the procedure have occurred.

The main problem with this test is that the result can be normal when the patient actually has progressing heart disease due to reduced blood flow to the heart. If this reduced blood supply is less than 50% of normal, then exercise will not cause a positive stress test, thus failing to recognize significant heart disease. This is a dangerous situation because the physician will not treat the patient aggressively for heart disease. Even when the test is positive and suggestive of serious heart disease, it gives no indication as to where the coronary vessel obstruction might be located. According to the US Preventive Services Task Force, "The primary tangible harm of screening exercise tolerance testing is the potential for medical complications related to cardiac catheterization done to further evaluate a positive result." They do not recommend this test be done in individuals without chest pain at rest (called unstable angina).

A better approach for George to learn about the condition of his heart is to have his physician order a coronary artery calcium heart scan. This test costs only $150 or less, takes 10 minutes, and is noninvasive. Based on the resulting score of this test, George can accurately predict his chances of having a cardiovascular event for the next ten or more years. The result will also tell his physician how aggressively to treat him. If his score is zero, then George has a predictable, excellent ten year survival prognosis. However, George should repeat the calcium heart scan in five years in case the score increases above zero and aggressive medical treatment is needed.

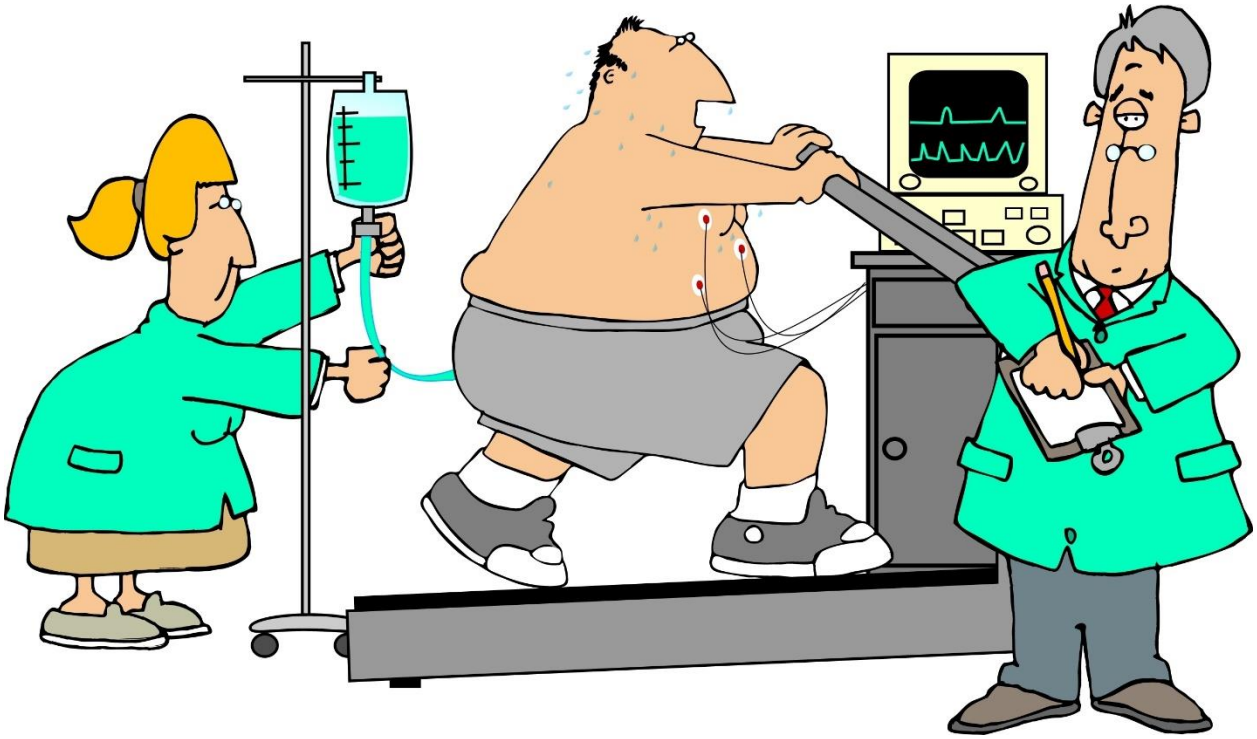


Figure legend – As the name implies, a cardiac stress test stresses the heart muscle and changes its electrical activity. This occurs when sufficient blood supply to the heart becomes limited by atherosclerotic plaques. There are several disadvantages to performing this test, the primary one is its poor sensitivity to detect underlying atherosclerotic heart disease. We rarely recommend this test.

Chapter D3: Why Should I have another calcium heart scan in 5 years?

Clinical Vignette

Five years ago Jack Griego, a 42 year old carpenter, was worried about his heart because his father had a heart attack at age 55 years. Jack felt fine and had no other risk factors for heart disease. His laboratory studies at that time were normal. His doctor suggested that he get a calcium heart scan to check on his heart status. He did as his doctor suggested and was greatly relieved that his calcium heart scan score was zero. His doctor suggested that he get a repeat scan in five years. Five years later Jack underwent a repeat calcium heart scan. During the past five years he has gained 23 pounds and developed both diabetes and hypertension. His repeat heart scan now has a score of 233. His doctor immediately encouraged him to lose weight, start to exercise, and take medication to lower his cholesterol level. If he follows his doctor's advice, his repeat heart scan probably saved his life.

Comment

A calcium heart scan should be considered an evaluation of the current status of your heart. It reflects all the previous years of your life and the risks to which your heart was exposed. It does not exclude mild heart disease since calcium collects in your heart vessels after the heart has developed atherosclerotic plaques containing no calcium. When the scan turns positive, you know that you definitely have plaques in your heart's blood vessels which can rupture at any minute. Risk factors such as hypertension, diabetes, smoking, and high LDL cholesterol definitely increase your chances of making plaques in your heart arteries. A repeat heart scan every five years will keep you informed of your heart's status. The higher the score, the more chance you have of dying of a heart attack. It is a great wake up call to get energized to improve your lifestyle and lower your risk factors. Many studies have proven that heart disease is reversible if you identify it early and reduce your risk factors.

Why five years? You should think of a coronary artery calcium heart scan as a preventive measure to catch heart disease early, before serious damage has been done. This approach is accepted for the prevention of other diseases, such as colon cancer (colonoscopy), cervical cancer (PAP smear), and breast cancer (mammography). Once the calcium score turns positive, the chance of a future heart attack greatly increases, so aggressive medical therapy is warranted. If you have significant risk factors for heart disease (diabetes, hypertension,

obesity, smoking, or high LDL cholesterol levels) then a rescan in less than 5 years is recommended. People who take preventive testing seriously enjoy longer happier lives.

Figure legend – A calcium heart scan takes 10 minutes and is painless and noninvasive. It is the best test to see if you have atherosclerotic heart disease. As with any screening test, the score can become elevated as you get older. Therefore, if your score is zero, repeat it in 5 years. It may save your life!

D.

DO I HAVE HEART DISEASE?

Citations

1. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol. 2000; 36(4):1253-1260.

2. Cho I, Shim J, Chang HJ, Sung JM, Hong Y, Shim H, et al. Prognostic value of multidetector coronary computed tomography angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol. 2012; 60(21):2205-2215.

3. Dedic A, Genders TS, Ferket BS, Galema TW, Mollet NR, Moelker A, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology. 2011; 261(2):428-436.

4. Elias-Smale SE, Proenca RV, Koller MT, et al. Coronary artery calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J AM Coll Cariol,. 2010;56(17):1407-1414.

5. Hayward RSA. Clinical practice guidelines on trial. CMAJ. 1997; 156(12):1725-1727.

6. Leening MJ, Elias-Smale SE, Kavousi M, et al. Coronary calcification and the risk of heart failure in the elderly: the Rotterdam Study. JACC Cardiovasc Imaging. 2012;5(9):874-880.

7. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013; 368:2004-2013 doi: 10.1056/NEJMra1216063

8. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. J Am Coll Cardiol 2005; 46(7):1225-1228.

9. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med. 1987; 106(6):793-800.

10. Newman AB, Naydeck BL, Ives DG, et al. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcome sin adults 70 to 99 years old. Am J Cardiol. 2008;101(2):186-192.

11. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010; 362(10):886-895.

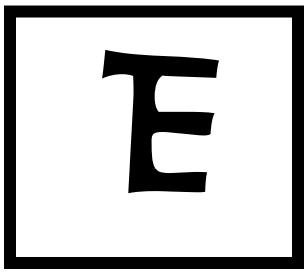
12. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997; 336(14):973-979.

13. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995; 92: 2333-2342 doi:10.1161/01.CIR.92.8.2333

Sagrado Corazón Catholic Chapel in

Costillo, New Mexico

Thunderhead over central New Mexico



CAN I REVERSE HEART DISEASE ?

Chapter E1: How do I reverse my heart disease?

Clinical Vignette

Harold Caruthers is a 66 year old retired plumber. He is enjoying retired life by visiting his grandchildren and rooting for his favorite football team. His risk factors for heart disease include prediabetes, mild hypertension, and a younger brother who recently had a heart attack. His physician recommended that he get a coronary calcium heart scan to check on the status of his heart. Much to his dismay, his calcium score was returned at 660, and most of the calcium was located in the anterior descending coronary artery (dangerous location). He wants to know how he can reverse this slowly progressive development of heart disease plaque.

Comment

The good news is that plaques in the coronary heart vessels are reversible. The bad news is that it takes a finite time to do this and requires a change in lifestyle habits and medication. Harold needs to remember that his heart disease has been developing since he was born and therefore he should not expect instant reversal. Medical studies have shown that coronary heart plaques start to become stabilized within 30 days of starting aggressive medical therapy and lifestyle changes. Furthermore, heart disease reversal can be shown to start to occur within one year, with more reversal at two years. Presumably, this reversal of heart disease continues for as long as the individual maintains a favorable lifestyle and aggressive medical therapy.

Another chapter details the lifestyle changes that are necessary to reverse atherosclerosis but briefly it entails “eating smart.” This term means reducing the amount of cholesterol, saturated fat, and trans fats in your diet. It means reading the labels on the foods that you buy at the store. It also means taking medication to reduce your LDL cholesterol level below 50 mg/dl. Your success at reversing your atherosclerosis is easy to monitor. If your LDL cholesterol is significantly above 50 mg/dl and you have poorly controlled cardiovascular risk factors, your heart disease is progressing. If your LDL is below 50 mg/dl and all risk factors are controlled, you are reversing your atherosclerosis.

As detailed in the chapter on inflammation, reducing the blood marker for inflammation (hsCRP) is also very important, since inflammation is necessary for atherosclerotic plaque buildup. Your goal should be an hsCRP level below 1.0 mg/L. Inflammation is reduced by medication (rosuvastatin, ezetimibe, and aspirin) and a reduction in cardiovascular risk factors. All of these factors are described in detail in other chapters in this book.

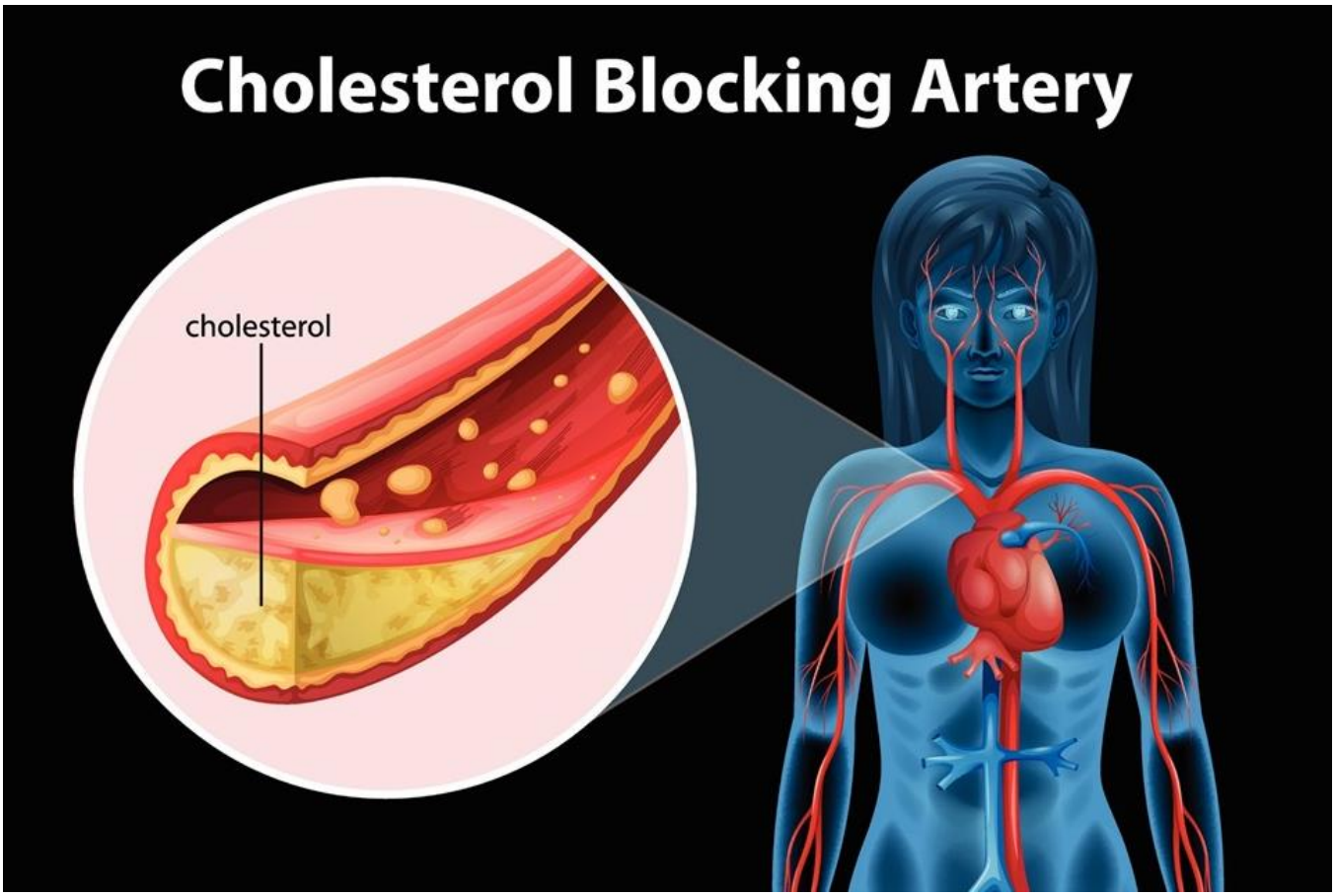


Figure legend – At any given time, cholesterol (primarily LDL cholesterol) is both accumulating in the walls of your arteries and being simultaneously removed by LDL cholesterol receptors on your liver. Reversal of atherosclerosis requires that removal exceed buildup. This is best accomplished by reducing your level of LDL cholesterol level via improved lifestyle and medication.

Chapter E2: How long will it take to reverse my heart disease?

Clinical Vignette

Dan Brownlee is a 49 year old bus driver who quit smoking cigarettes 2 years ago. He blames his obesity on his sedentary job and his hypertension to the stress of dealing with the public. His diabetes is not well-controlled. On the advice of his physician he had a coronary artery calcium scan. His physician told him that his score was 1,135, which put him at major risk for a heart attack within the next ten years. This high score caused him much concern and he assured his physician that he would improve his lifestyle and take his blood pressure medications. He knows that he needs to reduce his LDL cholesterol level to less than 50 mg/dl with appropriate medications and his hsCRP to less than 1 mg/L. If he follows his physician's advice, he wants to know "How long will it take me to reverse the plaques in my heart?"

Comment

Dan must first understand that his heart disease has been developing since he was an infant. It has been accelerated by his less than ideal lifestyle and his poor compliance with taking prescribed medications. The rate of reversal of his heart disease will depend to a great extent on his willingness to comply with his doctor's recommendations. Assuming that he is compliant and gets his diabetes, hypertension, and obesity under control, his outlook is good.

The first goal of therapy is to stabilize the plaques in his arteries. Stabilization includes reducing the inflammation in the plaque, thickening the plaque's cap, and reducing the amount of LDL cholesterol in the plaque itself. Studies have demonstrated that plaques can be stabilized within 30 days of starting a statin. Furthermore, reversal of some plaques can be demonstrated after 12 months and at two years, more reversal can be demonstrated. The rate of reversal depends on many factors, but control of atherosclerotic risk factors is paramount. Since atherosclerotic plaques can erupt into the coronary artery lumen at any time, Dan should not delay in initiating his lifestyle and medication changes.

Complete removal of the atherosclerotic plaque is not necessary to prevent a heart attack. In fact, the calcium in Dan's plaques will probably remain in place for the rest of his life. It will do him no harm. But it is the reason that we do not usually recommend repeating the coronary artery calcium score once the individual has a high value. It will always be high.

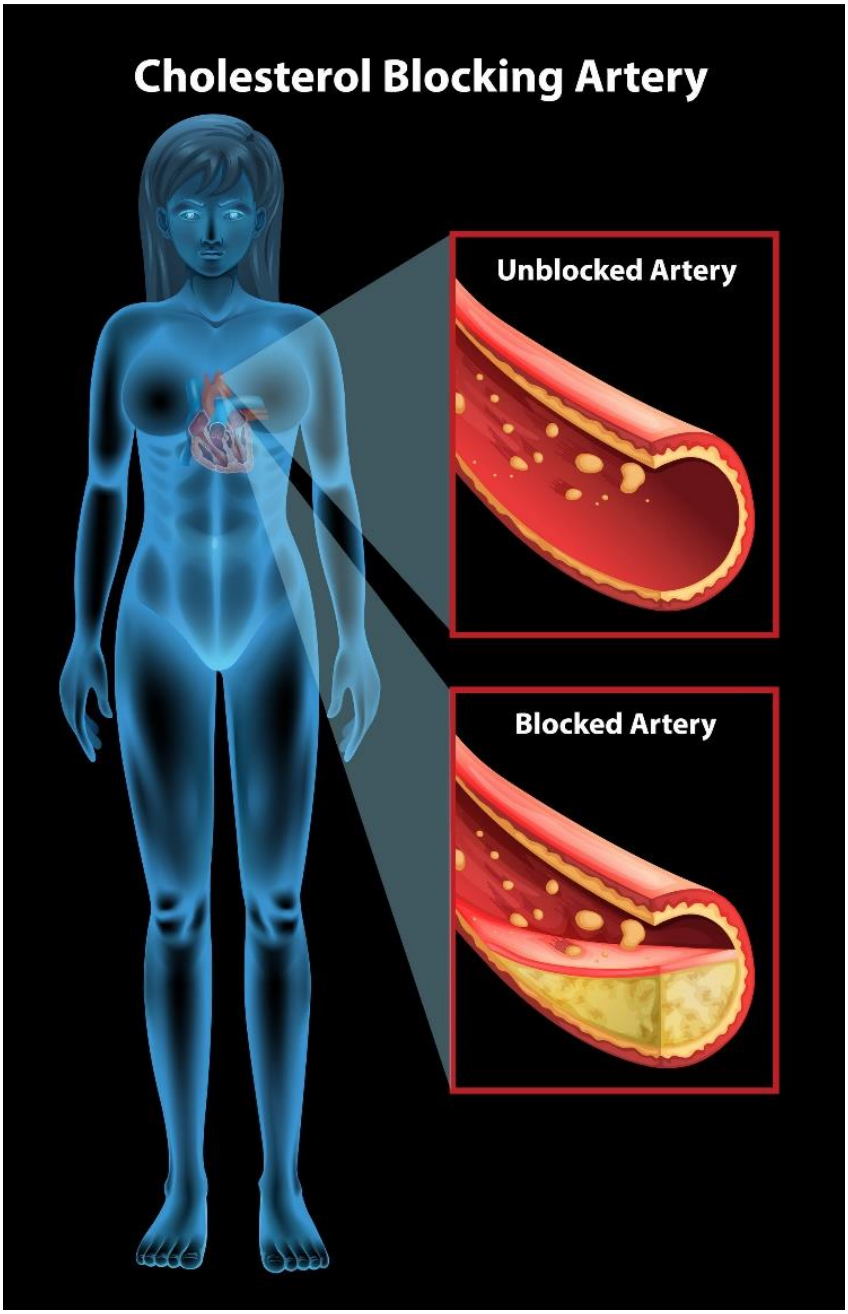


Figure legend – Atherosclerosis starts in childhood and continues throughout life. However, this process can be reversed by controlling cardiovascular risk factors and reducing LDL cholesterol. The reversal process begins within one month of initiating changes in risk factors and is easily demonstrable within one year. Within two years, many studies have shown dramatic reversal with a concomitant decrease in the number of heart attacks.

Chapter E3: What therapy do national organizations recommend to save my heart?

Clinical Vignette

Stanley Parks is a 44 year old primary care physician who has a busy practice in a small Colorado town. He tries to keep up-to-date with medical advances by relying on treatment guidelines published by national organizations. He recently read that the American Heart Association does not recommend specific LDL cholesterol nor hsCRP goals. Instead, they recommend placing the individual at risk of a heart attack on statins. The greater the risk, the more potent the statin. The amount of risk is determined by the number and severity of specific risk factors. Stanley would like to know why we recommend a different approach.

Comment

Stanley's question is frequently asked by many healthcare practitioners. There are several parts to the answer. First, there are at least 21 national and international organizations that have published guidelines on the prevention of heart disease. A recent review of all of these guidelines comes to one major conclusion, i.e., that none of the guidelines agrees with the other. This may seem strange because all the members of the guideline committees have access to the same medical information. However, each guideline committee is composed of different experts who have their own beliefs and biases on how to prevent heart disease. Thus, a physician can choose to follow any guideline he/she wants and still deliver the medical standard of care. No wonder Stanley is confused.

Second, many physicians have criticized the American Heart Association guidelines as being blinded to the fact that every study that has examined the benefits of lowering LDL cholesterol has concluded that the lower the LDLc achieved, the fewer heart attacks have occurred. In other words, "the lower, the better." This conclusion is true even when the LDL cholesterol level starts at 70 mg/dl and is reduced significantly below that number. This is one reason we recommend an LDL cholesterol target of <50 mg/dl, a concentration present when you were born and that is absolutely safe.

Third, having specific goals for both LDL cholesterol and hsCRP increases patient compliance because he/she knows the target and why the physician is recommending therapy. Studies have shown that 50% of patients no longer take their statins at the end of two years for various

reasons, including lack of a specific goal. It is important that patients know that they are reducing their cardiovascular risk when they are taking statin medication. They can do this by monitoring their LDL cholesterol level.

Fourth, there is a huge amount of medical literature on the prevention and treatment of heart disease. It takes many hours of reading and study to keep abreast of this literature. Many so-called experts do not have the time to stay up-to-date on the latest advances on the cause of heart disease and its optimal treatment. Thus, recommendations from various organizations are bound to be different.

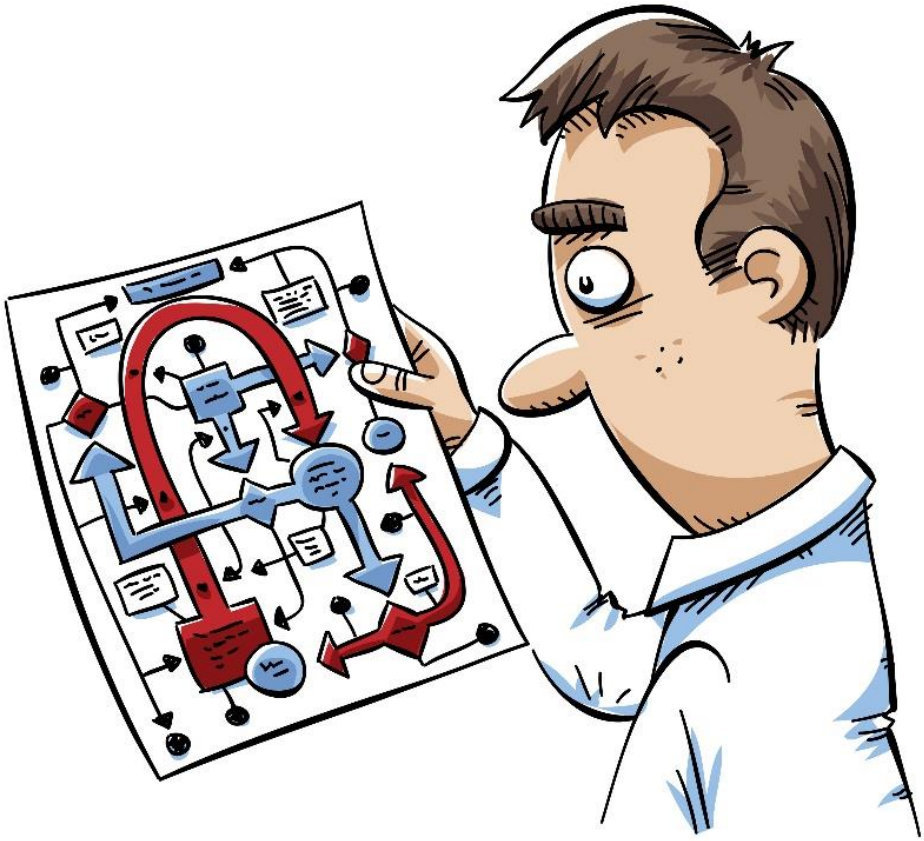


Figure legend – There are 21 national and international organizations that publish treatment recommendations for individuals at elevated risk for heart disease. Not surprisingly, their recommendations are not in good agreement with each other since the experts on the recommendation panels are all different with various backgrounds and levels of expertise. Our recommendations are based on what causes a heart attack and what has been shown to prevent and reverse heart disease.

E.

CAN I REVERSE HEART DISEASE?

Citations

1. Bedi U, Singh M, Singh P, Molnar J, Khosla S, Arora R. Effects of statins on progression of coronary artery disease as measured by intravascular ultrasound. J Clin Hypertens (Greenwich) 2011; 13:492-496.

2. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990; 323(19):1289-1298.

3. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. Lancet. 2012; 380(9841):581-590. doi: 10.1016/S0140-6736(12)60367-5.

4. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. Lancet 2010; 376:1670-1681 http://dx.doi.org/10.1016/S0140-6736(10)61350-5.

5. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M. Effect of statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009; 54:293-302.

6. Jensen LO, Thayssen P, Pedersen KE, Stender S, Haghfelt T. Regression of coronary atherosclerosis by simvastatin: a serial intravascular ultrasound study. Circulation. 2004; 110(3):265-270.

7. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 1990; 264(23):3007-3012.

8. Keraliya A, Blankstein R. (2017) Regression of coronary atherosclerosis with medical therapy. NEJM 2017; 376(14):1370.

Marker for Continental Divide Trail.
Notice trail in right hand corner of figure.

Geronimo Hot Springs where the famous Indian Chief often bathed in central New Mexico

Geronimo (1829-1909),
Chiricahua Apache warrior 1907.

F

COSTS AND BENEFITS

Chapter F1: What if I already had a heart attack?

Clinical Vignette

Jack French is a 55 year old male business man employed by a local stationery store chain. He had a heart attack three years ago, followed by triple bypass surgery. He has been doing reasonably well since his heart attack, but occasionally gets chest pain and shortness of breath when he walks uphill. He is worried that his bypass heart arteries are becoming clogged with cholesterol like they did before he had a heart attack. His cardiologist has him on 80 mg/day of Lipitor (atorvastatin). His LDL cholesterol is 92 mg/dl and his hsCRP is 3.5 mg/L (unfortunately, neither substance is at goal). He asks if there is anything else he should do to prevent another heart attack.

Comment

Jack is wise to be concerned about the arteries in his heart. It is common for people who have had a heart attack followed by a surgical procedure (either a stent or a quadruple cardiac bypass) to think that they are cured from atherosclerosis. Nothing could be further from the truth. It turns out that the veins or arteries that are used to bypass clogged heart arteries also become clogged at a higher rate than his original heart arteries. Jack will have many diseased heart arteries that were not bypassed that have the ability to become obstructive and to cause a second heart attack.

The good news is that Jack can do much to reduce his risk for a second heart attack. He should follow the same recommendations as individuals with a high coronary artery calcium score. He needs to reverse all of the atherosclerosis in both his heart and his bypassed arteries. This includes reducing any risk factors for heart disease (smoking, hypertension, and diabetes), increasing his exercise program, and avoiding foods high in cholesterol and saturated fat. We would also recommend that he speak to his doctor about changing his Lipitor regimen to 10 mg/day of rosuvastatin and 10 mg/day of ezetimibe. This regimen is more effective than 80 mg of atorvastatin in reducing his LDL cholesterol with fewer side effects. Those two medications will also reduce the inflammation in his arteries. Jack's goal should be an LDLc below 50 mg/dl and a hsCRP below 1.0 mg/L. Adding a baby aspirin (81 mg/day) to his regimen will further reduce his hsCRP by about 20%.

There is no reason for Jack to get a coronary artery calcium score. He already knows that he has serious heart disease. He is lucky to have survived a heart attack and open heart surgery. It is always better to prevent heart disease than to try to reverse it after a heart attack. Some parts of Jack's heart muscle will never work again.

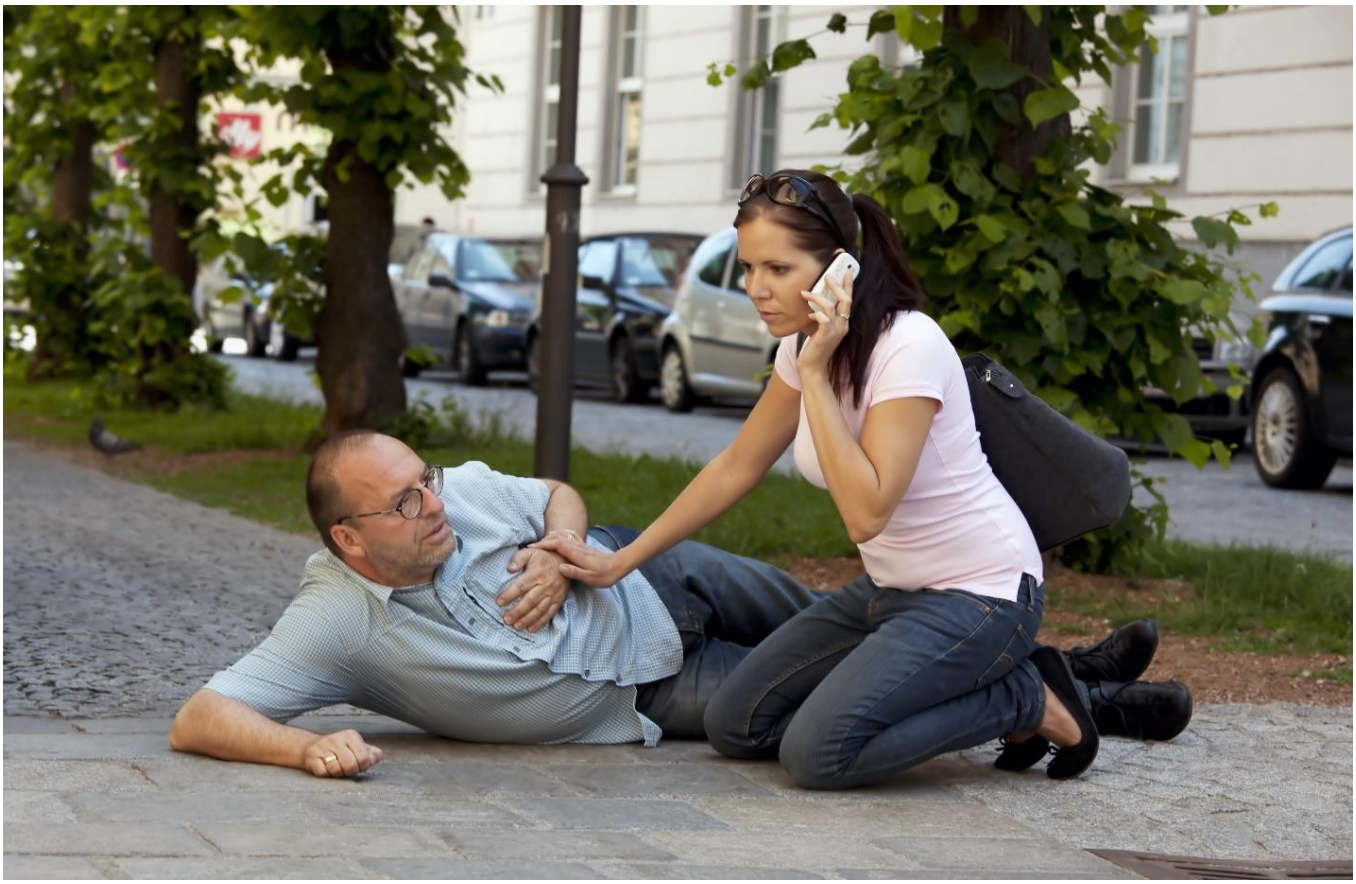


Figure legend – A person who already has had a heart attack (and survived) will have some dead heart muscle in his heart. For this reason, his heart will not pump blood as efficiently as a normal heart. This may result in the inability to climb stairs, walk without oxygen, or require several medications to maintain the heart in a functional condition. Once an individual has had a heart attack, he/she is at a very high risk for another heart attack. Every effort should be made toward controlling heart attack risk factors. Reducing his LDLc below 50 mg/dl and his hsCRP below 1.0 mg/L should be his two goals to avoid future heart attacks.

Chapter F2: How much will preventing a heart attack cost?

Clinical Vignette

Jeff Small is a 33 year old tennis and golf instructor at a local country club. He stays in good physical shape and works out regularly at the gym. Unfortunately, he was born with a genetic predisposition to atherosclerosis, having elevated levels of LDL cholesterol. His father had a heart attack at the age of 41 years and his grandfather also died of a heart attack at a young age. He has some health insurance but his copay is substantial. He realizes that preventative treatment will be lifelong and he reasonably asks "How much will prevention cost me?"

Comment

We are pleased that Jeff asked this question. Consideration of cost should always be included in a treatment plan. In any cost analysis, certain assumptions need to be made. First, the cost will be different for different individuals based on their medical policy and the copay for which they have signed up. We will assume that Jeff's copay is 20% for hospitalization costs. Second, costs change (usually increase) for medical procedures so we will use 2018 estimated costs. Third, the more medical procedures that are done and the longer the hospitalization, the higher the costs.

Based on the above assumptions, it is possible to estimate both the cost of prevention and the cost of an atherosclerotic event (such as a heart attack). First, what does it cost to prevent a heart attack? The cost of lifestyle changes and "eating smart" is zero. These health changes should be done irrespective of preventing heart disease. The only other cost is the prescribed medications. The maximum cost of all three preventive medications added together will not exceed one dollar/day. Many insurance plans actually provide these medications at no cost to the policy holder. If we assume that Jeff will live to the age of 80 years, then his maximum lifetime cost for medications will be $17,155 (47 years X $1.00/day X 365 days = $17,155). This payment will be spread over 47 years at $365/year.

The second consideration is what Jeff's expenses will be if he has a cardiovascular event (for example, acute chest pain or heart attack). An emergency room visit and subsequent hospitalization can easily be $10,000. A coronary angiogram (to identify the location of the obstruction) costs at least $5,000. A stent (a wire mesh to open the arterial blockage) costs at

least $30,000. This best scenario for Jeff will easily cost $45,000. Since Jeff's co-pay is 20%, he would incur a bill for $9,000 in one year! A less favorable outcome for Jeff would be a major heart attack ($100,000 with a co-pay of $20,000) followed by a surgical coronary bypass procedure ($500,000 with a co-pay of $100,000). Jeff will also be placed on several much more expensive medications (with many serious side effects) for the rest of his shortened lifespan. It is also likely that Jeff will have additional heart attacks and several hospitalizations for heart failure.

From the above summary, it should be clear that prevention of a heart attack is much less expensive than ignoring the cardiac risk factors and developing a deadly cardiovascular event. And the pain and suffering of a heart attack for Jeff and his family have not even been considered!

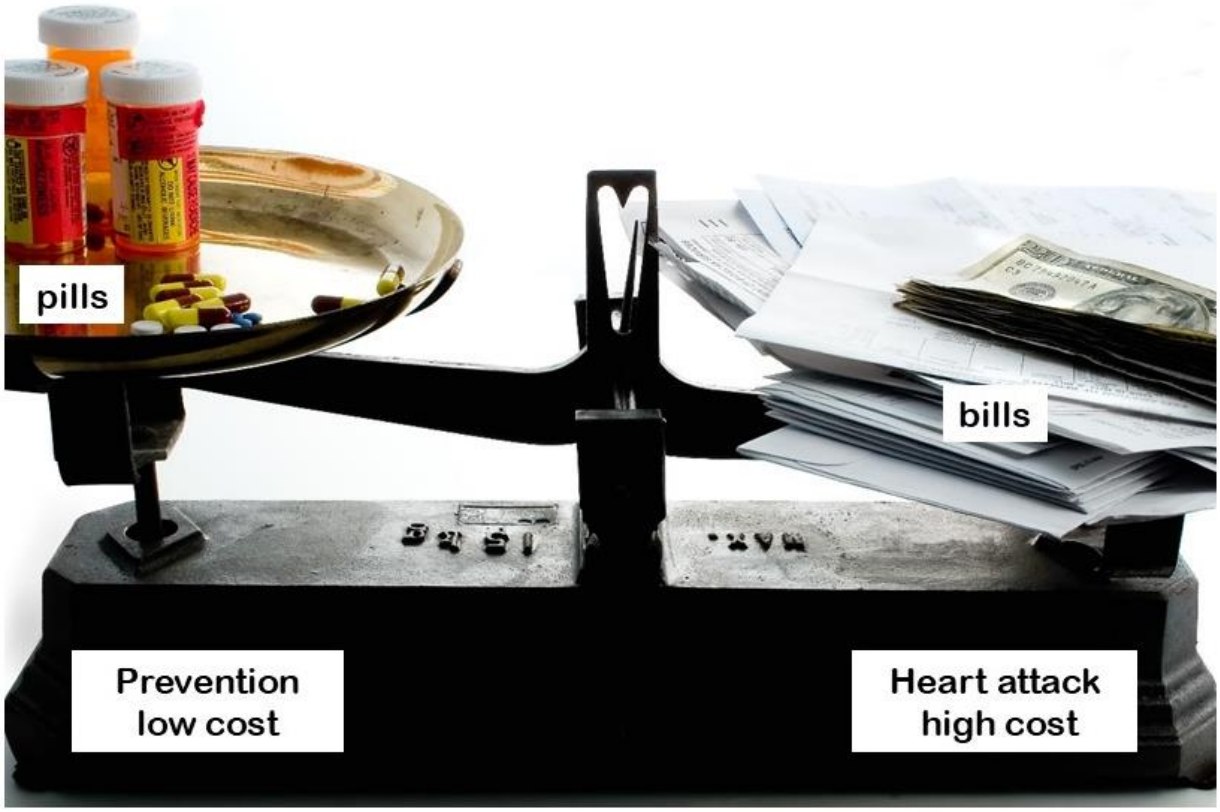


Figure legend – Bills versus pills - Prevention of atherosclerosis is much cheaper than treating a heart attack. If you want to save money, obtain a calcium heart scan and if positive, take ezetimibe plus rosuvastatin at $1 per day, full price. Most medical insurance companies now provide these medications either at no co-pay or minimum co-pay.

Chapter F3: How much will I benefit from triple therapy?

Clinical Vignette

Suzanne Block is a 55 year old waitress with a positive family history of heart attacks in her mother and grandmother. Her coronary artery scan score is 809 and she is very concerned for her future health. She has no other cardiac risk factors except for an LDL cholesterol of 157 and an elevated inflammation marker (hsCRP) of 3.3 mg/L. Her physician has recommended a maximum dose of a statin. However, she has read this book and believes that triple therapy might be better. Suzanne would like to know what results she can expect from triple therapy (once daily rosuvastatin 10 mg, ezetimibe 10 mg, and a low dose of aspirin of 81 mg).

Comment

As you might expect, people respond differently to medications. However, almost all individuals in our clinic reduce their LDL cholesterol below 50 mg/dl on triple therapy as long as they follow a prudent diet. The reason that various people respond differently are multiple:

First, the higher the starting LDL cholesterol value, the greater will be the percent response to triple therapy. This is good news for Suzanne because her baseline LDL cholesterol is significantly elevated.

Second, statins (e.g., rosuvastatin) work by suppressing the liver's production of cholesterol. People have different liver sensitivity to statins so that the greater the sensitivity, the greater the suppression. The reason for this variability is not known. What is known is that the greatest percent suppression is at the lowest statin dose (75% effectiveness). Therefore, we always start therapy with a low statin dose of rosuvastatin (10 mg/day).

Third, different people normally absorb cholesterol from their gut at variable amounts. Therefore, ezetimibe, which blocks 50% of cholesterol absorption, will have a greater effect at lowering LDL cholesterol in people with a normally greater percent absorption of cholesterol.

Fourth, the benefits of triple therapy depend on the food intake of saturated fats. Avoidance of saturated fats and cholesterol will greatly improve the response to triple therapy. "Eating Smart" should be part of the lifestyle change that individuals at risk for heart disease should take seriously.

The good news is that all three components of triple therapy will reduce inflammation, so Suzanne can expect her hsCRP to be significantly reduced (approximately 30%). Aspirin itself will reduce it 20%. Most importantly, good compliance with the medications and lifestyle change is paramount to obtaining a great response to triple therapy. We suggest that you use a pill box and take your medications at the same time every day.

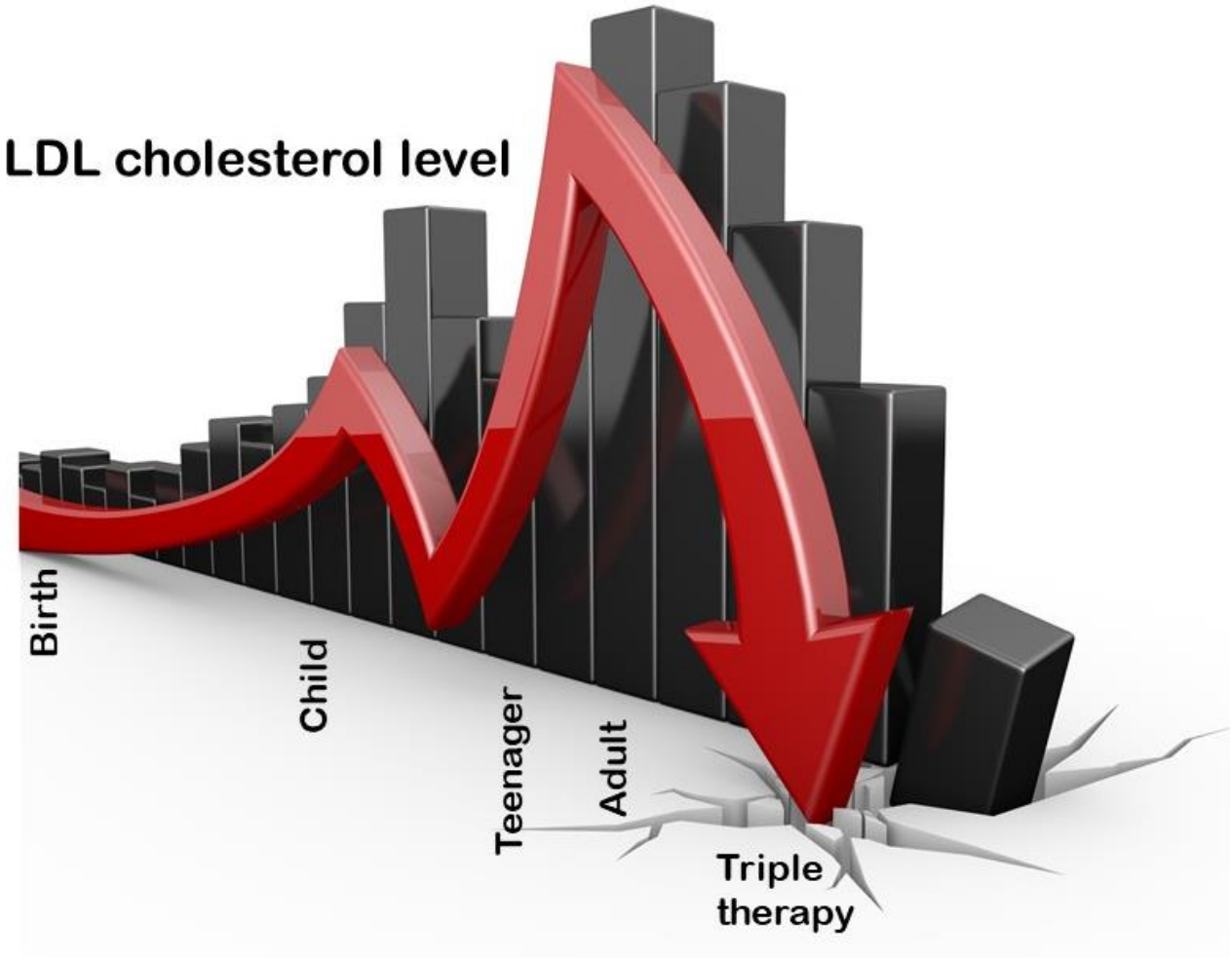


Figure legend – Triple therapy should reduce your LDL cholesterol to the healthy level at birth (50 mg/dl). We have found that our patients are both pleased and amazed at their response to this approach to preventing heart disease. Remember to wait at least six weeks to remeasure your LDL cholesterol response because the changes that occur require this amount of time to see a maximal response.

F.

COSTS AND BENEFITS

Citations

1. Hannan EL, Samadashvili Z, Cozzens K, Walford G, Holmes DR, Jacobs AK, et al. Appropriatensss of diagnostic catheterization for suspected coronary artery disease in New York State. Circ Cardiovasc Interv 2014; 7:19-27.

2. Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silver MG, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: Estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes 2014; 7:453-460.

Winter in The Gila National Forest near Silver City, New Mexico. The Continentel Divide Trail runs from left to right through these mountains.

GETTING SMART ABOUT HEART DISEASE

Chapter G1: What is my Lipid profile?

Clinical Vignette

Nancy Kraul is a 44 year old lady who visits her doctor once a year for an annual checkup. She believes that preventing disease is much better than trying to treat it after it has occurred (a very good plan). She always gets a set of blood tests before her visits so that her doctor can make certain that all of her organ systems are in good order. At her last visit, her doctor told her that her cholesterol level was too high and she needed to improve her lifestyle (lose weight and exercise more) to get the level down. She is worried because her older sister had a heart attack last year. She wants to know more about what a high cholesterol really means.

Comment

Your doctor never really orders just a cholesterol level. What he/she does order is a lipid profile. This test is a grouping of four different blood tests, all of which measure a different fat that circulates in your blood. The first component of a lipid profile is the total cholesterol. It represents the total amount of cholesterol in all the fat particles in your blood. The second component is the HDL cholesterol. The HD stands for “high density” which comes from the fact that it is very dense (i.e., heavy) when spun in a centrifuge. It carries the cholesterol that is traveling from your heart arteries back to your liver for disposal. It is often called the “good cholesterol” because it is reducing atherosclerosis. The third component of the lipid profile is the triglyceride level. This is the fat that your body burns for energy. It is an important indicator of problems with energy metabolism, often seen in diabetes and obesity. The final component in the lipid profile is the LDL cholesterol. The LD stands for “low density” which comes from the observation that it is less dense (lighter) than HDL cholesterol when spun in a centrifuge. It is often called the “bad cholesterol” because it is the cholesterol that gets deposited into your arteries.

The total cholesterol level is not a very useful number because it contains both the good cholesterol (HDL cholesterol) and the bad cholesterol (LDL cholesterol). The total cholesterol can be high because you have lots of good cholesterol (HDL cholesterol) or lots of bad cholesterol (LDL cholesterol). Obviously, you would want to have a lot of the former and very little of the latter, but the total cholesterol does not tell you about either component. Therefore,

it's best to focus your attention on the other components of the Lipid profile. We have more to say about these components in other chapters.

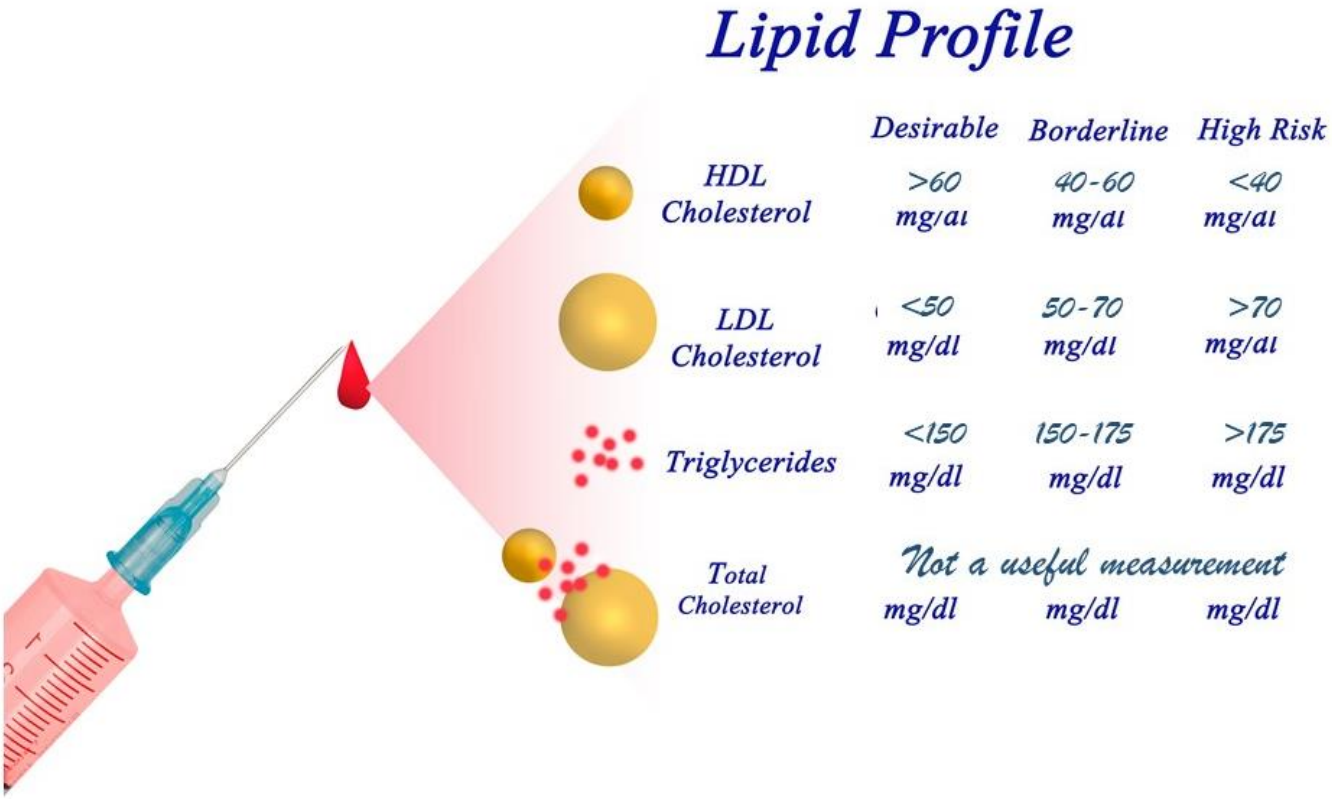


Figure legend - The components of the lipid profile. As shown above, the total cholesterol contains all of the cholesterol that is present in the other components of the lipid profile. The HDL cholesterol is the heaviest component, the triglycerides are the lightest. The LDL is midway between these two in weight. Each of these components has a different function in your body. You should compare your values with the values shown in the above chart. Are you at risk?

Chapter G2: What should I tell my doctor?

Clinical Vignette

Greg Fineman is a 44 year old mechanic who is worried about a heart attack because until recently he had most of the major risk factors for heart disease. Six months ago he had a coronary artery calcium score of 1,530. This encouraged him to lose weight, quit smoking, and take his diabetes and high blood pressure medications. His physician was not worried about his LDL cholesterol since it was normal at 90 mg/dl. However, Greg now understands that he needs to reduce his LDL down to 50 mg/dl and his CRP below 1.0 mg/L if he wants be sure of reversing his proven heart disease. Greg asks "Won't my physician be upset if I ask him to order an hsCRP (for inflammation assessment) and prescribe rosuvastatin and ezetimibe to lower my LDL?

Comment

Greg's concern about his physician being upset is a very common misconception that many patients have about requesting a new treatment. The primary goal for 99% of physicians is to find the best treatment for their patients. Physicians also realize that medical therapy is rapidly changing and just keeping up to date is a major challenge. In fact, studies have demonstrated that on average, it takes 17 years for major medical advances to actually reach the patient. This long duration may surprise you but there are several reasons that it takes so long.

First, medical therapy for every disease is rapidly changing such that every year new medicines and techniques become available. Since the practicing physician is no longer attending school, keeping current on various topics is almost impossible. Most physicians try to keep up to date by reading medical journals and attending medical seminars on new therapies. This has to be done either after a long day in the office or during vacation time. Not an easy task. *Second*, the Food and Drug Administration (FDA) must approve a new treatment before physicians will prescribe it and health insurance companies will cover it. However, the FDA usually requires many long and expensive clinical trials to test the medication's efficacy and to define its side effects. This requirement can take many years and cost millions of dollars to obtain the necessary clinical trial data. *Third,* medical insurance companies need to decide whether to cover the cost of the new drug or procedure and what the patient's copay will be (you are probably familiar with this problem). *Fourth*, scientific societies (e.g., the

American Heart Association) need to publish recommendations of how they believe the drug should be used. Many committees making these recommendations only meet every few years and their members may have significant conflicts of interest with the new therapy. We have included a chapter describing this problem.

From the above paragraph, you can understand why your physician may not be familiar with the latest treatments to prevent heart attacks. However, physicians appreciate learning new treatments that will help their patients. We suggest you give your physician a copy of the chapters from this book that address your specific treatment. Each chapter has pertinent references documenting the scientific basis for its position. You can also tell him/her that he can contact us for questions by emailing the authors at HSC-endo@salud.unm.edu. Trust us, he will appreciate your contribution.

Figure legend – Physicians have a very difficult time keeping up to date with the latest treatments and technology such as the coronary artery calcium heart scan. Patients can help physicians by providing them with new information and appropriate reading material. Your physician will appreciate it.

Chapter G3: Ten golden rules for saving your heart

Clinical Vignette

Armand Hanover is a 55 year old dentist with a wife, three children, and one grandchild. He enjoys interacting with his family, especially during the holidays. He has read this book and has made several changes in his lifestyle to reach the recommended health goals. He would like to know whether the key points that are made in this book can be condensed to ten rules that he can remember and follow.

Comment

Armand presents a challenge to the authors because each of the 50 chapters makes a separate clinical point. After much discussion, here are our ten most important points that we would like Armand to remember.

Rule #1 - Heart disease is preventable and reversible. With appropriate lifestyle and therapy, no one should have a heart attack or die from atherosclerotic heart disease.

Rule #2 - Fifty percent of people who have a heart attack die before arriving at the hospital. The other 50% of people will have impaired physical activity depending on the amount of heart muscle damage they incur.

Rule #3 – Control of correctable cardiac risk factors for heart disease (hypertension, diabetes, smoking, obesity, and LDL cholesterol) is extremely important for reducing the occurrence and progression of heart disease.

Rule #4 – Heart disease starts before birth and continues to increase throughout life. This is why increasing age is a non-correctable risk factor for having a heart attack. This is also why diagnosis and treatment to prevent heart disease should start early in life.

Rule #5 – Reversal of established heart disease occurs when LDL cholesterol is reduced below a concentration of approximately 65 mg/dl. The presence of cardiac risk factors will require a lower number. Our goal of 50 mg/dl provides a safety margin to assure atherosclerosis reversal.

Rule #6 - Throughout the entire range of LDL cholesterol, the lower the LDL, the less heart disease occurs. A diet low in saturated fats is critical for achieving a low LDL.

Rule #7 – The two main causes of heart disease are LDL cholesterol and inflammation (measured by C-reactive protein). Both are required to develop atherosclerotic plaques.

Rule #8 – Everyone's LDL goal should be less than 50 mg/dl, the level you were born with. No adult needs any circulating LDL to be healthy because all cells can make their own cholesterol.

Rule #9 – Everyone's inflammation goal should be a C-reactive protein less than 1.0 mg/L. Low dose coated aspirin (81 mg) /day will reduce inflammation about 20%.

Rule #10 – Rosuvastatin 10 mg/day and ezetimibe 10 mg/day are the two best medications to lower LDL cholesterol. Side effects at these low dosages are very rare.

We hope we have met Armand's request for ten rules to remember.

Figure legend – Preventing heart disease is not difficult. However, it will not happen if you don't remember a few important rules. Changing your lifestyle to reduce your risk factors and taking medication to reduce your LDL cholesterol and inflammation are critical ingredients for preventing and reversing heart disease.

G.

Getting Smart About Heart Disease

Citations

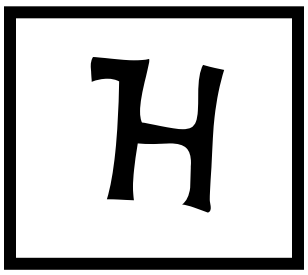
1. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012; 307(12):1302-1309.

2. Hermiller JB, Tenaglia AN, Kisslo KB, Phillips HR, Bashore TM, Stack RS, et al. In vivo validation of compensatory enlargement of atherosclerotic coronary arteries. Am J Cardiol 1993(Mar15); 71(8):665-668.

3. Kelley GA, Kelley KS, Franklin B. Aerobic Exercise and Lipids and Lipoproteins in Patients with Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials. Journal of cardiopulmonary rehabilitation. 2006; 26(3):131-144.

4. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103:1813-1818.

Winter in the Gila National Forest near Silver City, New Mexico



WHAT SHOULD I KNOW ABOUT RISK ?

Chapter H1: Why should I worry about cardiac risk factors?

Clinical Vignette

Toby Jones is a 55 year old used car salesman who reluctantly went for a medical checkup at the insistence of his employer. Toby has been overweight his whole life, smokes one pack of cigarettes per day, has type 2 diabetes, and was told that his cholesterol was too high. His favorite hobby is to watch late night TV and snack on potato chips. Two weeks after his checkup, Toby's doctor called him and said that he was worried about Toby's risk factors for heart disease. The doctor warned Toby that his LDL cholesterol was 145 mg/dl, his hemoglobin A1C was 8.8%, his blood pressure was 160/100, and his hsCRP (a measure of inflammation) was 6.6 mg/L. All of these values are significantly above normal levels. The doctor advised Toby to have a coronary calcium heart scan as soon as possible. Toby wondered why the doctor was so concerned about risk factors when he felt fine and had no pain in his chest, even with climbing stairs. Should Toby ignore his doctor's advice?

Comment

Toby needs to realize that his heart disease started when he was an infant and has been progressing ever since. Sooner or later it will catch up to Toby, as it will to everyone with significant risk factors. If it takes 200 years to catch up with you, it obviously will not be a problem. However, if it becomes manifest when you are 40 years old, your health and life span may be greatly shortened. So what determines how rapidly heart disease progresses? To a great extent, atherosclerotic risk factors are the determining factors.

There are numerous potential risk factors for heart disease, but the most important ones include 1) a family history of heart disease, 2) smoking, 3) diabetes, 4) hypertension, and 5) high blood cholesterol (LDL) levels. More recently, inflammation has been added to this list. Studies have demonstrated that the more risk factors you have, the faster your heart disease progresses. The way that these risk factors increase heart disease is to damage the internal lining of the heart's blood vessels (called the endothelial layer), increase inflammation, and add LDL cholesterol to the heart's coronary artery plaques. Controlling these risk factors (such as stop smoking), will decrease the rate at which heart disease progresses (or better yet, it may even reverse heart disease). It is a good bet that Toby's coronary artery calcium score will be dangerously high. He needs to greatly improve his lifestyle and take medication to reduce his

blood pressure and hypercholesterolemia. If he does not take the doctor's advice seriously, he probably will not live to see his 60th birthday.

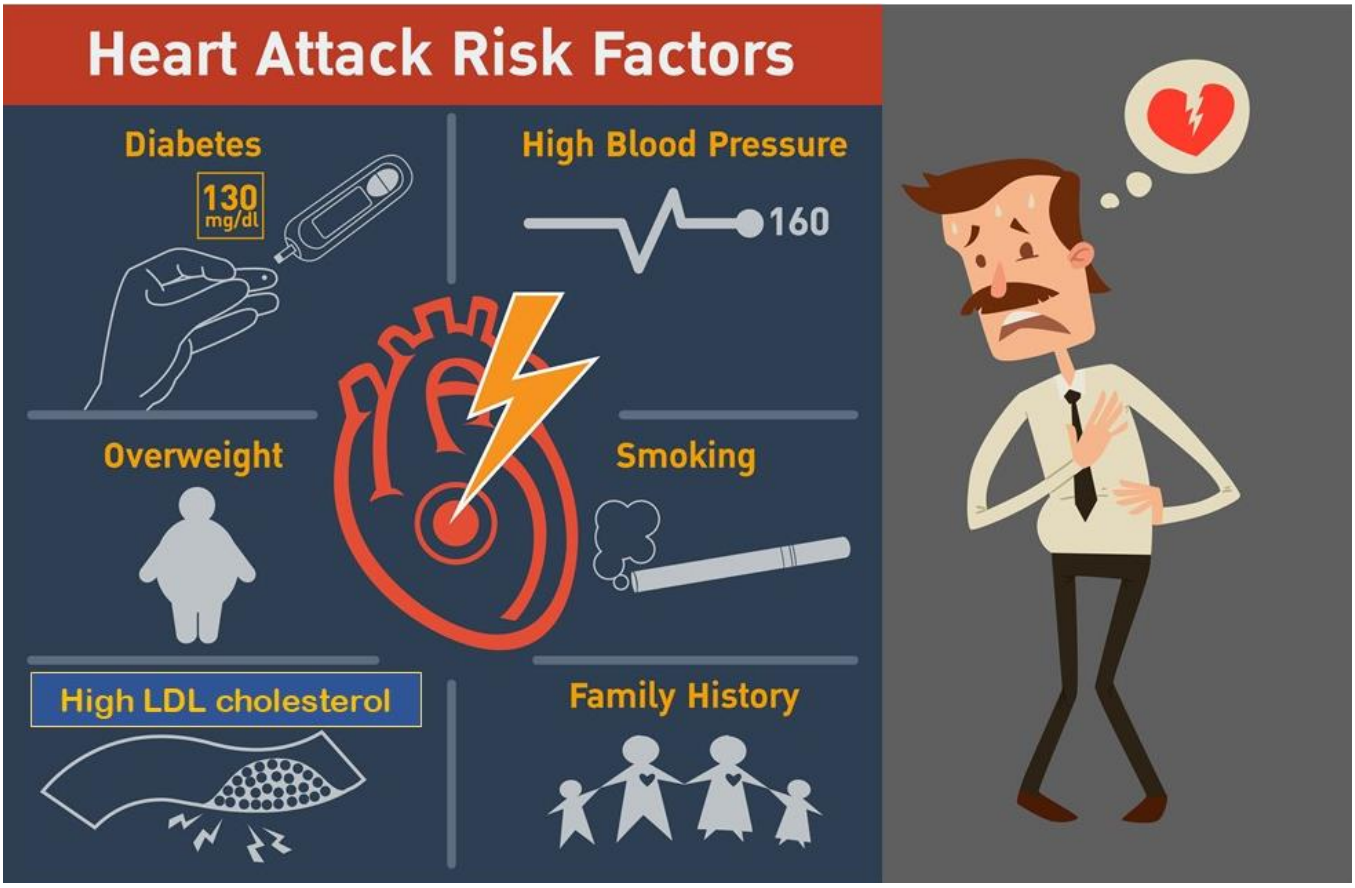


Figure legend – Illustrations of major risk factors for heart disease. Each of these risk factors contribute to the increase in the rate at which heart disease develops. Many of these risk factors can be reduced or eliminated with improved lifestyle and medications. On the other hand, ignoring them usually results in a catastrophic heart attack. Have you monitored your risk factors lately?

Chapter H2: How do we know what constitutes risk factors?

Clinical Vignette

Paul McAndrew is a 47 year old high school teacher who teaches his students to do critical thinking about facts and to avoid unproven myths. When he was waiting in his doctor's office, he picked up a flyer that said that age, hypertension, diabetes, smoking, and high blood fats were all important risk factors for heart disease. As he read about it, he noticed that the article suggested that he should change his life style to reduce his risk, but it contained no evidence that these five items increased heart disease. When he discussed this article at the dinner table that evening, his 15 year old son told him he was passing around "Fake News." Paul thought he should ask his doctor for additional facts about risk factors and the proof supporting their validity.

Comment

Paul asked his doctor an excellent question, i.e., what is the basis for risk factors causing heart disease? The answer goes back to the history of public health in the town of Framingham, Massachusetts. In 1948 the National Heart Institute decided to identify common factors or characteristics that contribute to heart disease. So they enrolled all the men and women in the town of Framingham between the ages of 30 – 62 years who had no signs or symptoms of heart disease. They followed them for 10 years to allow the prediction of the 10 year risk (prediction) of developing heart disease. This study has been continued by adding all next generations and spouses, with the latest groups starting in 2016. They recorded who developed heart disease and when and whether any of the common factors or characteristics that they identified were present. Thus, the term "risks factors" was used to describe these common characteristics that predict heart disease.

This is exactly how the daily weather channel predicts tomorrow's rain, snow, or sunshine. They consider whether the clouds, wind, temperature, and other factors have appeared from satellite information, put them into a computer, and the computer prints out a prediction of risk for bad weather for tomorrow. Usually it is correct, but sometimes other unknown factors change the outcome. This is similar to predicting risk factors for heart disease.

Relative to heart disease, we now have 15 years of prediction of heart attacks from coronary artery calcium heart scans. We have found that adding the calcium heart scan to the Framingham list of risk factors provides the best prediction of who is at risk for developing heart disease (you can do this yourself by going to the MESA website at this link: https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx. Surprisingly, only the calcium heart scan proves you actually have heart disease, while the rest of the factors are predictions, like tomorrow's weather. You should take responsibility for identifying your risk factors and follow your doctor's advice in reducing them. As the title of this book suggests, only you can save your heart. Risk factors are not "Fake News," they are based on real data, available to everyone.

Figure legend – Cardiac risk factors are an important cause of heart attacks. Some are not preventable such as male gender, advancing age, and genetics. However, several risk factors are preventable including diabetes glucose control, hypertension, smoking, and LDL cholesterol. Studies have shown that 50% of heart attacks are due to uncontrolled risk factors. Are you addressing yours?

Chapter H3: Why is the Risk/Benefit ratio important to my heart?

Clinical Vignette

Charlie Matia is a 65 year old retired auto worker who loves to watch professional football. He is an avid reader of the local paper's sports page and makes small bets on his favorite team, the Denver Broncos. He is in general good health and feels well except when he exercises, which occasionally causes him chest pain. His physician ordered a coronary calcium heart scan and the results demonstrated a score of 1,840. His physician then prescribed a statin medication and told Charlie that the medication's risk/benefit was strongly in favor of benefit. Charlie left his doctor's office wondering what the risk/benefit had to do with his heart.

Comment

Charlie may not realize it but he uses the "risk/benefit" ratio many times every day to make decisions. For example, when Charlie walks across a street, he is unconsciously calculating the benefit of being on the other side of the street against the risk of being hit by a car or truck. If the risk exceeds the benefit (e.g., crossing an interstate highway at rush hour), Charlie will choose another way to cross the street. When Charlie bets on the Denver Broncos, he is using the risk/benefit ratio to determine what odds to give his friends that the Broncos will win. He will try to maximize the benefit (of winning money) and minimize the risk (of losing money).

When Charlie's doctor stated that the risk/benefit ratio of the prescribed statin was strongly in favor of benefit, he meant that any side effects of the medication were far less important than the benefit Charlie's heart would get from the effects of the medications. More specifically, the medication would prevent Charlie from having a heart attack vs. the unlikely chance that his blood sugar might go up a small amount. Every study that has been done that has tested statin therapy has concluded that the benefit of the drug is much greater than the risk of taking the drug (even in people with no chest pain). Thus, most people reading this paragraph would encourage Charlie to take his statin and ezetimibe medication.

In the real world, however, people don't always make the healthy risk/benefit decision and simply quit taking their medicine. For example, 50% of people like Charlie are no longer compliant about taking their statin medication after two years, for no particular reason and in spite of the fact that it could save their life. Similarly, compliance with medication for high blood

pressure falls into the same category of non-compliance, in spite of the fact that hypertension is one of the critical risk factors causing heart disease. The same can be said for taking diabetes medication. It should be remembered that atherosclerosis is a preventable/reversible disease but only if patients follow the correct risk/benefit ratio and take their medications as prescribed.

Figure legend – Treatment is indicated when the risk/benefit ratio is in favor of benefit. Statin and ezetimibe therapy are almost always indicated when the individual has a positive coronary artery calcium score and he/she is not at the goals of an LDL cholesterol of less than 50 mg/dl and the C-reactive protein (hsCRP) of less than one.

H.
WHAT SHOULD I KNOW ABOUT RISK?

Citations

1. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358(24):2545-2559.

2. Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA 2014; 311(5):490-497. doi:10.1001/jama.2013.285122

3. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009 Jun 11; 360(24):2503-2515.

4. Berry JD, Dyer A, Cai X, Garside DB, Ning N, Thomas A, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012; 366:321-329.

5. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, et al. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol. 2002; 155(1):38-47.

6. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. 1997; 146(6):483-494.

7. de Craen AJM, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomized controlled trials. BMJ 2009; 338:b2376

8. Gæde P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen Oluf. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348:383-393.

9. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003; 290(7):891-897.

10. Grundy SM. Primary prevention of coronary heart disease: Integrating risk assessment with intervention. Circulation 1999; 100:988-998.

11. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol 2004; 94(1):20-24.

12. Maher JE, Raz JA, Bielak LF, Sheedy PF 2nd, Schwartz RS, Peyser PA. Potential of quantity of coronary artery calcification to identify new risk factors for asymptomatic atherosclerosis. Am J Epidemiol. 1996; 144(10):943-953.

13. Schade DS, Eaton RP. Residual Cardiovascular Risk—Is Inflammation the Primary Cause? World Journal of Cardiovascular Diseases 2018; 8:59-69. https://doi.org/10.4236/wjcd.2018.81007

14. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart J-C, Haffner S, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes. Diabetes Care 2006; 29:1220-1226.

15. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of atherosclerosis. Eur Heart J 2014; 35(33):2232-2241. doi: 10.1093/eurhrtj/eht508. Epub 20313 Dec 23

16. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. JAMA 2016; 316(12):1289-1297. doi:10.1001/jama.2016.13985

17. Starkman HS, Cable G, Hala V, Hecht H, Donnelly CM. Delineation of prevalence and risk factors for early coronary artery disease by electron beam computer tomography in young adults with type 1 diabetes. Diabetes Care 2003; 26(2):433-436.

18. Verma S, Wang CH, Li SH, Dumont AS, Fedak PW, Badiwala MV, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation. 2002; 106(8):913-919.

19. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003; 326(7404):1419.

20. Weis U, Turner B, Gibney J, Watts GF, Burke V, Shaw KM, et al. Long-term predictors of coronary artery disease and mortality in type 1 diabetes. QJ Med 2001; 94:623-630.

21. Weissler AM. Traditional risk factors for coronary heart disease. JAMA. 2004; 291(3):299-300.

22. Whisler RL, Proctor VK, Downs EC, Mortensen RF. Modulation of human monocyte chemotaxis and procoagulant activity by human C-reactive protein (CRP). Lymphokine Res. 1986; 5(3):223-228.

23. Wilson PWF, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, O'Leary D, Wolf PA. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. N Engl J Med 1997; 337:516-522.

24. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. for the HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016; 374:2021-2031. http://www.nejm.org/doi/full/10.1056/NEJMoa1600176

25. Yusuf S, Phil D, Lonn E, Pais P, Bosch J, Lopez- Jaramillo P, et al. for the HOPE-3 Investigators. Blood pressure and cholesterol lowering in persons without cardiovascular disease. N Engl J Med 2016; 374:2032-2043.

26. Zhang YX, Cliff WJ, Schoefl GI, Higgins G. Coronary C-reactive protein distribution: its relation to development of atherosclerosis. Atherosclerosis. 1999; 145(2):375-379.

1

STATINS AND HEART DISEASE

Chapter I1: What if Statins cause me Muscle Aches?

Clinical Vignette

Sandra Jacoby is a 48 year old secretary in a large corporation. She has had type 1 diabetes for 12 years. Her diabetes has been under very good control with a hemoglobin A1C of 7.0. Her hypertension is also well-controlled with a morning blood pressure of 130/90. On the advice of her physician, she had a coronary artery calcium scan last week and the results demonstrated a score of 430. She was not surprised by this high score because her LDL cholesterol is 130 mg/dl. This level of LDL was probably inherited from her father, who had a heart attack at age 44 years. Her physician recommends that she start medical therapy (10 mg/day of rosuvastatin and 10 mg/d of ezetimibe) to reduce her risk of having a heart attack. However, she does not want to start a statin because she remembers being prescribed a statin five years ago and it caused her muscle aches. What should she do?

Comment

Sandra's concern is understandable and a common complaint of people prescribed a statin. What are the facts? First, statins can cause muscle aches. From studies in which volunteers were given either a statin or a placebo (that is, a dummy pill), the incidence of muscle aches is one in 2,000 people on a *high dose* of a statin (thus, it is rare). Second, the side effects of statins are dose dependent. That means that the higher the dose of the statin, the more likely the chance of muscle aches. Third, muscle aches are very common in people not taking statins (we can bet that you can remember times when you had aches and pains in your muscles from exercising or carrying heavy objects). Fourth, when people who say they get muscle aches from stains are rechallenged with a statin or a placebo, they almost never can tell which medication was the statin. Thus, we would bet Sandra 2,000 to one (our $2,000 against her $1) that Sandra does not get muscle aches from a low dose of a statin.

What should her doctor do? Because Sandra is convinced that she gets muscle aches from statins, her doctor should prescribe a very low dose (5 mg) of rosuvastatin once a week and see if Sandra has any side effects. Trust us – she won't. He should then slowly increase the frequency of the medication to twice per week, then three times per week, etc. When she is taking 5 mg/day of rosuvastatin each day, he should slowly increase the dose to 10 mg/day. *This is still a very low dose of rosuvastatin*. There is rarely any need to raise the dose above

10 mg/day as long as she also takes ezetimibe (which never causes muscle aches). This is the approach we take in our clinic and we have never had a patient not being able to take 10 mg of rosuvastatin and 10 mg of ezetimibe, once per day.

Figure legend– Many activities cause muscle aches. It is very, very unusual for statins to cause muscle aches compared to the myriad of activities of daily living that do. If you think statins cause you muscle aches, try a very low dose of rosuvastin (5 mg) once a week and see if they occur. The chances are less than one in two thousand that they will!

Chapter I2: Do statins cause diabetes?

Clinical Vignette

Mathew Sparks is a 50 year old package delivery worker for FedEx. He has a positive family history for heart disease with both one sister and his father suffering a heart attack at an early age. His LDL cholesterol is 134 mg/dl, his CRP is 4.6 mg/L, and his calcium heart score is 677 (high risk for a heart attack). Unfortunately, he also has a strong family history of diabetes, with two brothers and one sister having type 2 diabetes. Their diabetic complications include eye, kidney, and peripheral nerve disease. Mathew refuses to take a statin because he was told it causes diabetes. Mathew wants to know "What should I do?"

Comment

Mathew asks a question that many people ask who are concerned about taking statins. They want to know if they are substituting one serious disease (heart disease) for another (diabetes). The answer is not complicated but does require an explanation. First, one of the several definitions of diabetes is a fasting morning blood sugar concentration greater than 126 mg/dl. Second, statins may raise fasting blood sugar about 8 mg/dl. Therefore, if a person has a fasting blood sugar of less than 100 mg/dl, statins will raise that blood sugar to 108 mg/dl (nowhere near the diabetes range). However, if a person has a fasting blood sugar of 120 mg/dl, than statins would push that person into the diabetic range. *Note that statins will never cause diabetes in a normal (non-diabetic or non-prediabetic) person*. Third, the effect of statins on blood glucose is related to the dose of a statin. A recent study has shown that 10 mg/day of rosuvastatin does not raise blood glucose but higher doses may. This is the reason that we recommend 10 mg/day as the optimal dose of rosuvastatin. Fourth, if higher doses of rosuvastatin are required (rare), then a small dose of an antidiabetes medication will cancel the statin's effect on blood glucose. Fifth, every study that has examined the risk of diabetes from taking a statin versus the benefit of that statin in reducing heart disease has concluded that the benefit far outweighs the risk of the small elevation in blood sugar caused by the statin.

Therefore, to answer Mathew's question, he should definitely be on triple therapy by taking 10 mg/day of rosuvastatin (plus 10 mg/day of ezetimibe plus 81 mg/day of aspirin) to save his heart. Keep in mind that the small rise in fasting blood sugar is easy to treat. In contrast, a heart attack is difficult to treat (assuming that Mathew lives long enough to get to a hospital).

Figure legend – The risk of a heart attack far outweighs the risk of any small increase in blood sugar. The first may kill you, the second never does. The first is difficult to treat since dead heart muscle cannot be restored. The second is easy to treat with a small dose of diabetes medication. A low dose of 10 mg/day of rosuvastatin does not raise blood sugar but does save lives and prevents heart attacks.

Chapter I3: Statin side effects – fiction versus truth?

Clinical Vignette

Kathy Corelli is a 51 year old librarian whose father had a heart attack at age 49 and a mother who died of heart failure after a massive heart attack at age 52. During her last health checkup, her doctor strongly recommended a statin medication to lower her elevated LDL cholesterol. He warned her that she was at high risk because of her positive family history for heart disease and an elevated LDL cholesterol. She agreed to think about taking a statin but her best friend warned her, "Beware - statins cause dementia and cataracts!" What should she do?

Comment

We have one piece of advice for Kathy: consider the facts. The popular press and the internet is full of bad advice about statins. In contrast, there are many good scientific studies assessing the side effects of statins. Here is a list of the claimed side effects of statins and conclusions of experts based on scientific evidence.

1) Statins cause cataracts – Many studies looking at this potential side effect have concluded that there is no good evidence that they do. Cataracts are a natural result of aging, so this occurrence is sometime confused with a side effect of statins.

2) Statins cause dementia – Many studies have examined this question. There are just as many studies that show that statins prevent dementia, as may be a cause of it. What is certain is that statins prevent atherosclerotic strokes that can lead to dementia. Statins do not cause Alzheimer's disease.

3) Statins cause liver disease – This potential side effect used to be a concern, but now the FDA says it occurs so rarely that the doctor should not even bother to monitor for it.

4) Statins cause muscle aches – There is a specific chapter on this issue. Suffice it to say that statin-caused muscle aches are rare. Serious muscle disease is only seen in individuals on very high statin dosages who are also taking other drugs that interfere with statin breakdown. It does not occur with the low dosages of statins (10 mg/day) plus ezetimibe that we recommend.

5) Statins cause diabetes – There is a specific chapter on this issue also. Statins at high dosages (>20 mg /day) may result in diabetes but not at low dosages. When the risk/benefit ratio was considered, for every one case of diabetes that occurred, five heart attacks were prevented. Diabetes can be treated with medication, but heart attacks kill 50% of people before they even get to the emergency room. No diabetes was observed when 10 mg of rosuvastatin was prescribed.

If the side effects of statins are rare, why do so many people complain of side effects when they take statins? There are at least two reasons that people complain. First, it is human nature to want to blame a pain or event on some identifiable reason. The easiest reason is to blame a medication instead of some natural phenomenon such as aging. We are all guilty of doing this. Second, when we hear or see someone state that statins cause many side effects, we assume it must be true and apply it to ourselves. The English word for this phenomenon is "nocebo". The best protection against this false impression is to ask for the proof of causation. Scientific studies provide the best proof of causation. Kathy should take a low dose of a statin (10 mg) plus ezetimibe (10 mg) and she will not experience any statin side effects.

Figure legend – all medications have side effects, some more, some less. What is important is whether the health benefits of the medication greatly outweigh the risks. All credible scientific studies show that the benefits of statins greatly outweigh the risks. Would you rather have a heart attack than a small increase in your fasting sugar concentration? You can treat the latter, if necessary, but the former may kill you.

I.

STATINS AND HEART DISEASE

Citations

1. Colhoun HM. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet 2004; 364:685-696.

2. Cushman WC, Goff DC. More HOPE for prevention with statins. N Engl J Med 2016; 374:2085-2087

3. Davidson M et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. Am J Cardiol 2002; 89:268-275.

4. DeGoma EM, Martin SS, Smith DA. Review: Statins are not associated with cognitive impairment, Alzheimer disease, or dementia. Ann Intern Med 2014; 160(10) doi: 10.7326/0003-4819-160-10-201405200-02010

5. Dubuc G, Chamberland A, Wassef H, Davignon J, Seidah NG, Bernier L, Prat A. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated concertase-1 implicated in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2004; 24:1454-1459. doi: 10.1161/01.ATV.0000134621.14315.43

6. Dykun I, Lehmann N, Kälsch H, Möhlenkamp S, Moebus S, Budde T, et al. Statin Medication Enhances Progression of Coronary Artery Calcification: The Heinz Nixdorf Recall Study. J Am Coll Cardiol. 2016; 68(19):2123-2125. doi: 10.1016/j.jacc.2016.08.040.

7. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, MD, Cain VA, Blasetto JW, for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003; 92(2):152-160.

8. Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (Single-patient) trials for statin-related myalgia. Ann Intern Med 2014; 160(5):201-210 doi: 10.7326/M13-1921.

9. Kamari Y, Bitzur R, Cohen H, Shaish A, Harats D. Should All Diabetic Patients Be Treated With a Statin? Diabetes Care. 2009; 32(Suppl 2):S378-S383.

10. LaRosa JC et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352:1425-1435.

11. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326:1423 doi: 10.1136/bmj.326.7404.1423

12. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. 2011; 124(2):146-153.

13. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J 2018; 0:1-18 doi:10.1093/eurheartj/ehy182

14. Meek C, Wierzbicki AS, Jewkes C, Twomey PJ, Crook MA, Jones A, et al. Daily and intermittent rosuvastatin 5 mg therapy in statin intolerant patients: an observational study. Curr Med Res Opin 2012(Mar); 28(3):371-8 doi: 10.1185/03007995.2012.657302.

15. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. Lancet. 2012; 380(9841):581-590.

16. Nakamura T, Obata JE, Kitta Y, Takano H, Kobayashi T, Fujioka D, Saito Y, Kodama Y, Kawabata K, Mende A, Yano T, Hirano M, Sano K, Nakamura K, Kugiyama K et al. Rapid stabilization of vulnerable carotid plaque within 1 month of Pitavastatin treatment in patients with acute coronary syndrome. J Cardiovasc Pharmacol 2008; 51:365-371.

17. Newman CB, Tobert JA. Statin Intolerance – Reconciling clinical trials and clinical experience. JAMA 2015; 313(10):1011-1012 doi:10.1001/jama.2015.1335.

18. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman J, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011; 365:2078-87.

19. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA 2007; 297:499-508. doi:10.1001/jama.297.5.499.

20. Olsson AG, Pears J, McKellar J, Mizan J, Raza A. Effect of rosuvastatin on low- density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol 2001; 88:504-508.

21. Reid FDA, Cook DG, Whincup PH. Use of statins in the secondary prevention of coronary heart disease: is treatment equitable? Heart 2002;88:15-19.

22. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE et al. Statins and cognitive function Ann Intern Med 2013; 159:688-697.

23. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. for the Pravastatin or Atorvastatin evaluation and infection therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352:20-28.

24. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd JD, Willerson, JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008(21); 359:2195-2207 doi 10.1056/NEJMoa0807646.

25. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012; 380:565-571.

26. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto Jr AM, et al. for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. 2001; 344(26):1959-1965.

27. Swiger KJ, MD; Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. Mayo Clin Proc 2013; 88(11):1213-1221.

28. Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. Atherosclerosis. 2009; 202(2):491-497. doi: 10.1016/j.atherosclerosis.2008.05.014.

29. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003; 289(13):1681-1690. doi: 10.1001/jama.289.13.1681

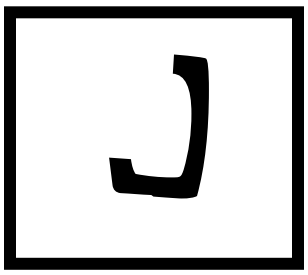
30. Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C, and the TNT Steering Committee Members and Investigators. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? Am J Cardiol 2004; 93:154-158. doi:10.1016/j.amjcard.2003.09.031

31. Welder G, Zineh I, Pacanowski MA, Troutt JS, Cao G, Konrad RJ. High-dose atorvastatin causes a rapid sustained increase in human serum PCSK9 and disrupts its correlation with LDL cholesterol. J Lipid Res 2010 Sept; 51(9):2714-2721. doi:10.1194/jlr.M008144

32. Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F, Dailing C, Karlsberg RP, Budoff M. Effect of statin treatment on coronary plaque progression - A serial coronary CT angiography study. Atherosclerosis 2013; 231:198-204.

Famous Rio Grande Gorge Bridge near
Taos, New Mexico

Long Horn festival in Tucumcari, New Mexico
along Route 66



AMAZING EZETIMBE & ASA

Chapter J1: What is this new drug called ezetimibe?

Vignette

Abel Alexander is a 38 year old insurance salesman who is going to college in the evenings to obtain a Masters of Science degree. His current course on major diseases affecting the U.S. population includes the epidemiology and treatment of cardiovascular disease. His textbook includes a description of statin therapy but no mention of ezetimibe (Zetia®). His textbook was published only three years ago so he assumes that it is up-to-date. Abel wants to know why his textbook does not mention ezetimibe and "What does this drug do?"

Comment

We are not surprised that Abel's textbook does not include ezetimibe as a recommended treatment for cardiovascular disease. Textbooks require several years of writing and editing before they are ready for printing. They then need to be distributed to bookstores and sold, a process which may take many months. In a field such as medicine in which new therapies are being approved by the Food and Drug Administration almost monthly, it is impossible for textbooks to include recently available medications.

Ezetimibe (brand name Zetia®) has actually been available for many years but not for the treatment of cardiovascular disease. It was an excellent therapy for a rare genetic disease called *sitosterolemia* in which the intestine absorbs too many plant sterols. This raises blood cholesterol levels and results in the early onset of cardiovascular disease. Ezetimibe blocks the intestinal cholesterol receptor, which absorbs both cholesterol and plant sterols. By blocking the cholesterol receptor, the absorption of plant sterols are also blocked and the sitosterolemic patient's outlook is much improved.

It was not until 2015 that a very large clinical study of the use of ezetimibe in combination with statin treatment was demonstrated to significantly reduce cardiovascular disease. This milestone clinical trial required 7 years to complete and involved 18,000 patient volunteers. Since this time, many other studies have been done demonstrating that ezetimibe reduces circulating LDL cholesterol about 20 to 25%. The maximum effect of this drug occurs at a dose of 10 mg/day, and that is the only dose commercially available. Ezetimibe should always be used in conjunction with a low dose of a statin medication (i.e., rosuvastatin) because they

work very well together to lower LDL cholesterol. Ezetimibe also reduces triglycerides and raises HDL cholesterol, but its beneficial effects are thought primarily to be due to LDLc lowering. Ezetimibe is available as a generic medication at a very inexpensive price. Although it blocks 50% of cholesterol absorption, it causes no intestinal side effects, since it does not block other types of fat absorption.

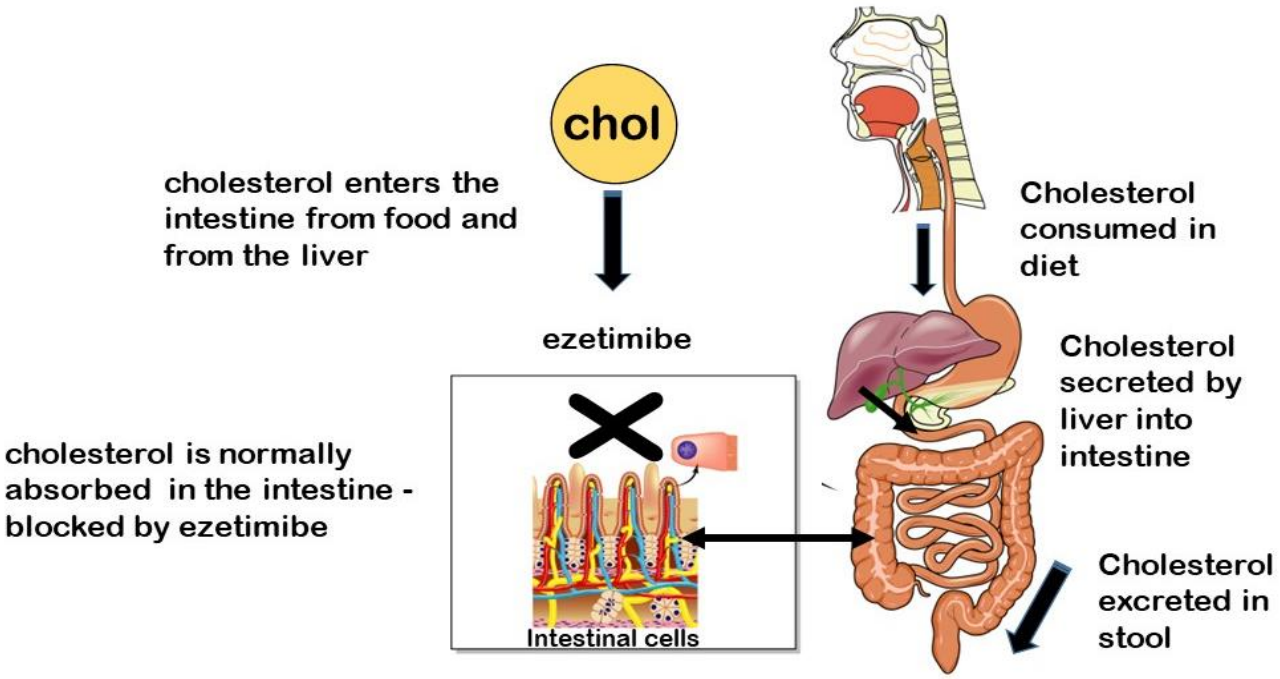


Figure legend – Ezetimibe blocks cholesterol absorption in the intestines, a process which results in less cholesterol going to the liver. When statins also block the production of cholesterol by the liver, the net result is much less cholesterol available to the liver to make bile acids. Bile acids are secreted by the liver into the intestine to help digest fats. When the liver needs more cholesterol, it increases the LDL receptors on its surface, which in turn removes LDL cholesterol from the blood, lowering the level of circulating LDL cholesterol. Thus, ezetimibe works very well with statins to help individuals achieve their LDL cholesterol goal of <50 mg/dl.

Chapter J2: Aspirin – The last word?

Clinical Vignette

Thomas Franklin is a 66 year old retired farm worker. He has known heart disease, having had a stent placed in one of his coronary arteries three years ago. His family doctor prescribed a first-generation statin to lower his LDL cholesterol. It decreased from 125 mg/dl to 90 mg/dl. His doctor retired last year, and he was assigned a new physician recently graduated from medical training. When he saw this doctor, she recommended changing his medication to a more powerful statin (rosuvastatin 10 mg/day) plus adding ezetimibe 10 mg/day and low dose aspirin 81 mg/day. She was also concerned that Thomas' hsCRP was elevated at 3.6 mg/L, indicating excess inflammation. He understands that the rosuvastatin and ezetimibe will significantly lower his LDL cholesterol further. However, he wants to know what purpose aspirin serves.

Comment

Aspirin is a medication that has been used for many years to treat arthritic pain and fever. Its benefits and side effects are well known. More recently, it has been recommended to prevent heart attacks in individuals with significant risk. It is inexpensive and does not require a physician's prescription. Studies have shown that it works well in combination with statins to reduce heart attacks and strokes.

Aspirin has two major beneficial effects in man. First, it reduces inflammation throughout the body. It does this by blocking several chemical reactions in the body. As discussed in another chapter, inflammation is a necessary contributor to the development of atherosclerotic plaques. Specifically, inflammation enhances the movement of macrophages (white blood cells) into the coronary arteries and ingesting LDL cholesterol particles to form a fatty streak. These fatty streaks develop into unstable plaques, which can rupture into the coronary artery lumen (see figure). A blood clot forms around this rupture and obstructs the coronary artery, causing a heart attack. Aspirin's inhibition of inflammation will help prevent these unwanted events.

The second beneficial effect of aspirin is to inhibit the formation of blood clots. It does this by blocking the ability of blood platelets to clump together, which is the initial stage of a blood clot. Without a blood clot, it would be unusual for a ruptured plaque to obstruct a coronary artery.

Since this activity of aspirin is different from that of statins and ezetimibe, its beneficial effects add to those of these medications.

The ability of aspirin to block the formation of blood clots does have a down side – that is, in about 4% of people, it can cause excessive bleeding from cuts, bruises, and other traumatic events. However, this side effect can be minimized by not taking a dose greater than 81 mg/day and restricting its use to people at high risk for heart disease. In this category are people with a history of known heart disease (such as Franklin) and anyone with a coronary artery calcium score above 100. We also recommend not using aspirin in anyone over the age of 75 years because of increased risk of falling and bruising. We also recommend stopping aspirin after the LDL cholesterol has been 50 mg/dl or less for at least two continuous years because by the end of two years, atherosclerotic plaques should be stabilized. In the case of Franklin, we would recommend that he start triple therapy as soon as possible (rosuvastatin 10mg/d, ezetimibe 10 mg/d, and aspirin 81 mg/d).

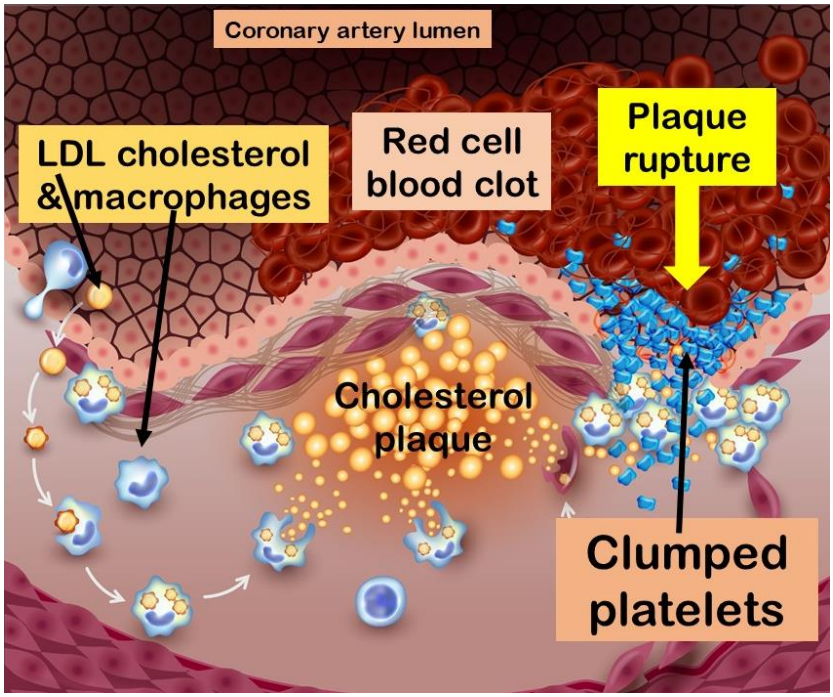


Figure legend – Rupture at the side of an atherosclerotic plaque causing platelets (blue particles) to clump, plugging the tear in the artery wall with blood cells (red) that form a blood clot. If the clot is large enough, the artery is blocked, resulting in a heart attack. Aspirin can help prevent this clot.

Chapter J3: Is low dose statin plus ezetimibe better than a high dose statin?

Clinical Vignette

Margaret Vazquez is a 45 yr old mother of two children, who thought herself perfectly healthy until one afternoon when she suddenly developed acute chest pain, sweating, rapid heartbeat, and severe pain in her left arm extending into her jaw. The emergency room quickly confirmed an acute heart attack. Her cardiologist prescribed 80 mg of Lipitor® (atorvastatin) to reduce her LDL cholesterol. She had a friend whose husband had a similar experience, and his doctor started him on a much lower dose (10 mg/day) of a statin called (rosuvastatin) as well as a low dose of a second pill called ezetimibe. Margaret wants to know why her friend's doctor put her husband on ezetimibe plus a low dose of the rosuvastatin.

Comment

Margaret asked a very good question and one which some doctors do not appreciate. All brands of statins block the liver's production of cholesterol at the same metabolic step. However, statins differ in their potency to lower the liver's cholesterol production. The most potent statin is rosuvastatin, which is up to four times more potent than Lipitor (atorvastatin). Ten mg of rosuvastatin has about the same LDLc lowering effect as 40 mg of atorvastatin. That is one reason that we recommend rosuvastatin as the best statin to use (all statins are available in a generic formulation). The other reason is that as the dose of a statin is increased, only a small benefit is achieved. The reason for this unusual result has only recently been discovered. It is a protein called PCSK9 (we agree this is a crazy name).

Statin medications block the liver's production of cholesterol. Unfortunately, the liver reacts to this blockage by producing PCSK9 protein. This protein destroys the liver's LDL receptor so that the liver can no longer clear the blood of LDL cholesterol. The result is to blunt the statin's ability to lower blood LDL cholesterol. The higher the dose of a statin, the more of this harmful protein is made. This is why high doses of atorvastatin are *not* much better than low dosages of atorvastatin. To put this concept in perspective, 75% of a statin's ability to lower LDLc is achieved at the 10 mg dose and only a 6% beneficial effect is seen when the dose is doubled (This is called the 6% rule).

The way your doctor can fool the liver is to add a second drug to the patient's regimen that works at a different place other than the liver. Ezetimibe does just that, by blocking cholesterol absorption at the intestine. Thus, the best approach to lowering LDLc is to combine a low dose of rosuvastatin with a low dose of ezetimibe (10 mg).

Remember that the side effects of statins are dose related. The higher the dose, the more side effects (these side effects do not follow the 6% rule). Therefore, if the physician wants to achieve the maximum lowering effect of statin drugs with the least amount of side effects, he/she will prescribe a low dose of the combination rosuvastatin and ezetimibe. Margaret needs to discuss this approach with her cardiologist if she wants the best treatment possible for preventing another heart attack.

Figure legend – Ezetimibe blocks the absorption of cholesterol consumed from food. It works hand-in-hand with rosuvastatin to block the liver's production of cholesterol. Side effects are very, very rare. This is an excellent combination of medications to save your heart by lowering your LDL cholesterol level.

Chapter J4: What is Great About Triple Therapy for Heart Disease?

Clinical Vignette

Mark Cannon is a 50 year old heavy equipment operator who is proud of the fact that he takes no medications to stay healthy. He feels great, smokes 2 packs of cigarettes/day and is significantly overweight. During his last annual physical exam (a job requirement), his doctor suggested a coronary artery calcium scan because of his cardiovascular risk factors. "No problem," he thought until his calcium heart scan detected calcium in his heart's arteries, resulting in a final score of 988. The doctor recommended losing weight, improving his lifestyle with exercise three times per week, and triple medication therapy to counteract his elevated LDL cholesterol (145 mg/dl) and elevated inflammation (hsCRP = 3.5 mg/L). He grudgingly agreed but asked, "Why three medications? Won't one do the job?"

Comment

Mark asked a good question, "Why triple therapy?" The answer is that prescribing any medication is a balance between good and bad (often called the "Risk/Benefit ratio"). In Mark's case, the physician wants to maximally reduce his LDL cholesterol level (to < 50 mg/dl) and inflammation level (hsCRP to <1.0 mg/L) without causing major side effects (diabetes and muscle aches from statins and bleeding from aspirin). For many medications (including statins and aspirin), the occurrence of side effects is dose dependent (the higher the dose, the more the side effects). Although this may sound counterintuitive, the benefits of medications are not always dose dependent. For statins, 75% of the benefit is achieved at the lowest dose (10 mg/day of rosuvastatin). Doubling this dose only achieves a 6% increase in benefit (often called 6% rule), so keeping the dose low to avoid side effects is a wise approach. At high dosages, statins can raise blood sugar and may cause diabetes. This is also true for muscle aches. These side effects are rarely, if ever, seen at the 10 mg dose of a statin. For ezetimibe, there is only one dose available (10 mg/day), so dose response is not question. Ezetimibe has almost no side effects when used with a statin but it does greatly improve statin's ability to lower LDL cholesterol by blocking intestinal cholesterol absorption. For aspirin, the lowest dose (81 mg) is also recommended, since no added benefit in lowering inflammation has been observed in clinical trials with higher dosages. In contrast, higher dosages of aspirin do cause more bleeding.

Triple therapy (albeit different medications) is also used to treat other diseases (for example, diabetes and hypertension) in order to maximize benefits and minimize side effects. For atherosclerosis, triple therapy is definitely indicated, and Mark should recognize that it is to his benefit that all three medications were recommended by his physician. He also needs to accept the fact that improved lifestyle and triple therapy will likely save his life. Keep this approach in mind the next time your health caregiver prescribes medication for you.

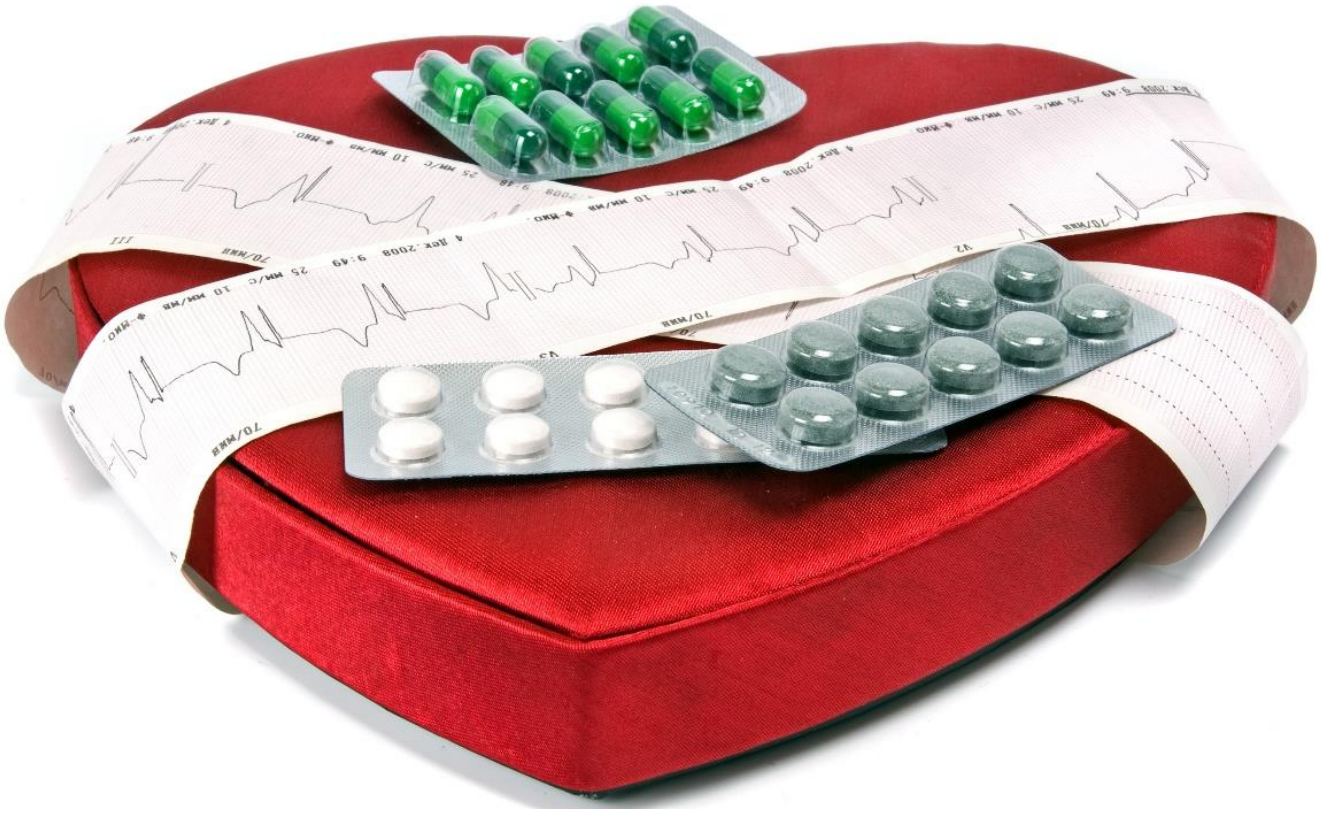


Figure legend #13 – A coronary artery calcium score above 100 is best treated with triple therapy. This approach will maximize the benefits of the drugs while minimalizing their side effects. If you are on a statin only and not at your LDL or hsCRP goal, you should request triple therapy from your doctor. Triple therapy consists of rosuvastatin 10 mg/d, ezetimibe 10 mg/d, and coated low dose aspirin 81 mg/d.

Chapter J5: With triple therapy, when will my heart calcium disappear?

Clinical Vignette

Agnes Moore is a 60 year old mother of two children and three grandchildren. She takes many herbal medications that she buys at the health food store. She recently had a coronary artery calcium scan and her score was 665. She was started on triple therapy (rosuvastatin 10 mg, ezetimibe 10 mg, and aspirin 81 mg, all once per day). On this therapy, her LDL cholesterol dropped to 45 mg/dl and her hsCRP to 1.3 mg/L. She would like to know how long it will take to get rid of the calcium in her heart arteries so that her calcium score is zero and she can stop her medications.

Comment

It will probably come as a surprise to Agnes that the calcium in her heart is actually beneficial to her. Her body deposits calcium in atherosclerotic plaques to stabilize them and prevent them from rupturing into the arterial lumen. Think of the body's defenses as isolating a foreign invader (an atherosclerotic plaque) by walling it off to prevent it from doing damage. The most dangerous plaques are those with no calcium in their walls. They are the most likely to rupture into the arterial lumen. Agnes should appreciate that triple therapy does not reduce the calcium in her plaques. In fact, one way that statins prevent heart attacks by stabilizing plaques is to increase the calcium in atherosclerotic plaques. Therefore, Agnes can expect a slow increase in her coronary artery calcium score as her plaques become more stabilized. Her score will never return to zero. The calcium does not prevent the removal of cholesterol and inflammation from the plaque, so eventually when all the plaques are removed by triple therapy, the calcium will still be there. It is not harmful but a good reminder of the danger of elevated LDL and inflammation.

Agnes should also remember that atherosclerosis is a chronic disease which started when she was an infant and will continue until she dies. If she stops therapy, she will then return to her previous state of increasing atherosclerotic plaques and be at risk for heart attacks. As long as she is having no side effects from the medication, we would advise her to continue triple therapy. Of course, if she needs surgery or some other medical intervention, she can always stop the therapy for short intervals of time. Once she has been on triple therapy for two years

with her LDL below 50 mg/dl, she can stop the aspirin since her plaques should be stabilized and reversing.

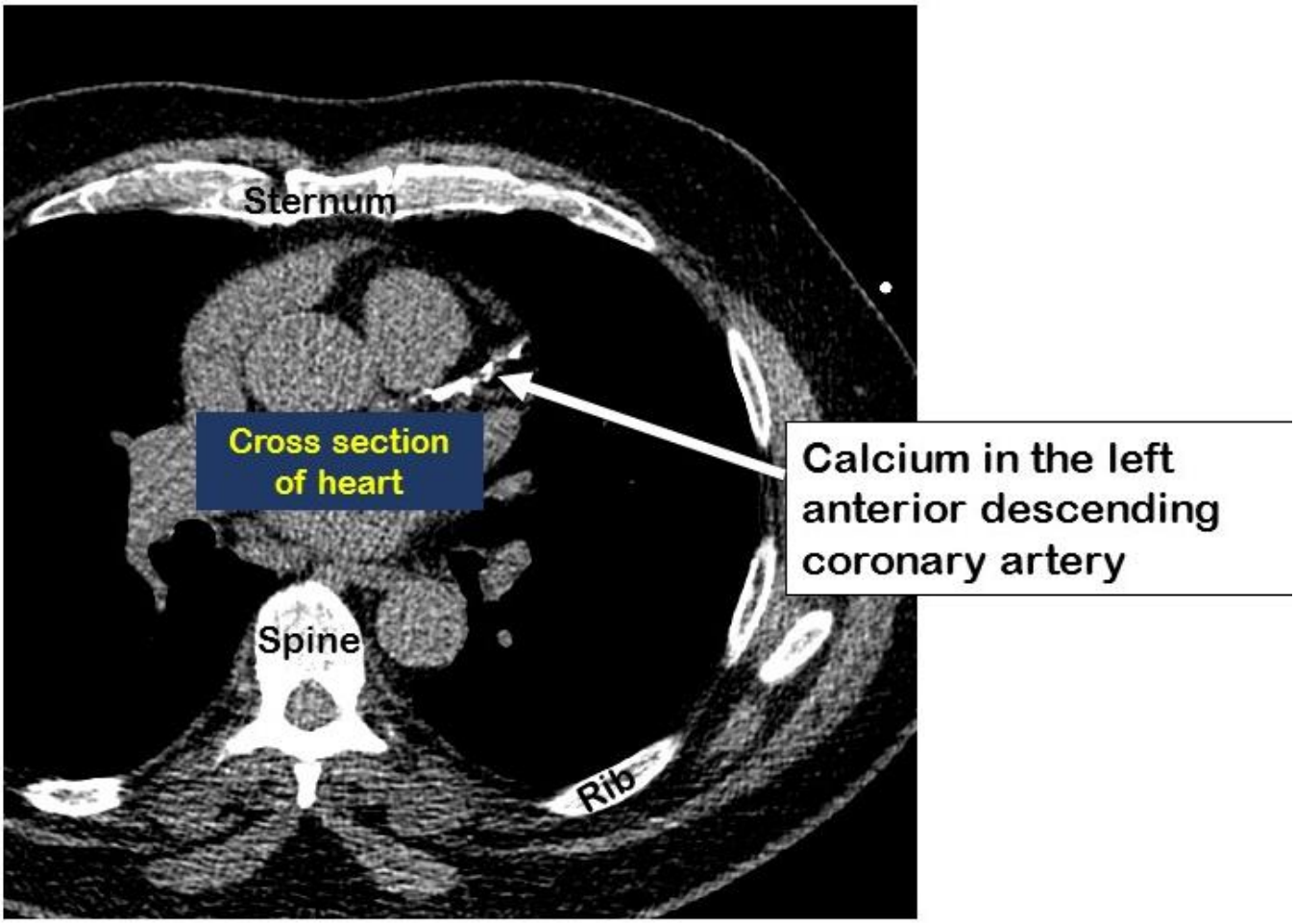


Figure legend – A coronary artery calcium scan identifies calcium in the atherosclerotic plaque. This is a sensitive way of quantifying your risk of future heart attacks. However, this does not mean that the calcium is harmful. Studies demonstrate that plaques without calcium, which are not seen on a coronary artery calcium scan, are more likely to rupture and cause heart attacks. Depositing calcium in the arteries is one way that your body protects you.

J.
AMAZING EZETIMIBE

Citations

1. Altmann SW et al. Niemann-Pick C1 Like 1 Protein is critical for intestinal cholesterol absorption. Science 2004; 303(5661):1201-1204.

2. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet. 2011; 377(9784):2181-2192.

3. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP, for the Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation 2003; 107:2409-2415.

4. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, Knopp RH, Lipka LJ, LeBeaut AP, Yang B, Mellars LE, Cuffie-Jackson C, Veltri EP, Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001; 23(8):1209-1230.

5. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA. 2007; 297(18):2018-2024.

6. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015; 372(25):2387-2397. doi: 10.1056/NEJMoa1410489.

7. Clausss S, Wai K-M, Kavey W, Kuehl K. Ezetimibe treatment of pediatric patients with hypercholesterolemia. J Pediatr 2009; 154:869-872.

8. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. Lancet. 2001; 357:89–95

9. Connor WE, Lin DS. The intestinal absorption of dietary cholesterol by hypercholesterolemic (type II) and normocholesterolemic humans. J Clin Invest. 1974; 53(4):1062-1070.

10. Davidson MH. Reducing residual risk for patients on statin therapy: The potential role of combination therapy. Davidson Reducing residual risk for patients on statin therapy. Am J Cardiol 2005; 96[suppl]:3K–13K.

11. Eidelman R, Hebert P, Weisman S, Henekens C. An Update on Aspirin in the Primary Prevention of Cardiovascular Disease. Arch Intern Med. 2003;163:2006-2010.

12. Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol. 2008; 52(25):2198-2205.

13. Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, Cho M, Musliner TA, Gumbiner B., for the Ezetimibe Study Group. Efficacy and safety of Ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002; 90:1084-1091.

14. Gagné C, Gaudet D, Bruckert E. for the Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002; 105:2469-2475.

15. Hansson L, Zanchetti A, Carruthers G, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowing and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet. 1998;351:1755-1762.

16. Jarcho JA et al. Proof that lower is better - LDL cholesterol and IMPROVE-IT. N Engl J Med 2015; 372(25):2448-2450.

17. Jia L, Betters JL, Yu L. Niemann-Pick C1-Like 1 (NPC1L1) Protein in intestinal and hepatic cholesterol transport. Annu Rev Physiol 2011; 73:239-259. Doi:10.1146/annurev-physiol-012110-142233

18. Lauridsen et al. Genetic variation in the cholesterol transporter NPC1L1, ischemic vascular disease, and gallstone disease. Ear Heart J 2015; 36:1601-1608.

19. Maron DJ, Hartigan PM, Neff DR, Weintraub WS, Boden WE, COURAGE Trial Investigators. Impact of adding ezetimibe to statin to achieve low-density lipoprotein cholesterol goal (from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial). Am J Cardiol. 2013(Jun 1); 111(11):1557-62. doi: 10.1016/j.amjcard.2013.02.005. Epub 2013 Mar 25.

20. Mehta SR. Aspirin for prevention and treatment of cardiovascular disease. Ann Intern Med 2009; 150:414-416.

21. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med. 2005; 353(22):2373-2383.

22. Ridker P, Cook N, Lee M, Gordon D, Gaziano M, Manson J, et al. A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women. N Engl J Med. 2005;352(13):1293-1304

23. Silbernagel G et al. High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis. J Am Coll Cardiol 2013; 62:291-299.

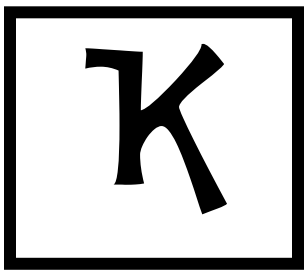
24. Steinhubl SR, Bhatt DL, Brennan DM, Montalescot G, Hankey GJ, Eikelboom JW, Berger PB, Topol EJ, on behalf of the CHARISMA Investigators. Aspirin to prevent cardiovascular disease: The association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med 2009; 150:379-386.

25. Sudhop T, Lütjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by Ezetimibe in humans. Circulation 2002; 106:1943-1948.

26. Taylor AJ, Bindeman J, Feuerstein I, Le T, Bauer K, Byrd C, Wu H, O'Malley PG. Community-Based Provision of Statin and Aspirin After the Detection of Coronary Artery Calcium Within a Community-Based Screening Cohort. J Am Coll Cardiol 2008; 51(14):1337-1341.

27. Temel RE, Tang W, Ma Y, Rudel LL, Willingham MC, Ioannou YA, et al. Hepatic Niemann-Pick C1-like 1 regulates biliary cholesterol concentration and is a target of ezetimibe. J Clin Invest. 2007; 117(7):1968-1978.

28. Yeste D, Chacon P, Clemente M, Albisu MA, Gussinye M, Carrascosa. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. J Pediatr Endocrinol Metab 2011;22(6): 487–492. DOI: https://doi.org/10.1515/JPEM.2009.22.6.487.



MY FAMILY AND HEART DISEASE

Chapter K1: Should I ask my relatives to be screened for Heart Disease?

Clinical Vignette

Lisa McKinney is a 55 year old clerk at a local grocery store. She has a large family with three sisters and four brothers. Her grandfather had heart disease (type unknown) and her mother had a stroke in her early 60's. She read about the benefits of a coronary artery calcium scan in Time magazine, so she asked her doctor to order it. Her score was 377 and her doctor started her on triple therapy to reverse the atherosclerotic plaques in her heart. Lisa would like to know if she should talk to her relatives about the benefits of the scan and what criteria they should meet to be scheduled for a calcium heart scan.

Comment

The issue concerning who should be screened for heart disease with a coronary artery calcium scan is important. There is no reason to scan someone who you know will have a positive scan or someone you know who will have a negative scan. For this reason, we do not recommend screening anyone with known atherosclerotic heart disease (e.g., they have already had a heart attack). The reason is that their scan will almost always be positive. Using the same line of reasoning, we do not recommend screening anyone with absolutely no risk factors for heart disease (this is very rare because major risk factors include diabetes, hypertension, abnormal blood fats, age greater than 50 years, and smoking, whereas minor risk factors include obesity, positive family history of heart disease or stroke, male gender, kidney disease, insulin resistance, and several inflammatory diseases. Therefore, the majority of asymptomatic adults should be screened.

The next question is at what age people should be screened. Since many individuals have heart attacks in their 40's, screening after age 40 may be too late. Here is our recommendation. If an adult has more than one major risk factor, we recommend coronary artery calcium screening after the age of 30 years. If a person has only one major risk factor, we recommend screening after the age of 40 years. Since age is a major risk factor for atherosclerosis, everyone who has not been screened by the age of 50 years should be screened. We don't believe that anyone is too old to be screened as long as they are relatively healthy (a projected lifespan of at least 5 years) and a situation in which a heart attack would be detrimental to their wellbeing.

Coronary artery calcium scanning is a much under-utilized diagnostic test in the United States. Remember that it is noninvasive and reasonably priced. There are not many tests that have these two characteristics that can save your life. It is much better to be scanned and have a zero score than not to be scanned and have a heart attack. Wouldn't you agree?

To answer Lisa's question, she should communicate the above criteria to her relatives and recommend a scan for any of them who meet the age and risk categories. She will be doing them a great favor and they should appreciate her caring for their health.

Figure legend – Who should receive a coronary artery calcium scan and when to recommend this scan depends upon a person's age and the number of cardiovascular risk factors. The text above gives our recommendations for whom to scan. However, if a person is anxious about the possibility of heart disease, we recommend a scan to set that person's mind at ease.

Chapter K2: What information can I believe from the Internet?

Clinical Vignette

Frank Spafford is a 39 year old executive in a small family owned business that relies on the internet for customer orders. He is computer savvy, spending much of his time sitting in front of a computer monitor. He also has type 2 diabetes, hypertension, obesity and a strong family history of heart disease. He wants to avoid the fate of his father who died at age 48 of a heart attack and a 46 year old brother who is currently in the hospital with heart failure. When he uses the internet to get information on preventing heart disease, he gets confused because of the many conflicting recommendations. He asks "What should I believe on the internet?"

Comment

We sympathize with Frank's dilemma. How should he go about separating the valid information from the false information on heart disease? We can make four recommendations that should help Frank decide what information to believe.

1) Does the author of the information have a vested interest in your believing that their information is real? If so, beware!! For example, the dairy industry has a vested interest in your thinking that dairy products do not raise cholesterol. They want you to buy their eggs, butter, and cheese. These products do raise your cholesterol level and should only be eaten in strict moderation.

2) Does the author of the information have any recognized education and training in the area of heart disease? You would be amazed about how many people believe they are experts on any subject after they have watched a five minute video on YouTube! Authors that have expertise should always tell you their credentials (if they have any). Just because the website looks professionally made does not say anything about the validity of the information on it.

3) Does the author of the information have a product to sell to you directly online? Scams on the internet are legendary. "Buyer beware" is an axiom which you should always keep in mind. Many people believe that if something is written, it must be true. Nothing is farther from the truth.

4) Is the information based upon scientifically proven facts or just hopeful studies which have not been published in scientific journals? Seeing it on TV or in a newspaper advertisement

does not give it validity. In addition, it is often very difficult for the lay person to understand all the technical jargon that is used in scientific papers. However, asking a friend with expertise in the area of the information is a good start. Many universities and hospitals have knowledgeable professionals whom you can ask.

To summarize, there is valid information on the internet. However, sifting through all the bogus information is not easy. We sympathize with Frank's dilemma but if he follows our advice, he has a good chance of separating good information from bad information.

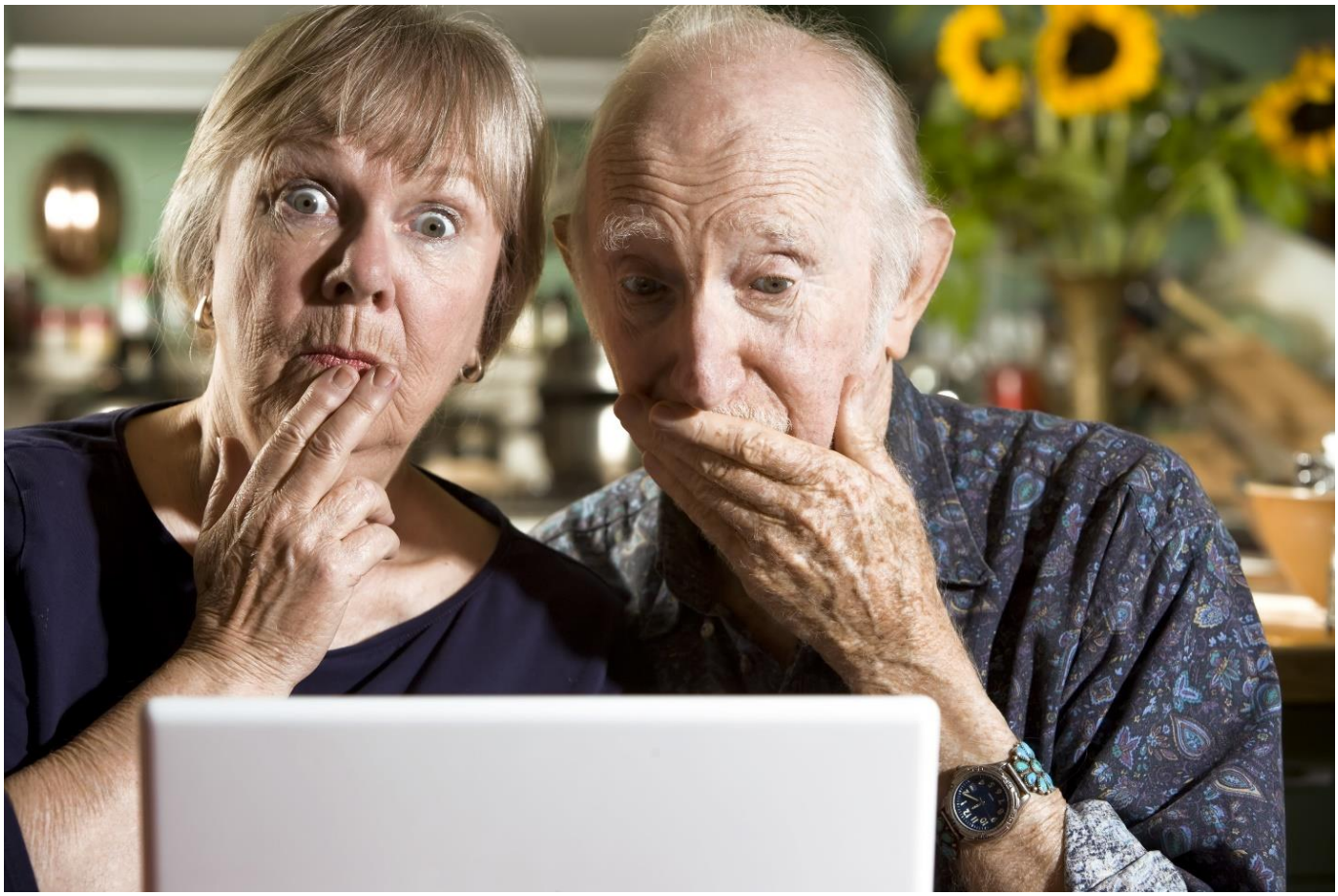


Figure legend – The internet is full of contradictory information. Often, the reader can't tell who is writing the information and what they stand to benefit from your believing it. The rule "Don't believe all you read" is certainly applicable to internet information.

Chapter K3: Who's got your numbers?

Clinical Vignette

Frank Beal is a 52 year old salesman who covers a 5 state area selling wholesale business furniture to small companies. On a recent trip to Arizona, he developed chest pain and diffuse sweating. A business colleague brought him to an emergency room for treatment. The emergency room physician asked Frank if he knew what his previously performed heart tracing showed (electrocardiogram) as well as his recent calcium heart scan score, lipid profile, and hsCRP concentration. Frank responded that he had no idea what his previous health values were. His own physician's office was closed for the weekend. The emergency room physician was disappointed and indicated that he would need to repeat all of these tests at significant expense to Frank. In addition, Frank was hospitalized overnight because the physician was nervous about Frank's chest pain.

Comment

Frank should have realized that an important part of taking care of one's health is knowing the results of his/her recent medical tests in case they are urgently needed. One of the major deficiencies of the U.S. health care system is the inability of physicians to access other systems' medical databases. There are several reasons for this lack but the primary reason is that hospital administrators are bound by strict HIPAA regulations to safeguard patients' medical data. It is unlikely that this problem will be resolved soon. Therefore, patients need to be able to inform physicians what their medical test results are. A good place to store these numbers is on your cell phone.

One of the more beneficial advances in medical record keeping is the development of patient portals. Almost all major healthcare systems now permit patients to access their own medical records. This is usually done by signing up with the healthcare system and providing a unique password for access to your medical records. All patients should sign up for access to their portal and print out all the tests that have been done in the last year. Critical results, such as records related to heart health, should be carried with the patient or be otherwise accessible if he/she is going to travel out of town. This approach is very easy to do now that cell phone cameras are widely available. Taking a picture of all important lab results is a great way to have ready access to your data.

Relative to heart health, we recommend that patients should have ready access to their previous electrocardiogram (heart tracing), coronary artery calcium scan, lipid profile, hsCRP and any previous medical description of chest pain. If Frank had taken our advice, he would have saved additional expenses and avoided an overnight stay in the hospital. Think of the old adage “a stitch in time saves nine.”

Figure legend – The above illustration shows has easy it is to save your own important laboratory numbers. You can do this through your own patient medical record portal (ask your clinic nurse for an application form). You should keep a permanent record of all of your critical health results so that you can access them at any time. Not only is this good health care but it will give you reassurance that medical tests will not be unnecessarily repeated.

K.

MY FAMILY AND HEART DISEASE

Citations

1. Bacha F, Edmundowicz D, Sutton-Tyrell K, Lee S, Fjayli H, Arslanian SA. Coronary Artery Calcification in Obese Youth: What Are the Phenotypic and Metabolic Determinants? Diabetes Care 2014; 37:2632–2639 | DOI: 10.2337/dc14-0193

2. Baker JL, Olsen LW, Sorensen TI. Childhood body mass index and the risk of coronary heart disease in adulthood. Ugeskr Laeger 2008; 170(33):2434-2437.

3. Bao W, Srinivasan SR, Wattigney WA, Bao W, Berenson GS. Usefulness of childhood low-density lipoprotein cholesterol level in predicting adult dyslipidemia and other cardiovascular risks: The Bogalusa Heart Study. Arch Intern Med 1996; 156(12):1315-1320. doi: 10.1001/archinte.1996.00440110083011

4. Berenson GS. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. Am J Cardiol. 2002; 90(10C):3L-7L.

5. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study – Implications for LDL Management. Journal of clinical lipidology. 2007; 1(6):583-592.

6. Daniels SR. Cardiovascular disease risk factors and atherosclerosis in children and adolescents. Current atherosclerosis reports. 2001; 3(6):479-85.

7. Gidding SSRJ, Rana JS, Prendergast C, et al. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score in young adults predicts coronary artery and abdominal aorta calcium in middle age: the CARDIA Study. Circulation. 2016; 133(2):139-146.

8. Ho M, Garnett SP, Baur L, Burrows T, Stewart L, Neve M, et al. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. Pediatrics. 2012; 130(6):e1647-1671. doi: 10.1542/peds.2012-1176.

9. McMahan CA, Gidding SS, Malcom GT, Tracy RE, Strong JP, McGill HC Jr, et al. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. Pediatrics. 2006; 118(4):1447-1455.

10. Morrison KM, Dyal L, Conner W, Helden E, Newkirk L, Yusuf S, et al. Cardiovascular risk factors and non-invasive assessment of subclinical atherosclerosis in youth. Atherosclerosis. 2010; 208(2):501-505. doi: 10.1016/j.atherosclerosis.2009.07.034.

11. Rewers M, Ehrlich J, Jensen L, Siegel R, Barriga K, Garg S, et al. High Prevalence of Asymptomatic Coronary Atherosclerosis Detected by Electron Beam Computed Tomography in Young Adults With IDDM. Diabetes. 1998; 47(1S):12A.

12. Ridker PM, Cook NR. Cholesterol Evaluation in Young Adults: Absence of Clinical Trial Evidence Is Not a Reason to Delay Screening. Ann Intern Med. 2017; 166(12):901-902. doi: 10.7326/M17-0855.

13. Schade DS, Murphy S, Exil V, Eaton P. A Pediatric Opportunity in Adolescents to Prevent Adult Heart Attacks. World Journal Cardiovascular Diseases 2018; 8(2):85-101 doi: 10.4236/wjcd.2018.82009

14. Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis Supplement I 1989; 9:I19 – I32

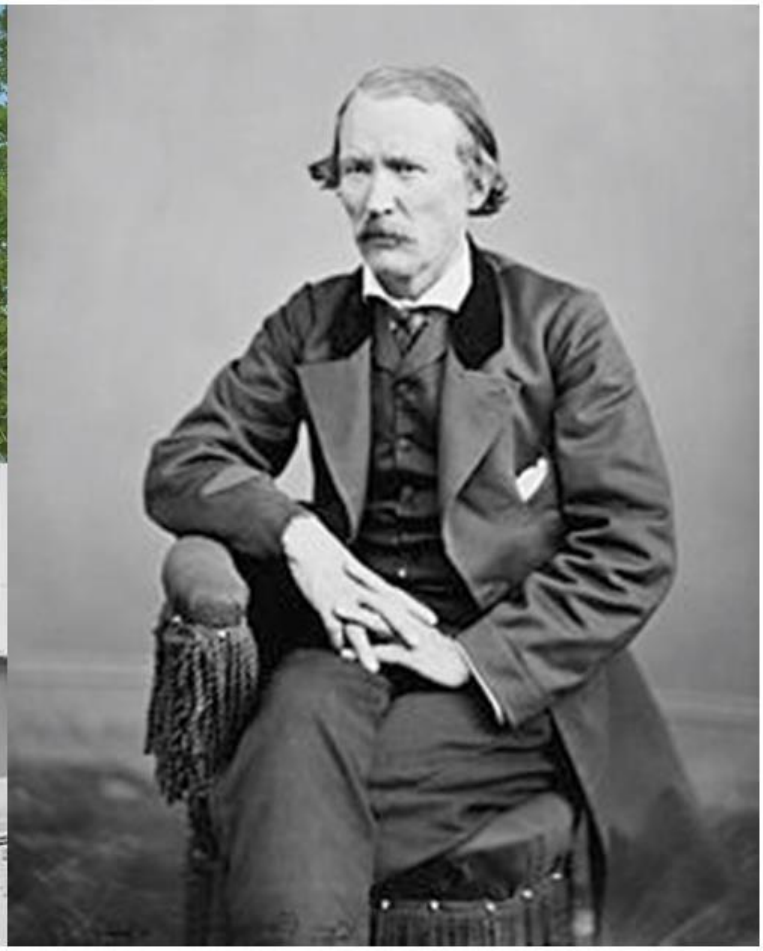
15. Tirosh A, Shai I, Afek A, Dubnov-Raz G, Ayalon N, Gordon B, et al. Adolescent BMI Trajectory and Risk of Diabetes versus Coronary Disease. N Engl J Med 2011; 364:1315-1325.

16. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, Young YB, Nissen SE. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults. Circulation 2001; 103:2705-2710.

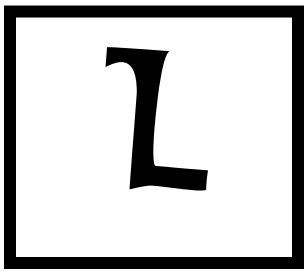
17. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. N Engl J Med. 2016; 374(25):2430-2440.

18. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child–Parent Familial Hypercholesterolemia Screening in Primary Care. N Engl J Med 2016; 375:1628-1637.

19. Wiegman A, Hutten BA, deGroot E, Rodenburg J, Bakker HD, Büller HR, Sijbrands EJG, Kastelein JJP. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: A randomized controlled trial. JAMA 2004; 292(3)331-337.



Born in Kentucky and raised on the Missouri frontier, Kit Carson became an experienced hunter and trapper by his 20s. After meeting explorer John C. Frémont in 1842, Carson was an active participant in extending the boundaries of the United States to its present size. He became a federal Indian agent in the 1850s and later served the Union Army in the Civil War. Carson, who died in Colorado in 1868, is remembered as an icon of the frontiersman days of the American West. He is buried near his home in Taos, New Mexico



TOO MUCH OF A GOOD THING ?

Chapter L1: Will my high HDL cholesterol protect me?

Clinical Vignette

Shelley Johnston is a 40 year old married woman with three children. She takes estrogen medication to control the hot flashes that have occurred for the last three years. She is overweight with type 2 diabetes. Her mother had a heart attack at age 46, so she is worried that she also may be at risk. At her last routine medical checkup, her laboratory results demonstrated an elevated LDL cholesterol (133 mg/dl) and an elevated hsCRP (6.0 mg/L). However, her doctor told her not to worry, since her HDL cholesterol was also elevated (88 mg/dl). He said that the high HDL cholesterol cancelled out the harmful effects of the elevated LDL and hsCRP. Shelley wants a second opinion about the safety of depending upon her HDL to prevent a heart attack.

Comment

Shelley is right to seek a second opinion. HDL is a very small fat particle that is secreted from both your liver and intestine into the blood. It has many functions in the body, but the main one is to carry cholesterol from the arteries to the liver for disposal. In that role, it is responsible for removing atherosclerotic plaques by reducing their quantity of cholesterol. It also has a secondary role of reducing inflammation. Without these two activities, it is likely that we would all have heart attacks at very young ages.

Studies of large numbers of people have demonstrated that the higher the HDL level is in the blood, the less heart disease there is. These studies are undoubtedly what Shelley's doctor is referring to. However, it is also clear that the benefit of a raised HDL is different in different people. That is because what is measured in routine blood tests is the concentration of HDL in the blood, not whether HDL is actively removing cholesterol from atherosclerotic plaques. Think of a train waiting at the station. You assume that it will take you from your town to the next town but that assumes that the engine in the train has enough fuel or the engineer is available to start the train. It's the same for HDL. When the concentration is high, it is usually beneficial, but not always. Studies have demonstrated that a high concentration of HDL does not always mean a high level of cholesterol removal from plaques. Shelley is right to be suspicious and she should not depend on her high HDL to protect her from a heart attack.

Instead, she should obtain a coronary artery calcium scan and if positive, start treatment to lower her LDL and hsCRP to reduce the rate that she makes atherosclerotic plaques.

In contrast to a high HDL blood concentration, a low HDL is usually a heart attack risk factor. This fact is based on the observation that the HDL may be working but there is not enough of it to keep up with the deposition of LDL cholesterol in coronary artery plaques. HDL is lowered by smoking, obesity, and lack of exercise. This is one reason that these factors are risk factors for heart disease.

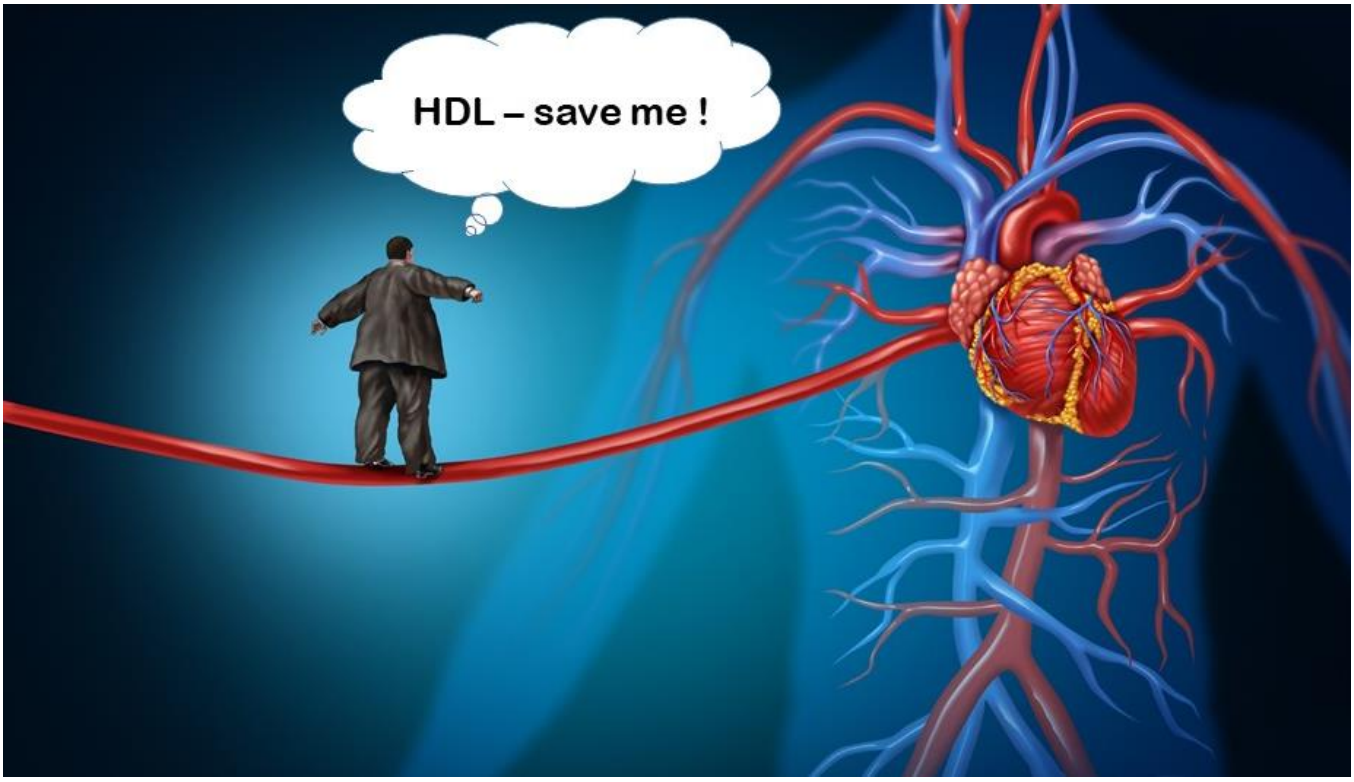


Figure legend – Normally, HDL removes the cholesterol from atherosclerotic plaques that LDL lays down in the coronary arteries. But just measuring the amount of HDL does not tell you how hard HDL is working to remove the plaque cholesterol. It may be that LDL is depositing twice the amount of cholesterol in your artery that HDL is removing. The point of this chapter is not to rely on your HDL level to protect you from a heart attack. If you get a coronary artery calcium scan and your score is zero, you know that your HDL is working at a high rate to remove any plaques that your LDL is depositing in your arteries.

Chapter L2: Is Cholesterol Good or Bad?

Clinical Vignette

Jesse Sanchez is a 40 year old high school teacher who is very interested in staying healthy. He exercises regularly at the local gym three times a week and eats a healthy diet of vegetables, fruits, plus lean meat and fish. He likes to use the internet for health advice but is confused when trying to understand the role of cholesterol in his body. Some of the internet blogs say cholesterol is good. Others say it is bad. What is the real story?

Comment

It is understandable that Jesse is confused. Many people are. So here are the facts. First, cholesterol is a big molecule that is shaped like four intersecting rings. It is a very stable molecule, which means that your body cannot break it up into smaller pieces. Once it is in your body, it stays there until your liver excretes it into your gut for removal in the stool. Second, every cell in your body can make all the cholesterol it needs. It is not necessary to consume any in the diet. Your cells need some cholesterol to stabilize various structures in the cell, particularly the membrane that forms the outside boundary of each cell. Think of a soap bubble. If there were cholesterol in the soap, the bubble might never pop. Cholesterol is also essential for stabilizing the outside of fat particles that circulate in your blood to carry energy to your muscles. Finally, cholesterol is an essential component of bile acids, which are necessary to digest the fat that you eat. For these functions, cholesterol is essential for life (cholesterol in this role is good). Third, cholesterol can cause two diseases in humans – cholesterol stones in your gall bladder and atherosclerotic plaques in your arteries. In these two roles, cholesterol deposits can result in abdominal surgery, a heart attack, or stroke. Fourth, the cholesterol that circulates in your blood comes from two sources: from your diet and from the cholesterol that your liver produces. Fifth, only animals can make cholesterol. Plants do not manufacture cholesterol (they use a different molecule to stabilize their cell membranes). This is the reason that strict non-dairy consuming vegetarians eat much less cholesterol than individuals consuming diets containing meat and dairy products. As a group, vegetarians have a much lower amount of circulating cholesterol in their blood. As you would expect, they also have fewer heart attacks.

Therefore, to answer Jesse's question, cholesterol is both good and bad. Too much causes disease. Too little is not compatible with human life. We are sure you can think of many other things in life for which too much of a good thing is bad (such as visits from your relatives). The point to remember from this is that since every cell in your body can make all the cholesterol it needs, it is not necessary to ingest any in your diet. However, there are other reasons (i.e., enjoyment) to occasionally eat a good steak.

Figure legend – Cholesterol is an essential component of cells that make up your body. However, when it is too high, damage and blockage of your arteries occur. Most people in the Western World have too much cholesterol in their blood, because of either unfortunate genetic inheritance or poor lifestyle (or both). Genetic effects can be counteracted with medication and lifestyle can be changed with a little effort. Do not let a high cholesterol level ruin your life!

Chapter L3: Does the cholesterol in my food make a difference?

Clinical Vignette

Bill Springer is an obese 44 year old construction worker and lover of fast food. For lunch he has two cheeseburgers, French fries, and a diet Coke (to lose weight). His coronary artery calcium score is 465 with an LDL of 122 mg/dl and a CRP of 4.6. He read on the internet that the cholesterol content of food does not affect the level of LDL in his blood. Bill would like to know if there is any evidence that the cholesterol in his cheeseburgers increases his blood LDL?

Comment

Bill raises an issue that is commonly stated on the internet that "cholesterol in food makes no difference." Before we answer Bill's question, it is important to understand how Bill's intestinal tract handles cholesterol. Cholesterol in the intestine comes from two sources. Seventy-five percent of it comes from the liver and 25% from the food that Bill eats. The liver secretes cholesterol into the intestine to help digest fatty foods. This cholesterol mixes with Bill's cheeseburger cholesterol and then about half of this mixture is reabsorbed back into Bill's body. This cholesterol is then used by the intestine and the liver to package triglycerides for the blood circulation. After the triglycerides are taken up by fat tissue and muscle, the cholesterol remnant that is left is LDL.

How do we know that cholesterol in the diet will increase LDL cholesterol? There are several lines of proof. First, volunteers have been fed diets containing different amounts of cholesterol. As expected, the more cholesterol in the diet, the more the volunteers' blood LDL increased. Second, if 50% of the absorption of cholesterol in the gut is directly blocked with a drug (i.e., ezetimibe), circulating LDL levels decrease by 20%. Third, animals that eat plants normally have very low LDLs unless fed a high cholesterol diet. There is a famous rabbit (the Watanabe rabbit) that when fed a high fat and cholesterol diet actually develops plaques in its coronary arteries. Finally, vegetarians who do not consume any cholesterol in their diet (vegans), have very low LDL cholesterol levels. The average American diet contains 400 milligrams of cholesterol.

This is a huge amount considering that none at all is needed for healthy living. Some foods are particularly high in cholesterol. For example, one egg yolk contains 170 mg of cholesterol. The next time you are at the grocery store, be sure and read the label for the content of cholesterol. You may be surprised at what you see. Small changes in your food choices can make a big difference in your cholesterol intake. "Eating Smart" does not mean giving up foods that you like. It means consuming foods that taste good and whose ingredients are good for your health (i.e., low in cholesterol & saturated fat).

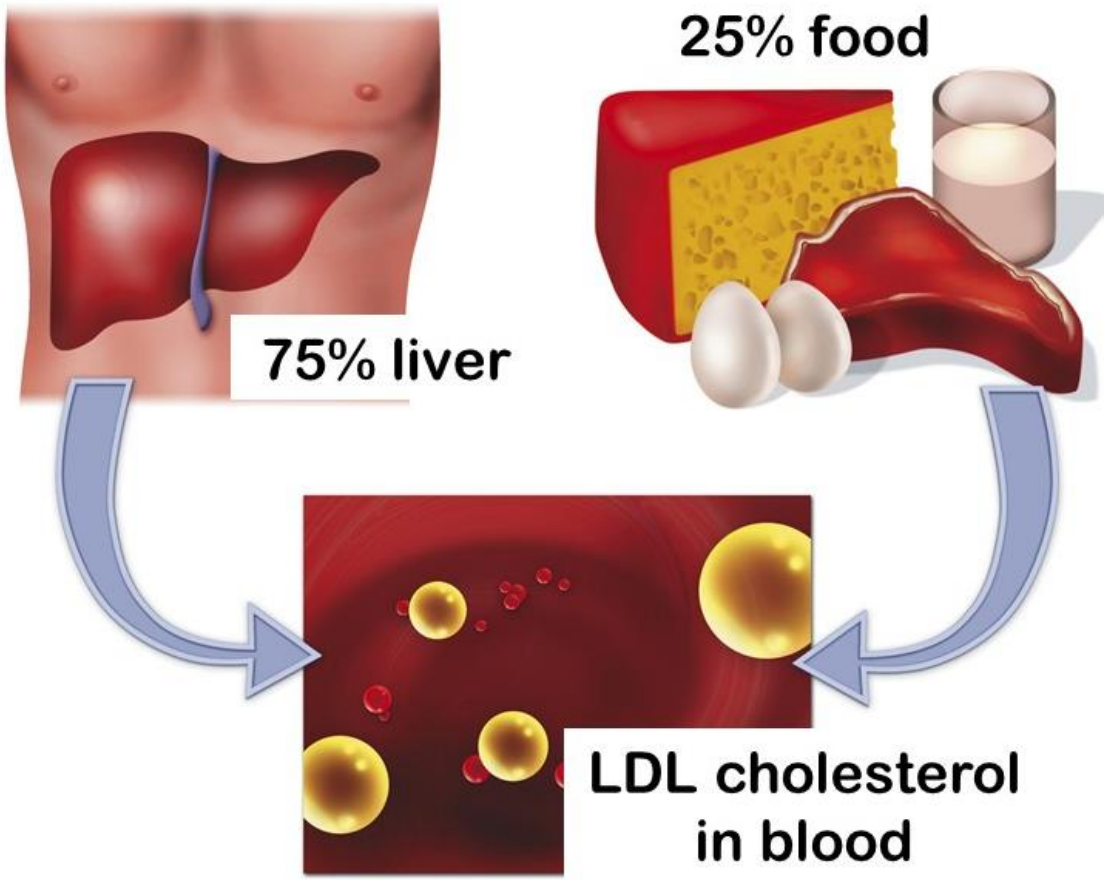


Figure legend – The food that you eat contributes 25% of the cholesterol that your body absorbs from the intestine. This cholesterol is repackaged by the intestine and the liver. Some of it ends up in circulating LDL particles. The LDL particles then enter the artery wall and eventually form plaques in your arteries. Reducing cholesterol in your diet will reduce your circulating LDL cholesterol and your chance for a heart attack.

1.

TOO MUCH OF A GOOD THING?

Citations

1. AIM-HIGH Investigators. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. N Engl J Med 2011;365:2255-2267.

2. Ansell B et al. Inflammatory/Anti-inflammatory Properties of High-Density Lipoprotein Distinguish Patients From Control Subjects Better Than High-Density Lipoprotein Cholesterol Levels and Are Favorably Affected by Simvastatin Treatment. Circulation 2003; 108:2751-2756.

3. Boden W and the AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. A Systematic Review and Meta-analysis. Ann Intern Med 2016; 165:491-500. doi:10.7326/M16-0361.

4. Couzin-Frankel J. LIPID BIOLOGY. Why high 'good cholesterol' can be bad news. Science. 2016; 351(6278):1126. doi: 10.1126/science.351.6278.1126.

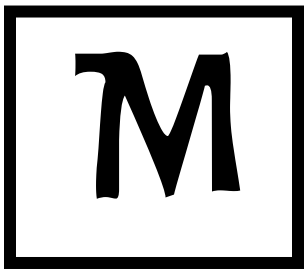
5. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease: A Mendelian Randomization Analysis. J Am Coll Cardiol 2012; 60(25):2631-2639.

6. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med 2014; 371:2383-2393.

7. Rosenson RS, Brewer HB Jr, Ansell BJ, Barter P, Chapman MJ, Heinecke JW, et al. Dysfunctional HDL and atherosclerotic cardiovascular disease. Nat Rev Cardiol. 2016; 13(1):48-60.

8. Saleheen D, Scott R, Javad S, Zhao W, Rodrigues A, Picataggi A, et al. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. Lancet Diabetes Endocrinol. 2015; 3(7):507-513.

9. Singh IM1, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA. 2007; 298(7):786-798.



CHOLESTEROL FOR CHEMISTS

Chapter M1: What is the structure of LDL cholesterol?

Clinical Vignette

Carol Block is a 50 year old graphics art designer for an advertising firm. She constructs ads for clients to help them sell their products. She believes that a "picture is worth a thousand words". She recently experienced chest pain while walking her dog up a long, steep hill. Her physician ordered a calcium heart scan to assess her risk of a future heart attack. Her score was 445 with most of the calcium in the anterior descending coronary heart artery (high risk location). She has started a program of "eating smart" consisting of low saturated fat foods and triple medication therapy to lower her LDL cholesterol and inflammation. Being an inquisitive person, she would like to know "what does LDL cholesterol really look like?"

Comment

Carol asked a very good question. LDL cholesterol (abbreviated LDLc) is not just a drop of grease that floats in your blood. It has definite and important structural characteristics. LDLc is called a "remnant particle" because it remains after most all the triglycerides are removed. The triglyceride is utilized by muscle and fat tissue for energy. The parts of the LDLc particle are:

1) The Beta protein (called apoB lipoprotein) - is a protein molecule made in the liver and secreted into the blood with triglyceride. ApoB has a very important function. It binds LDLc particles to the liver's LDL receptors that remove LDLc from the blood. As you would predict, people who cannot bind their LDL cholesterol to liver receptors have very high LDLc levels and usually severe heart disease.

2) Phospholipids – These molecules naturally stick together and form spherical membranes (similar to soap bubbles). Phospholipids have a unique property in that they are water soluble on the outside but lipid (fat) soluble on the inside. This characteristic is important because they can move around in the blood without forming a fat globule. However, like soap bubbles, phospholipids are not very stable so cholesterol molecules are spaced randomly between them to stabilize the membrane.

3) Cholesterol – this molecule comes in two forms. The simplest form is called unesterified cholesterol - that means that nothing is attached to it. This form is located in the phospholipid membrane for stabilization. Most of the cholesterol, however, locates itself on the inside of the

LDLc particle. This form of cholesterol is called “esterified cholesterol” because it has an additional molecule stuck to it (i.e., esterified to it). This attachment makes cholesterol more fat soluble so it naturally moves into the center of the LDLc particle, away from the blood (blood is mostly water). This part of the LDLc molecule eventually forms plaques in the heart arteries if not removed by the liver first.

Like most things in life, too much of anything is as bad too little. You need a small amount of LDLc to carry fat-soluble vitamins to your tissues, i.e., vitamins K, A, D, and E. People with no LDL cholesterol suffer from vitamin deficiencies and people with too much LDLc suffer from heart disease. If you keep your LDLc between 20 mg/dl and 50 mg/dl, you will have neither heart disease nor vitamin deficiencies.

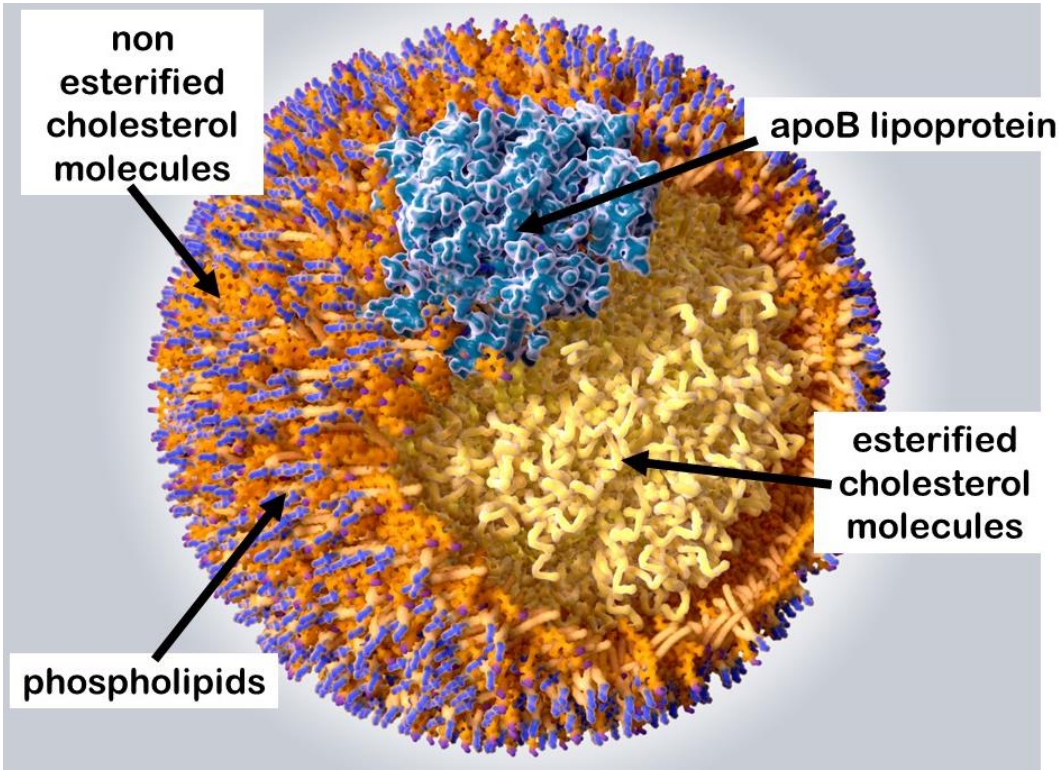


Figure legend – LDL particles have a definite structure that holds the particle together. The numerous dark blue phospholipid molecules form the spherical membrane and are stabilized by the orange non esterified cholesterol molecules. The yellow esterified cholesterol molecules move into the center of the particle because they are fat soluble. The lighter blue apoB lipoprotein molecule is critical for binding the LDLc particle to the LDL receptor on the liver.

Chapter M2: Are all LDL cholesterols created equal?

Clinical Vignette

Sam Brown is a 56 year old medically retired high school teacher who had a heart attack three years ago. During his retirement, he has gained 30 pounds which he says is because he can no longer exercise due to shortness of breath. He now leads a sedentary life watching TV and playing cards with his friends. His wife recommends a cardiac rehab program and his doctor agrees. His doctor warns Sam that his weight gain has increased his triglycerides and heart risk by making his LDL into small, dense particles. Sam asks – "are not all LDL particles the same?"

Comment

Before we answer Sam's question, a little background on how LDL forms plaques may be helpful. Low density lipoprotein (LDL) is a spherical particle that circulates in the blood and gets deposited in the arteries as a cholesterol plaque. However, on its way from leaving the blood and entering the arterial wall, two events must occur for it to form a plaque. First, it must get through the lining of the inside of the artery (technically called the endothelium). To do this, it must squeeze through a small opening between the cells lining the inside arterial wall. Second, after it gets into the arterial wall, it combines with an oxygen molecule. It is then engulfed by a macrophage (a white blood cell) and combines with other LDL particles to eventually form a fatty streak, then a plaque.

LDL comes in two sizes, big and fluffy or small and dense. As you might guess, the big, fluffy form has difficulty getting through the narrow spaces between the cells lining the inside of the arteries whereas the small, dense LDL particles easily slip through. If this were not bad enough, the small dense LDL particles very easily combine with oxygen molecules compared to the big, fluffy ones. So, all LDL particles are not created equal.

Everyone can make both big, fluffy LDL and small dense LDL particles. So why do some people make more of one kind than the other? It appears that the level of triglycerides that circulate with the LDL in the blood are the determining factor. You can find out what your triglyceride level is by looking at your lipid profile. The higher the triglyceride level, the more

small, dense LDL particles you make. A safe number for triglycerides is less than 150 mg/dl. Above this level, you can be sure that you are making too many small LDL particles.

Another problem that you may have wondered about is the measurement of LDL. As you may have deduced, an LDL cholesterol concentration does not tell you whether the LDL is big and fluffy or small and dense. Therefore you could have an LDL concentration of 80 mg/dl and in reality have a greater or lesser risk of heart disease than the LDL of 80 mg/dl would suggest (depending on the size of the LDL particle). The total level of LDL of 80 mg/dl could either be a few big LDL particles or many small LDL particles. You cannot tell which. This is one reason that we highly recommend an LDL goal of 50 mg/dl. At this level of LDL, you are in a safe zone no matter whether your LDL is big or small. If your triglycerides are high, reducing your triglyceride level is also a good goal.

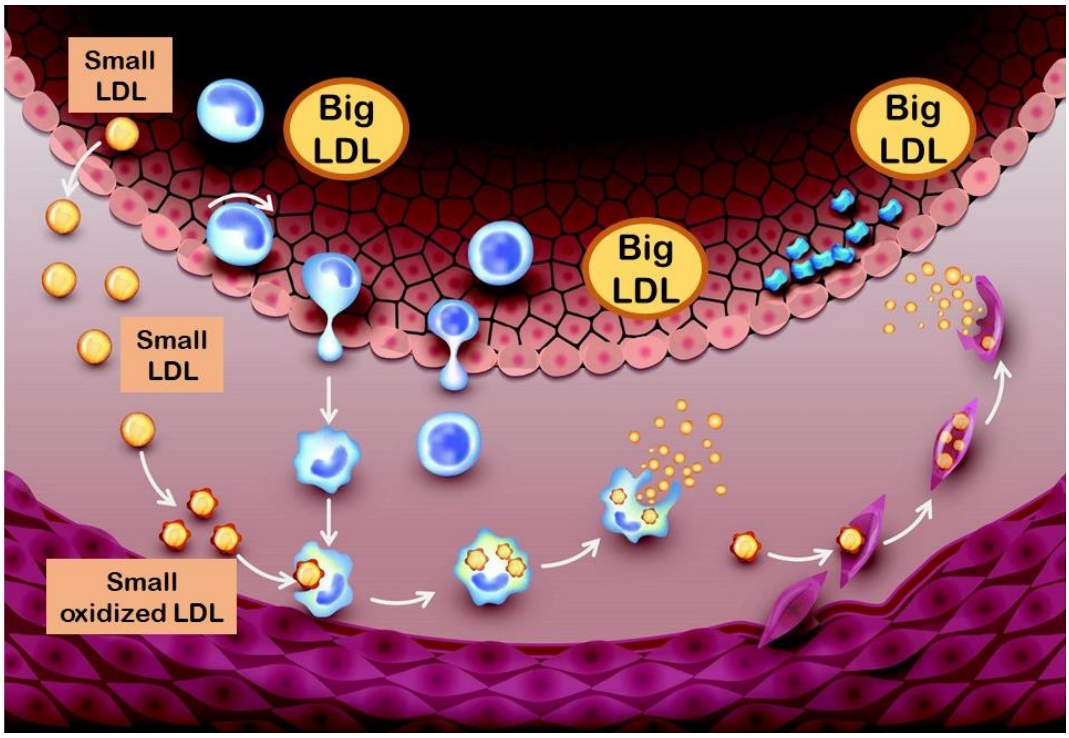


Figure legend – Small, dense LDL particles fit easily through the small spaces between the inside lining of the artery wall. These particles rapidly combine with oxygen and eventually form plaques. In contrast, large, fluffy LDL particles have difficulty getting through the lining and also have difficulty combining with oxygen. Your triglyceride level will tell you what type of LDL particles you predominantly make (if high triglycerides, then small LDLs).

Chapter M3: What does PCSK9 have to do with my heart?

Clinical Vignette

Brad Schafer is a 35 year old insurance salesman who has a positive family history of heart disease. His two brothers died of heart attacks in their late 30s and his father died of heart failure at the age of 44 years. He has known that his LDL cholesterol (LDLc) was high since being tested as a teenager. His doctor has treated him with a high potency statin plus ezetimibe for the last six years and Brad has been following a low saturated fat diet since age 21. His most recent lipid profile demonstrated a very high LDLc of 189 mg/dl in spite of the statin and diet therapy. His doctor suggested that he might be a candidate for PCSK9 antibody therapy. Brad has no idea what his doctor is talking about.

Comment

PCSK9 antibody is the newest kid on the block for the treatment of hypercholesterolemia. Since no one can pronounce the name of this chemical, everyone just abbreviates it by the letters “PCSK9”. From Brad’s family history of heart disease and his high blood level of LDLc, one can bet that Brad inherited his abnormal cholesterol gene from his father (as did his two brothers). About one in every 200 people have the same genetic makeup as Brad. Fortunately, there is a new treatment for Brad which will substantially lower his elevated cholesterol. Two companies have recently received approval by the Food and Drug Administration to sell an antibody based drug that inactivates PCSK9.

PCSK9 is a strange chemical that is secreted from the liver and then turns around and prevents the liver from removing LDLc from the blood. It does this by destroying the liver’s receptor for LDLc. This action results in very high LDLc levels. No one knows why this happens. PCSK9 does not appear to serve any useful purpose in the body so removal of it by the new antibody medication is very helpful in lowering LDLc. Some people are born with practically no PCSK9 and they are healthy with very low LDL cholesterol levels. These new antibody based drugs are taken once per month by injection and so far have very few side effects. The antibody attaches to the PCSK9 molecule to block the molecule from acting. The main drawback to their widespread use is their high cost (about $13,000 / year). Because of this cost, insurance companies have restricted their use to people like Brad who have a genetic cause of hypercholesterolemia.

If you are interested in learning more about PCSK9 and the antibody drugs that block their effects, there are several good short cartoon videos on the internet that show the drugs in action. They provide more detail on just how these drugs work to protect the liver's LDL receptor from PCSK9. We recommend this video link (https://www.youtube.com/watch?v=dOYgB7rAEAo) to our patients who may be candidates for their use. Brad should discuss these drugs with his doctor and ask his doctor to talk to the insurance company about authorizing its use. These drugs may save Brad's life!

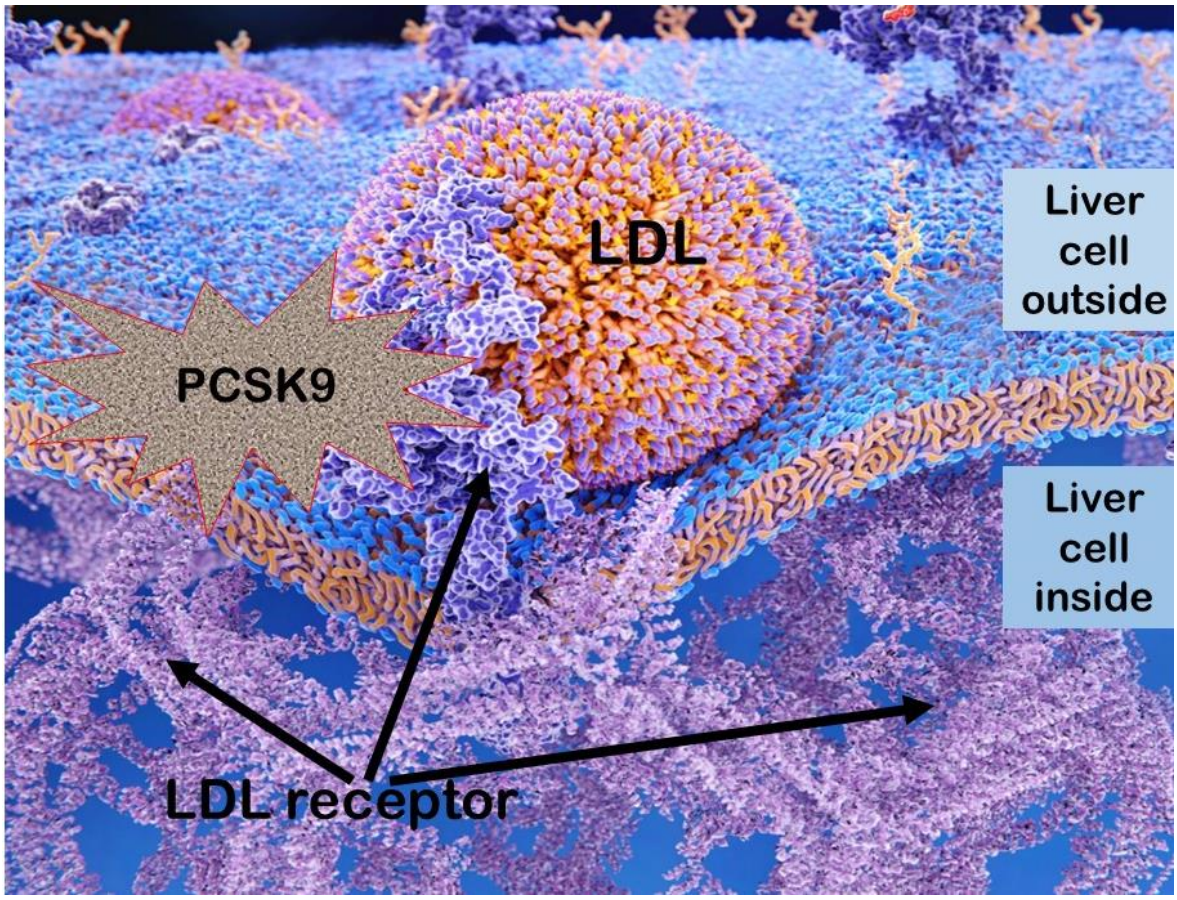


Figure legend -This drawing shows the liver's LDL receptor (lavender) holding onto an LDLc particle (light orange). The PCSK9 molecule (brown) is attaching itself to the LDL receptor and eventually causes its destruction. Blocking the PCSK9 molecule with an antibody will save LDL receptors and lower the blood LDL levels.

Chapter M4: Why do I need LDL liver receptors?

Clinical Vignette

Betsy Crawford is a 39 year old high school teacher. When her father had a heart attack at age 61, she wanted to know more about his disease. She found out that his LDL cholesterol was elevated at 122 mg/dl in spite of a healthy diet. She read in one of her health magazines that the key to longevity was to be born with extra liver LDLc receptors. "What does that have to do with my father's heart attack?" she asks.

Comment

We are pleased that Betsy asked this question and that her health magazine got it right. The hepatic LDLc receptor is a protein that is made by the liver for one purpose – to remove LDLc from the blood. The more LDL cholesterol receptors, the lower the circulating blood level of LDLc. This fact was proved conclusively in a patient with no functioning liver LDL receptors. This patient received a liver transplant and immediately reduced his circulating LDLc because the LDL receptors on his new liver removed the LDL cholesterol. Dr. Brown and Dr. Goldstein received the Nobel Prize for this discovery!

One way to have many LDLc receptors is to be born with them. You receive one gene for the LDLc receptor from your mother and one from your father. The total sum of the activity of these genes determines your starting receptor number level. Fortunately, there are additional ways to increase the number of liver LDLc receptors. One approach is to eat a low cholesterol diet. This diet depletes the liver of cholesterol, so it makes more LDL receptors to take up LDL cholesterol from the blood. Another way to increase your LDLc receptors is to take cholesterol-lowering medications. For example, both ezetimibe and statins increase the number of LDL liver receptors because they lower the level of cholesterol in the liver. As expected, the liver responds by making more LDL receptors to take up more LDLc from the blood.

As is shown in the diagram below, the LDLc receptor sits on the liver's surface waiting for an LDLc particle to attach to it. When it does, both the LDLc particle and the LDL receptor move into the liver cell. The LDL receptor then separates from the LDLc particle and this empty LDL receptor is recycled back to the liver's surface to attach to a new LDLc particle. It may surprise you to learn that this LDL receptor recycling occurs every 10 minutes. Meanwhile, the LDLc

particle is broken down into multiple parts. The cholesterol part is then made into bile acids and secreted into the bile ducts of the liver. Bile acids help you digest the fats that you ingest in your food.

To answer Betsy's question, the more LDL receptors you have on your liver, the more removal of LDLc from your blood will occur. This activity results in a lowering of your blood's LDLc concentration. The lower the LDLc concentration, the fewer heart attacks occur. Since heart attacks are the number one cause of death in the United States, reducing circulating LDLc results in a long lifespan for most people.

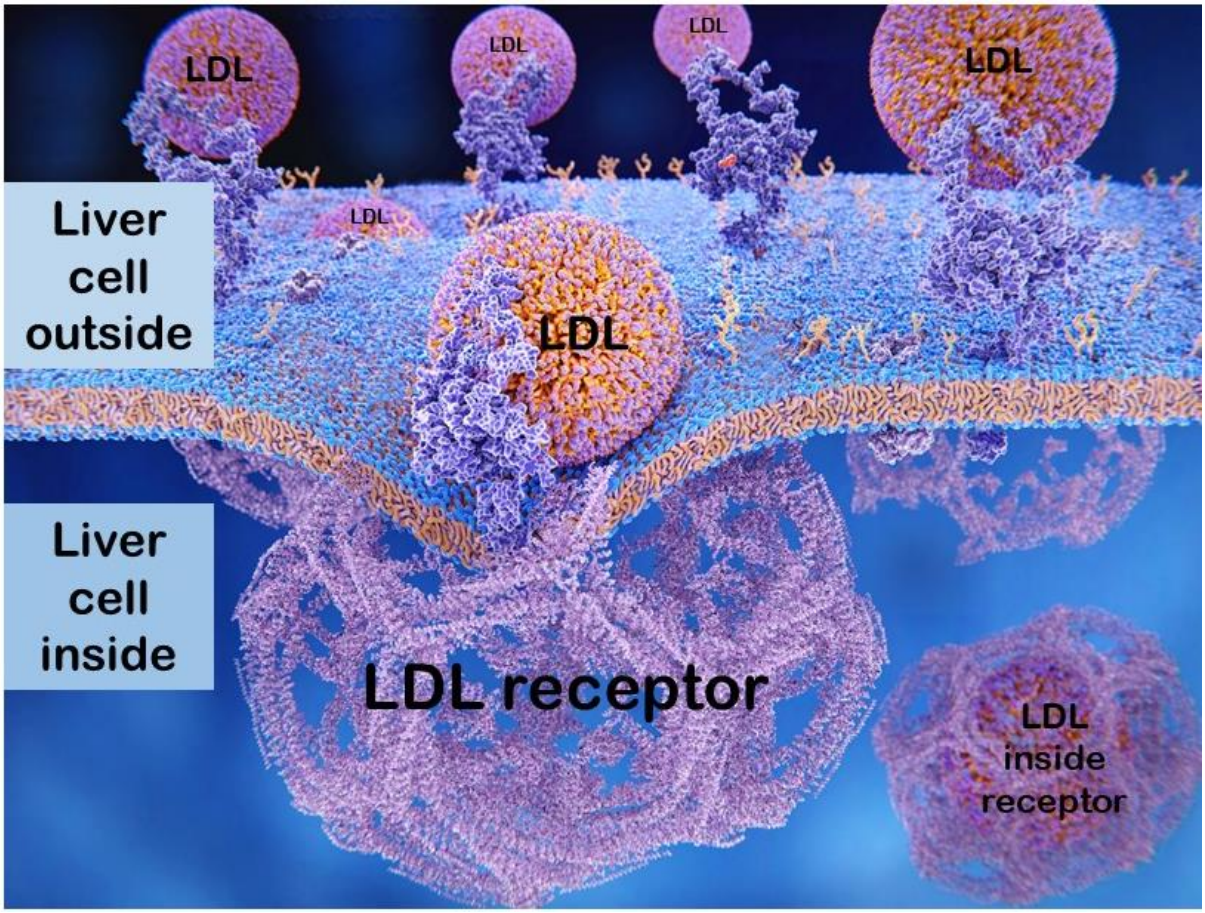


Figure legend -The liver's surface is a busy place with many different receptors doing various important functions. The LDL receptor lowers cholesterol by removing LDL particles. The figure illustrates the LDL receptor removing LDL particles. The LDL receptor then moves back to the liver's surface to catch another LDL particle. The LDL particle is broken up, thereby excreting cholesterol into the bile.

M.
CHOLESTEROL FOR CHEMISTS

Citations

1. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003; 34(2):154-156.

2. Akram ON, Bernier A, Petrides F, et al. Beyond LDL cholesterol, a new role for PCSK9. Arterioscler Thromb Vasc Biol 2010; 30:1279-1281.

3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R and the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005; Oct 8; 366(9493):1267-1278. Epub 2005 Sep 27.

4. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. for the Treating to New Targets Investigators. HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular Events. N Engl J Med 357:1301-1310.

5. Bilheimer DW, Goldstein JL, Grundy SM, Starzl TE, Brown MS. Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. N Engl J Med 1984; 311:1658-1664.

6. Zoler ML. Internal Medicine News. 2016 (Sept 20): ESC's new lipid guidelines keep LDL-cholesterol targets. https://www.mdedge.com/internalmedicinenews/article/113821/cardiology/escs-new-lipid-guidelines-keep-ldl-cholesterol. Accessed 6-11-18.

7. Brown MS, Goldstein, JL. Lowering LDL – not only how low, but how long? Science 2006; 311:1721-1723.

8. Brown MS, Anderson RG, Goldstein JL. Recycling receptors: The round-trip itinerary of migrant membrane proteins. Cell 1983; 32:663-667.

9. Davignon J and Dubuc G. Statins and Ezetimibe Modulate Plasma Proprotein Convertase Subtilisin Kexin-9 (PCSK9) Levels. Transactions of the American Clinical and Climatological Association. 2009;120:163-173.

10. Dayspring T, Dall T, Abuhajir M. Moving beyond LDL-C: incorporating lipoprotein particle numbers and geometric parameters to improve clinical outcomes. Research Reports in Clinical Cardiology. 2010; 2010(1):1-10.

11. Goldstein JL, Anderson, RGW, Brown MS. Coated pits, coated vesicles, and receptor-mediated endocytosis. Nature 1979; 279:679-685.

12. Goldstein JL, Brown MS. History of discovery: The LDL Receptor. Arteroscler Thromb Vasc Biol 2009; 29:431-438.

13. Havel RJ. The formation of LDL: mechanisms and regulation J Lipid Res 1984; 25:1570-1576.

14. Horton JD, Cohen JC, and Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J. Lipid Res. 2009;50:S172-S177

15. Lambert G, Sjouke B, Bhoque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. J Lipid Res 2012; 53:2515-2524.

16. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009; 119(7):931-939.

17. Robinson JG, Rosenson RS, Farnier M, Chaudhari U, Sasiela WJ, Merlet L, et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab: Pooled Data From Randomized Trials. J Am Coll Cardiol. 2017; 69(5):471-482. doi: 10.1016/j.jacc.2016.11.037.

18. Sabatine MS Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al., incl. Open-label study of long-term evaluation against LDL cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events N Engl J Med 2015 372:1500-1509 doi:10.1056/NEJMoa1500858

19. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. and the FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376:1713-1722. DOI: 10.1056/NEJMoa1615664.

20. Sachdeva A, Cannon CP, Deedwania PC, LaBresh KA, Smith SC, Jr, Dai D, et al. Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get with the Guidelines. Am Heart J 2009; 159:111-117.e2

21. Schade DS, Cavanaugh B, Ramo B, Eaton RP. The application of the LDL principle. World J of Cardiovascular Diseases 2016; 6:109-125.

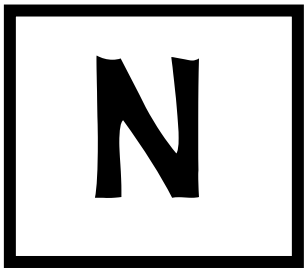
22. Schade DS, Helitzer D, Eaton P. Evidence that low density lipoprotein is the primary cause of atherosclerotic cardiovascular disease: A Bradford-Hill approach. WJCD 2017; 7:271-284.

23. Wikipedia editors. Cholesterol. https://en.wikipedia.org/wiki/cholesterol#biosynthesis. Accessed 1-23-17.

24. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E, et al for the PROVE-IT-TIMI 22 Investigators. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy – a PROVE IT-TIMI 22 sub study. J Am Coll Cardiol 2005; 46:1411-1416 doi: 10.1016/j.jacc.2005.04.064

25. Xaplanteris P, Fournier S, Pijls N, Fearon W, Barbato E, Tonino P, et al: Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018; 379:250-259. DOI: 10.1056/NEJMoa1803538

Old Jail in the ghost town of Chloride N.M.
In 1883 3,000 miners lived here.



ALTERNATIVE MEDICAL THERAPIES

Chapter N1: Are all cooking oils the same?

Clinical Vignette

Sarah Wingate is a 53 year old librarian who enjoys cooking meals for her husband Jack and their adult son. Last month, her husband went for his annual medical checkup. His blood work demonstrated an elevated LDL cholesterol, so his physician ordered a coronary artery calcium scan. The result was a score of 877, indicating that Jack was at high risk for a heart attack. The physician suggested that Sarah should "cook smart" by avoiding cooking with lard, bacon grease, or butter (saturated fats). In their place, he suggested cooking and making salad dressings with oils, but only "safe oils". Sarah asks, "Are not all cooking oils the same?"

Comment

Sarah asks a very reasonable question. Sarah understands that cooking with animal fats (lard, bacon fat, and butter) is not a healthy choice. Animal fats contain high levels of cholesterol and saturated fat. However, oils derived from plants do not contain cholesterol because plants do not have the metabolic machinery to make the cholesterol molecule. This fact does not mean that plant-derived oils can't raise the level of cholesterol in a person's blood. Remember that 75% of the cholesterol in the blood is made in the liver and 25% is derived from ingested food. Therefore, the liver is an important source of cholesterol production.

The liver's production of cholesterol is under the control of several factors including genetic influences, medications, and various food ingredients. One of the most important food ingredients is determined by the quantity of saturated fat it contains. Saturated fat is a descriptive term for a fat molecule that has no double bonds between its carbon atoms. When a fat molecule does have one or more double bonds, it is called "unsaturated." There are two types of unsaturated fat molecules, those with one double bond (call monounsaturated) and those with more than one double bond (called polyunsaturated). It turns out, for reasons that are unknown, that unsaturated fat molecules are beneficial and do not raise the liver's production of cholesterol. In contrast, saturated fats stimulate the liver to make cholesterol and should be avoided.

As shown in the figure, fat oils tend to be different based on whether they are saturated or unsaturated. The worst oil to consume is coconut oil, which contains 92% saturation. On the

other hand, olive oil is 86% unsaturated and should be preferred in cooking and salad dressings. Cooking with different oils induces different flavors in the food but chefs should try to use as much unsaturated oil as possible. One reason that the Mediterranean Diet is famous for its reduction in heart disease is that it is very high in the use of unsaturated oils, primarily extra-virgin olive oil. We endorse this approach to cooking smart. Sarah can help her husband reverse his heart disease by preparing foods using unsaturated oils.

Figure legend – As the computer screen shows, there are many different oils with which to prepare foods. Oils containing a high concentration of saturated fat (shown in orange) should be avoided, as they increase the circulating concentration of LDL cholesterol. In contrast, olive oil is low in saturated fat but high in unsaturated fat and is therefore a good choice, as it is widely available at a modest cost.

Chapter N2: Can I lower my LDL cholesterol with natural foods?

Clinical Vignette

Roy Jackson is a 42 year old rancher who raises Black Angus beef for market. In the evening, he loves to surf the internet to keep up with current events. He has an unfortunate family history of heart disease with his father dying at age 46 years of a heart attack. From the internet Roy learned that a coronary artery calcium scan was an excellent test to check on the health of his heart. To his credit, he had his physician order this test and Roy's score was 866, putting him at high risk. His lipid profile revealed that his LDL cholesterol was 123 mg/dl. His physician recommended that he take 10 mg of rosuvastatin and 10 mg of ezetimibe. Not a believer in pills, he asked "Can I take natural foods to lower my cholesterol instead of pills?"

Comment

Roy has learned from the internet that many foods and herbs lower cholesterol. He is correct. Many individuals would like to take this approach before starting any medications to lower their LDL cholesterol. We encourage this approach. We always recommend that they get a baseline lipid profile before starting natural foods and herbs so the patient knows his/her starting LDL cholesterol level. After three months, which will give their new diet a chance to lower their LDL cholesterol, they should repeat their lipid profile to see what they have achieved. Roy needs to remember that the goal to reverse his proven heart disease and reduce his high risk is an LDL cholesterol below 50 mg/dl.

The list of foods and herbs that are touted as lowering cholesterol are too extensive to be covered in this chapter. However, they all work through a limited number of pathways. Most obvious are foods that contain much fiber (mostly vegetables) which bind cholesterol in the gut and prevent its intestinal absorption. Other foods contain statin-like compounds that decrease the production of cholesterol by the liver (e.g., red yeast rice). Other foods (such as walnuts) are high in polyunsaturated fatty acids which have LDL lowering activity by pathways not well understood. Obviously, people choose different foods depending upon their individual preferences.

What the advocates of eating foods and herbs to lower LDL cholesterol do not tell you is how much (i.e., by what percentage) the foods they recommend will lower the cholesterol level. At most, this reduction is usually 10 to 20% of the original starting level. Since Roy is starting at an LDL cholesterol level of 123 mg/dl, at best his level after changing his diet will be approximately 100 mg/dl. This level of LDL cholesterol will not prevent Roy from having a heart attack. In fact, Roy will continue making plaques in his coronary arteries until he suffers a serious cardiac event. It is a foregone conclusion that Roy will eventually have to take medications to reach his LDL goal of less than 50 mg/dl.

Figure legend – the internet has much information on foods and herbs that lower cholesterol. Taken in reasonable amounts, these foodstuffs do not cause harm. However, rarely, if ever, will they be potent enough to allow an individual to reach the LDL cholesterol goal of <50 mg/dl. We encourage our patients to try whatever foods that they think are beneficial to lower cholesterol but not to delay more than a month in considering medication to reverse their atherosclerosis.

Chapter N3: Is exercise good for me and my heart?

Clinical Vignette

Josephine LeBlanc is a 48 year old woman who has a full time sedentary job at a government office. She is obese with prediabetes and hypertension which she blames on her stressful sedentary job. When she gets home in the evening, she fixes dinner for her family and then relaxes watching her favorite TV shows. She says that she occasionally snacks because "she gets hungry". She further says "people tell me to exercise but I tried that for three months and I did not lose a pound. What is the point?"

Comment

The point to be made for Josephine is that exercise has several beneficial effects to prevent cardiovascular disease. It is not a panacea for obesity. Numerous studies comparing sedentary people with people who exercise demonstrate a prolongation of life in the exercising group. However, whether it's the exercise itself or the lifestyle adopted by exercising people is not known. Compared to the comparative control group, exercising people are thinner, eat less red meats, consume more vegetables and fruits, and have fewer cardiovascular risk factors.

The beneficial metabolic changes that are caused by exercise include a person's increase in the sensitivity to circulating insulin resulting in an improvement in diabetes and prediabetes. Exercise also results in an elevation of HDL cholesterol which may reduce coronary events. Inflammation is also reduced resulting in a reduction of C-reactive protein.

However, exercise does not automatically result in weight loss. One problem with exercise is that it tends to lower blood sugar since muscles use glucose for energy. Lower glucose can increase appetite resulting in an increase in additional food intake. This then cancels the potential weight loss from the calories consumed during exercise. This is probably what happened to Josephine during the three months of her "exercise trial".

Exercise is often divided into aerobic and anaerobic activities. Aerobic exercise can be defined as brisk exercise that promotes the circulation of oxygen through the blood and is associated with an increased breathing and heart rate. Typical examples include jogging, swimming, and bicycling. However, anaerobic exercise also burns calories and walking is a good example. In the adult population, the type of exercise is often limited by medical

conditions that only permit certain activities that burn calories; walking is a good example. The important point is that everyone can do some type of exercise and staying active is vitally important for maintaining good health. Josephine needs to make a determined lifestyle change and include exercise in her daily routine. Studies have shown that a minimum of 30 minutes of exercise at least three time per week will result in important, beneficial health changes that reduce your cardiovascular risk factors.

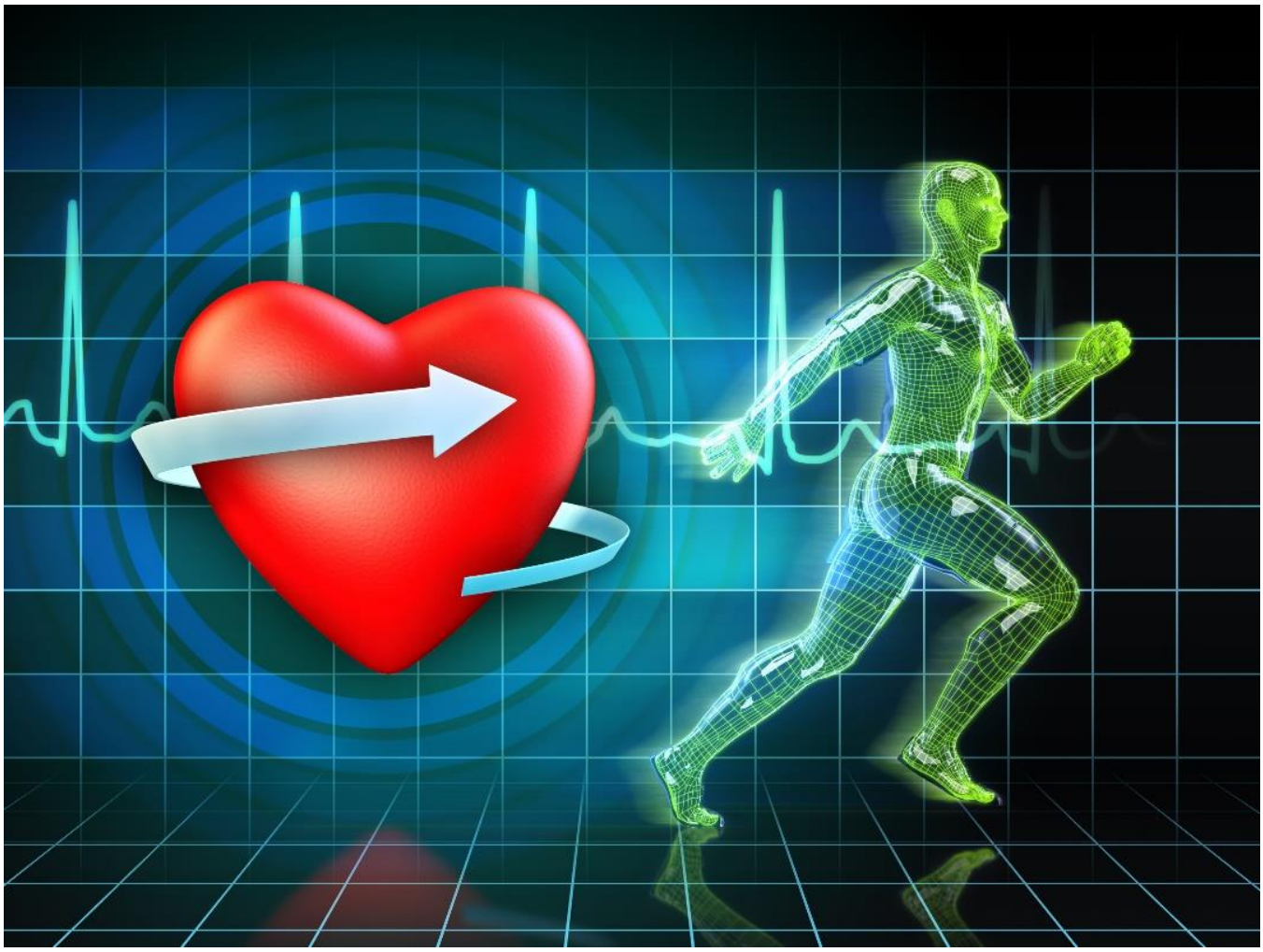


Figure legend – There are many types of exercise that are beneficial to your health. The important point is to choose one that you can do and to do it on a regular basis. It is part of making a lifestyle change and a commitment to reducing your risk factors for heart disease. Inexpensive pedometers are a good way to track your daily walking steps. Other devices, including “apps” on cell phones may also help.

N.
ALTERNATIVE MEDICAL THERAPIES

Citations

1. Connor WE, Cerqueira MT, Connor RW, Wallace RB, Malinow MR, Casdorph HR. The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. Am J Clin Nutr.1978(7):1131-1142.

2. Connor WE, Hodges RE, Bleiler RE. The serum lipids in men receiving high cholesterol and cholesterol-free diets. Journal of Clinical Investigation. 1961; 40(5):894-901.

3. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, et al. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. Am J Clin Nutr. 1999; 70(3 Suppl):516S-524S.

4. McMurry MP, Connor WE, Cerqueira MT. Dietary cholesterol and the plasma lipids and lipoproteins in the Tarahumara Indians: a people habituated to a low cholesterol diet after weaning. Am J Clin Nutr 1982; 35:741-744.

5. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: A systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010; 7(3)e10000252. Doi:10.1371/journal.pmed.1000252

6. Müller H, Lindman AS, Brantsaeter AL, Pedersen JI. The serum LDL/HDL cholesterol ratio is influenced more favorably by exchanging saturated with unsaturated fat than by reducing saturated fat in the diet of women. J Nutr. 2003; 133(1):78-83.

7. Phillips RL, Lemon FR, Beeson WL, Kuzma JW. Coronary heart disease mortality among Seventh-Day Adventists with differing dietary habits: a preliminary report. Am J Clin Nutr. 1978; 31(10 Suppl):S191-S198.

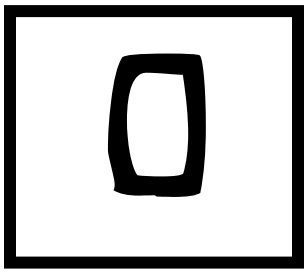
8. Rosqvist F, Iggman D, Kullberg J, Cedernaes J, Johansson HE, Larsson A, Johansson L, Ahlström H, Arner P, Dahlman I, Risérus U. Overfeeding Polyunsaturated and Saturated Fat Causes Distinct Effects on Liver and Visceral Fat Accumulation in Humans. Diabetes 2014; 63:2356–2368 DOI: 10.2337/db13-1622

9. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. Am J Clin Nutr. 2001; 73(5):885-891.

Contributed by: S. Murphy

Fall cottonwood trees in full color. New Mexico has one of the largest cottonwood forests along the Rio Grande bosque.

Elephant Butte Reservoir in central New Mexico. Note the old TB Hospital on the right-middle of the photo which is usually submerged



PLANTS ARE IMPORTANT !

Chapter O1: Why are dietary fats important to you?

Clinical Vignette

Sam Lemont is a 40 year old salesman in an outdoor equipment store. He is healthy and fit, working out at the gym three times per week. Unfortunately, he has a very strong family history of heart disease with his father and two brothers dying of heart attacks in their fifties. He would like to gain some more muscle mass in his arms and thighs to help his hiking stamina and outdoor activities. However, he doesn't seem to be able to gain weight, no matter how much he eats. His wife insists he eat a very low fat diet because she says, "Fat is bad for your heart." He wants to know "Is it true that fat will kill me?"

Comment

As with most things in life, fat is both good and bad; thus, "Not all fats are created equal." First, the good news. It was recognized 40 years ago that some fats in the diet are essential for good health. The body can synthesize most of the fats it needs for metabolism. However, two essential fatty acids, linoleic and alpha-linolenic, cannot be made in the body and must be obtained from food. These basic fats, found in plant foods, are used to build specialized fats called omega-3 and omega-6 fatty acids. In addition, most of the energy that our body needs every day comes from the fats called triglycerides. Fat is a very concentrated form of energy. It is the reason that you put gasoline (a fat) in your car and not wood chips (a carbohydrate). We all need some fat in our diet to build up our energy stores in case we become sick or engage in exercise.

Now for the bad news. Some fats serve no useful purpose and in fact, can be harmful to your heart. As detailed in another chapter cholesterol (a fat) can cause heart disease and gall stones. Since every cell in the body can make as much cholesterol as it needs, there is no beneficial purpose of consuming cholesterol after adulthood has been reached. This "bad" cholesterol is transported in your blood by low density lipoprotein particles (LDL cholesterol). It is left over (a remnant) after triglycerides are used for energy by your muscles. It is increased by the amount of saturated fat and cholesterol you eat from animal food sources. It is normally removed from the circulation by your liver. However, when the amount gets too high in your blood, it spills over and gets deposited in your heart arteries. Over time, it forms plaques in your arteries and causes a heart attack.

Returning to Sam's problem of not being able to gain weight, he should increase good fats (most oils) and avoid the bad fats (butter, margarine, and lard) in his diet. That way, his muscles will have sufficient energy to be at their maximum performance and Sam will gain some much needed muscle mass.

Figure legend – It is important to choose the right fat in your diet for cooking, salad dressing, and adding flavor to foods. There are many healthy oils to choose from which are heart healthy. Take your time to read the label and avoid foods that contain cholesterol, saturated, and trans fats.

Chapter O2: Should I take plant sterols to lower my cholesterol?

Clinical Vignette

Charlotte Weber is a 39 year old dietician who is determined to improve her health through eating smart. She has read extensively on foods that lower cholesterol and is convinced that taking one of the products at the health food store will reduce her LDL cholesterol (which is 123 mg/dl) to less than 50 mg/dl. She was motivated to improve her lifestyle when her coronary calcium score was reported as 122. Her only risk factor is type 2 diabetes which she blames on bad genes because both of her parents also had diabetes. She wants to know if taking the plant sterols will interfere with the 10 mg/day of rosuvastatin that her doctor prescribed.

Comment

Health food store products are very popular in the United States, and people spend billions of dollars per year buying them. Because these products are not under the regulation of the Food and Drug Administration, very few studies are available to prove or disprove the claims that health food product manufactures claim. Therefore, we cannot answer Charlotte's question directly with scientific studies, but we can address it indirectly by examining how plant sterols work.

Plants cannot make cholesterol, but they can make other molecules that look like cholesterol (called plant sterols). Plants use these molecules to build cell walls and stabilize other parts of their cells. When you eat plant foods (vegetables, fruits, etc.), you ingest plant sterols that mix with cholesterol molecules that you ingest when you eat animal foods (meat and dairy products). Recently discovered is a specific receptor on the surface of your intestinal cells that recognizes cholesterol and absorbs it into the body. Plant sterols fool this receptor into thinking that they are cholesterol and the receptor absorbs them also. However, another receptor in the same cell is not fooled by plant sterols and kicks them all back out into the intestinal lumen for excretion in the stool.

If the intestinal cholesterol receptor becomes overwhelmed with absorbing plant sterols, the end result is the absorption of very little cholesterol.

This in turn results in lowering the circulating cholesterol (LDL) by approximately 10 to 15%. Since statins work at the liver (and not at the intestine) to lower cholesterol synthesis, plant

sterols do not interfere with the beneficial effects of statins. In fact, the two approaches to lowering cholesterol work very well together to let Charlotte achieve her LDL goal of 50 mg/dl. The medication ezetimibe works in a similar way to plant sterols by blocking the intestinal cholesterol receptor. However, ezetimibe is more effective and reduces LDL cholesterol by approximately 20%.

Figure legend – Plant sterols provide a natural way to lower your LDL cholesterol level. They confuse the intestinal cholesterol receptor and as a result, much less cholesterol is absorbed into the body. A diet high in fruits and vegetables will provide a large amount of plant sterols and is one component of the "heart protecting" Mediterranean diet. Plants foods are also a good source of fiber, which binds cholesterol and prevents its absorption. People respond differently to diet and medications. Therefore, you should always confirm your benefit by a laboratory measurement of your LDL cholesterol to be sure you are reaching the goal of <50 mg/dl.

0.
PLANTS ARE IMPORTANT

Citations

1. Appleby PN, Thorogood M, Mann JI, Key TJ. The Oxford Vegetarian Study: an overview. Am J Clin Nutr. 1999; 70(3 Suppl):525S-531S.

2. Barnard ND, Cohen J, Jenkins DJA, Turner-McGrievy G, Gloede L, Jaster B, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 2006; 29:1777-1783.

3. Bloomfield HE, Koeller E, Greer N, MacDonald R, Robert Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet with No Restriction on Fat Intake. Ann Intern Med. 2016; 165(7):491-500. DOI: 10.7326/M16-0361

4. Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. Am J Clin Nutr. 2013; 97(3):597-603.

5. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997; 337(21):1491-1499.

6. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA. 2002; 288(20):2569-2578.

7. Mattson FH, Erickson BA, Kligman AM. Effect of dietary cholesterol on serum cholesterol in man. Am J Clin Nutr. 1972; 25(6):589-594.

8. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb. 1992; 12(8):911-919.

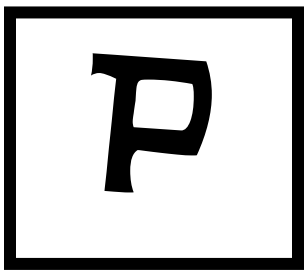
9. Mensink RP, Zock PL, Keater ADM, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003; 77(5):1146-1155.

10. Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. Lancet. 2003; 361(9356):477-485.

11. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis. Lancet 2007; 369:1090–1098.

Entrance to Monticello Canyon in New Mexico. The creek that carved the canyon was carved by Geronimo Hot Springs.

Malpais (bad lands) – 10,00 year old lava flow.
Valley of Fires, Carrizoz New Mexico



ALTERNATIVE APPROACHES TO PREVENTING HEART DISEASE

Chapter P1: What has age got to do with it?

Clinical Vignette

Sam Martin is a 70 year old retired carpenter who used to smoke a pack of cigarettes a day until he realized how dangerous they are. He recently spoke to his 36 year old son, Patrick, who has had type 1 diabetes since the age of thirteen. Both are healthy for their respective ages, but each is concerned about the possibility of developing heart disease. Their family doctor (who treats both father and son) is not concerned about heart disease, for the father because he is too old and the son because he is too young to worry about it. The Martins want to know, "What has age got to do with it?"

Comment

Sam and Patrick Martin are correct. It is never too early or too late to ask about the condition of your heart. People can die at any age from a heart attack. In fact, when the genetic disease called homozygous familial hypercholesterolemia (a horrible long, unpronounceable name) afflicts a person at birth, that person may have a heart attack before he/she ever reaches the teenage years. Screening for this or similar genetic conditions is now recommended at an early age because medical treatment is life-saving.

What is defined as old age is arbitrarily chosen by individual preference. Two centuries ago, old age was anyone over the age of 50 because the average lifespan was 45 years. At the present time, with the average expected lifespan is in the 70's. Many people living productive lives, live into their 80's and 90's. Old age has become a nebulous term. In addition, it is important to distinguish between chronological age and biological age. Chronological age is the number of years that a person has lived. Biological age is the current state of health of the individual and his/her expected life expectancy. For physicians who must recommend treatment goals, the biological age is the more important.

So should Sam's physician assess the health of Sam's heart and recommend treatment if abnormalities are found? There are no hard and fast rules. Our approach is simple. If an individual's biological health indicates that he/she will not live another five years, than treating potential heart disease will not necessarily yield a long-term beneficial result. On the other hand, if the person's expected lifespan is greater than five years, and a heart attack would be

detrimental to the remaining active years of the individual, than we recommend preventative treatment. We do not consider the chronological age of the individual in helping us decide if treatment is warranted.

What about Sam's son Patrick? Currently, few physicians aggressively diagnose and treat heart disease in individuals less than 40 years of age. We think this is a mistake. Thousands of individuals die of heart disease in their forties, and prevention requires several years to stabilize and reverse atherosclerotic plaques. Diagnosing heart disease in the third decade of life provides sufficient time to reverse the disease before a coronary blockage causes a heart attack. When a young individual has significant risk factors for heart disease (such as diabetes), performing a coronary artery calcium scan before age 40 makes very good sense. Patrick should have this test plus some other blood tests (lipid profile and hsCRP) to assess his risk and exclude any heart disease present. We recommend that both Sam and Patrick discuss this option with their family doctor and request the appropriate evaluation of their hearts, including a coronary artery calcium scan and appropriate blood tests.

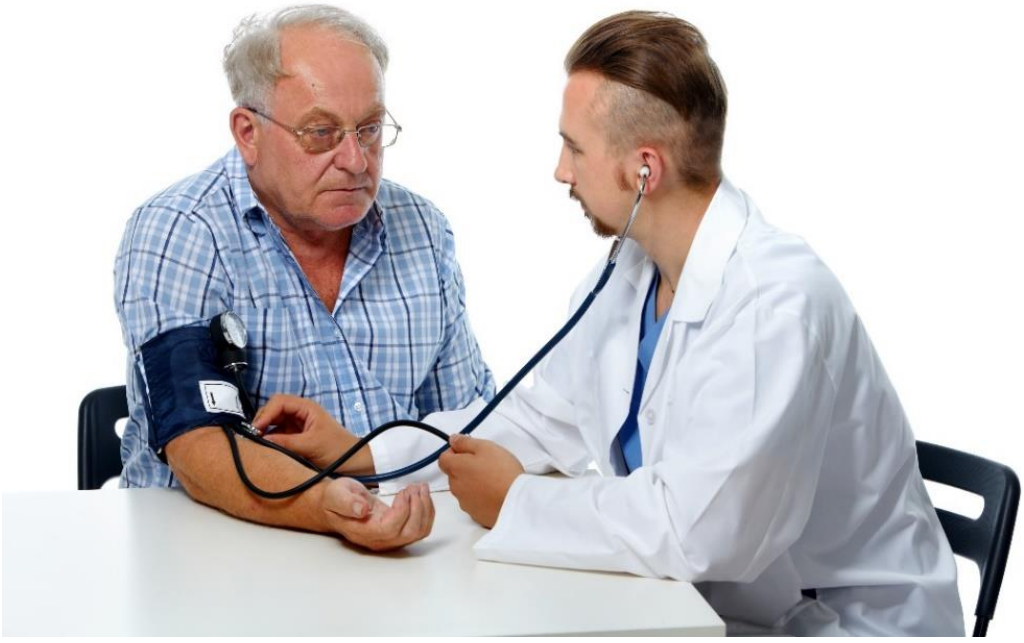


Figure legend – Age should not be used to exclude obtaining a coronary artery calcium heart scan. If an individual is relatively healthy and enjoying life, identification and prevention of heart disease is an important obligation for all physicians.

Chapter P2: Do I need Cardiac Rehabilitation?

Clinical Vignette

Alex Sanders is a 65 year old retired school administrator. He smoked for most of his life, has high blood pressure, and type 2 diabetes. His brother recently died of a heart attack on the golf course. Last month he had a heart calcium scan which greatly concerned him. His score was 1,145 with calcium in every heart vessel. His physician started him on medications to lower his LDL cholesterol and recommended a low saturated fat diet. However, Alex wants to do everything he can do to reduce his heart attack risk. His physician recommends that he join a cardiac rehabilitation program. "What is that?" he asks. "I thought those programs were only for people who have had a heart attack."

Comment

Cardiac rehab programs are for anyone who has an increased risk for heart disease, whether or not they have had a heart attack. A positive cardiac calcium scan qualifies a person for these programs. They are available in all major towns and cities. Studies have demonstrated that there are real benefits to joining these programs, including greater exercise tolerance, more energy, improved glucose control, weight loss, and a longer life span. Most programs consist of attendance three times weekly, electrocardiogram monitoring if necessary, and hour-long exercise sessions for 8 to 10 weeks. The goal of these sessions is to teach participants an individualized exercise program. It is important that the prescribed protocol be both safe and effective at improving cardiovascular health, that it will reduce coronary heart risk factors, and that it will address any psychosocial issues that may be present from knowing that the individual has heart disease.

Medical insurance companies often cover the cost of these programs, as well as the cost of medications to treat the hypertension, diabetes, and abnormal lipid profiles. For individuals who have not already have had a heart attack, cardiac rehab programs are very safe with the result of improved health. They are an excellent way of making a commitment to improve your health and assure your family that you are committed to a long life. We strongly recommend that Alex join one of the cardiac rehab programs in his town.

One advantage of cardiac rehab programs is meeting other people who also have a high risk of having a heart attack. Individuals who have had one heart attack are at very high risk of another heart attack. They have learned that prevention is the key to good health. Each will have a story to tell and a lesson to be learned. We guarantee you that you will enjoy your rehab sessions and so will your heart. This is a great way to get started with changing your lifestyle for the better. What have you got to lose?

Figure legend – Cardiac rehab programs benefit everyone. You do not need to have had a heart attack to reduce your risk. The rehab program that you choose will develop a program tailored to your needs and available time. These programs are widely available and are very modestly priced. Multifactorial rehabilitation programs consist of a baseline assessment, nutritional counseling and weight management, aggressive coronary artery risk factor management, psychosocial assessment, physical activity counseling, and exercise training. They are a great way to get your heart attack risks under control.

Chapter P3: To Stent or Not to Stent?

Clinical Vignette

Fred Grey is a 55 year old bus driver who leads a sedentary lifestyle. He smoked cigarettes for 21 years but quit 3 years ago when his physician warned him of smoking's dangers. He is overweight with a BMI of 29. Although he has a history of diabetes in his immediate family, he currently only has prediabetes for which his physician prescribed metformin. Someone told him that his cholesterol was "OK" but he does not know the number. In the last two months, he has been experiencing shortness of breath and chest "tightness' when he walks up two flights of stairs to his apartment but at no other time (called "stable angina"). His physician ordered a heart stress test, which was "positive". His physician now wants to refer him to a cardiologist for coronary angiography. If a heart artery constriction is seen, a "stent" will be placed in his heart artery to "open it up". He was also told that this procedure could cost up to $40,000, which his health insurance only partially covers. Fred wants to know if there is a less expensive alternative.

Comment

We are pleased to tell Fred that there is a better alternative than placing a stent in his heart artery. A cardiac "stent" involves threading a catheter up into one of the heart's arteries to the atherosclerotic plaque causing the narrowing (which has previously been identified with a coronary angiogram). A wire mesh is then placed in the narrowed segment of the artery and expanded with an inside balloon tipped catheter, thereby enlarging the artery (see figure). Recent medical studies have clearly demonstrated that intensive medical therapy is the treatment of choice for Fred's stable angina (i.e., chest pain occurring only when exercising). One study compared stents with medical therapy in patients who were not aware of which treatment they received. At the end of 2 months, all patients equally improved irrespective of the choice of treatment. Another study compared medical therapy with or medical therapy without stent placement. At the end of three years, the stent made no difference in the patients' quality of life. All patients improved to the same extent as a result of the medical therapy.

There are three drawbacks with stents placed is cardiac blood vessels. First, they are expensive as illustrated by Fred's case. Second, they do not prevent future heart attacks since

they are only enlarging one small part of an artery that likely has plaques throughout its length. Third, they do not result in an improved outcome for the patient, either in the short term or in the long term. Fourth, they are invasive with a small but real chance for medical complications.

The reason that medical therapy is as good as a heart artery stent is that a partially blocked heart artery undergoes “remodeling” with new blood channels developing which bypass the partial heart obstruction. In addition, medical therapy, which involves LDL cholesterol lowering medication and lifestyle changes, will result in reversing the heart artery atherosclerotic plaque. To accomplish this positive outcome, the patient lowers his/her LDL cholesterol below 50 mg/dl with a low saturated fat diet and the addition of ezetimibe and rosuvastatin.

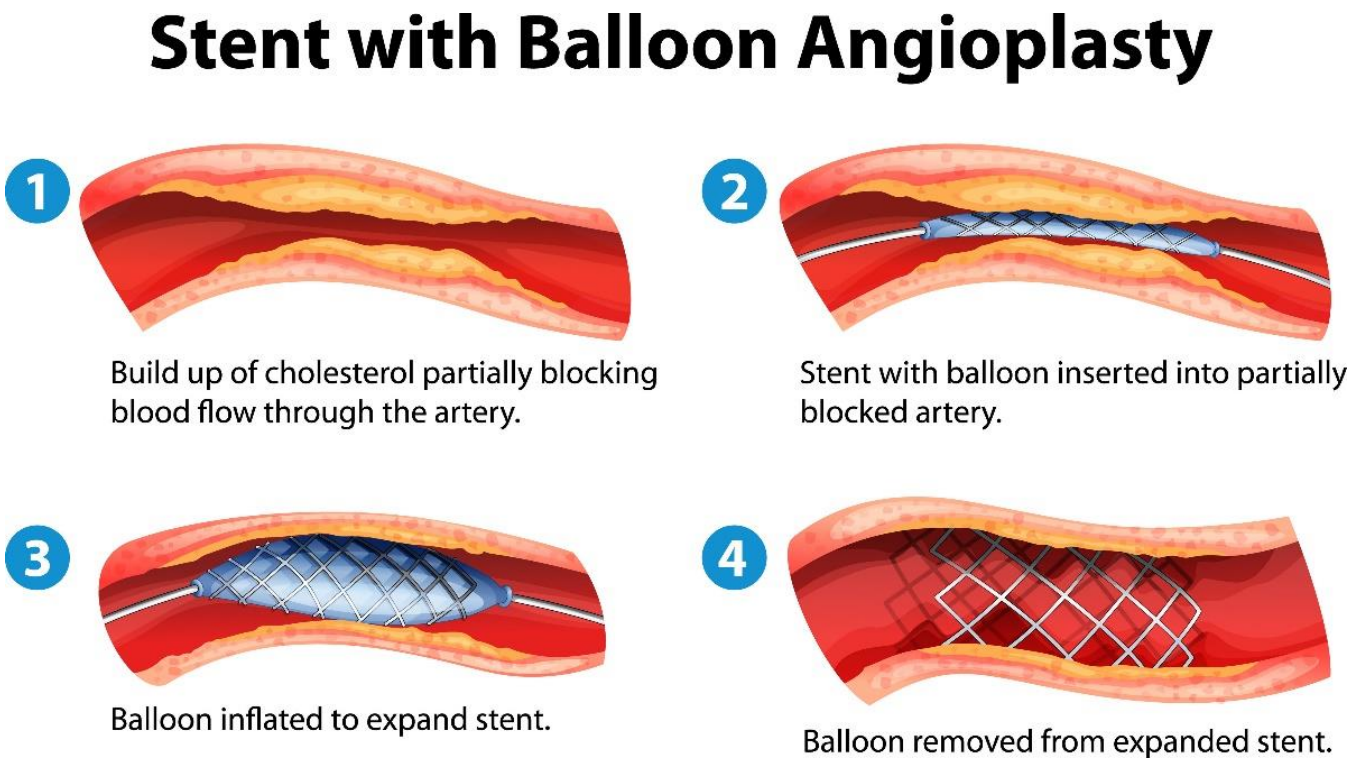


Figure legend – A wire mesh stent is placed in a heart artery at a location narrowed by atherosclerotic plaque. A balloon inside the stent expands, enlarging the stent and the narrowed artery. The balloon is removed leaving the stent in place in the enlarged artery. The plaque is squeezed against the artery wall with minimal consequences .Some patients receive multiple stents because most arteries have numerous places where the artery is narrowed.

P.

OTHER APPROACHES TO STOPPING HEART DISEASE

Citations

1. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, Keeble T, et al. on behalf of the ORBITA Investigators. Percutaneous coronary intervention instable angina (ORBITA):a double-blind, randomized controlled trial. 2017; doi: 10.1016/S0140-6736(17)32714-9 Last accessed 11-2-17.

2. Blair SN, Kohl III HW, Barlow CE, Paffenbarger, Jr. RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: A prospective study of healthy and unhealthy men. JAMA 1995; 273:1093-1098.

3. Boden WE, O'Rourke RA, Teo KT, Hartigan PM, Maron DJ, Kostuk WJ, et al, for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007; 356:1503-1516.

4. Brugts JJ, Yetgin T, Hoeks, SE, Gotto AM, Shepherd J, Westendorp RGJ, Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomized controlled trials. BMJ. 2000; 321(7253):73-77.

5. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. for the FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012; 367:991-1001.

6. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987; 316(22):1371-1375.

7. Katritsis DG, Ioannidis JPA. Percutaneous coronary intervention versus conservative therapy in nonactute coronary artery disease: A meta-analysis. Circulation 2005; 111:2906-2912.

8. Lin GA, Dudley RA, Redberg RF. Cardiologists' use of percutaneous coronary interventions for stable coronary artery disease. Arch Intern Med. 2007; 167(15):1604-1609.

9. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007; 49(21):2105-2111.

10. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med. 1999; 341(2):70-76.

11. Sedlis SP, Hartigan PM, Koon KT, Maron DJ, Spertus JA, Mancini GBJ, Kostuk W, Chaitman BR, Berman D, Lorin JD, Dada M, Weintraub WS, Boden WE, for the Courage Trial Investigators. Effect of PCI on Long-term survival in patients with stable ischemic heart disease. N Engl J Med 2015; 373:1937-1946.

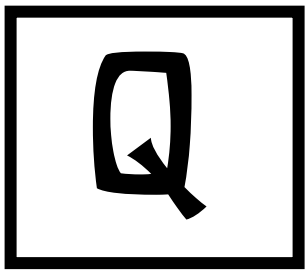
12. Stergiopoulos K, Boden WE, Hartigan P, Möbius-Winkler S, Hambrecht R, Hueb W, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. JAMA Intern Med. 2014; 174(2):232-240. doi: 10.1001/jamainternmed.2013.12855.

13. Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, et al and the Myocardial infarction genetics consortium investigators.et al. Myocardial infarction genetics consortium investigators. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med 2014; 371:2072-2082.

14. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, et al. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med. 2008; 359(7):677-687. doi: 10.1056/NEJMoa072771.

Contributed by: J. Padilla

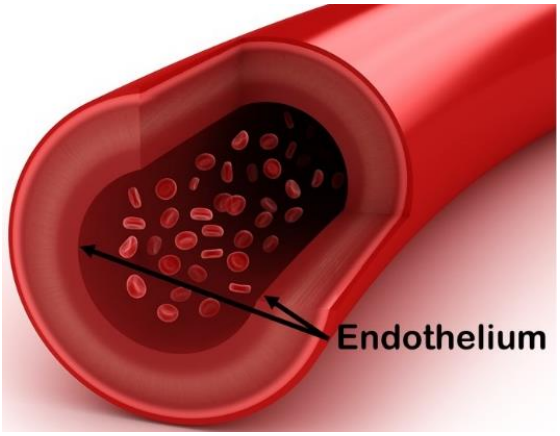
Sunset over the desert with Sandia Mountains in background near Albuquerque, NM



APPENDIX

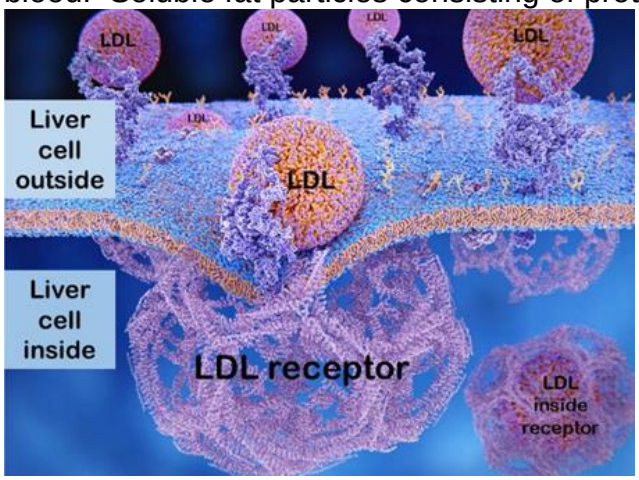
Q1: The Nuts and Bolts of a Heart Attack

Contrary to popular belief, a heart attack doesn't just happen. In fact, it silently threatens for many years before the catastrophic event occurs. Knowing how it occurs is the key to prevention. The figures and text below will provide you the "nuts and bolts" of how it happens so you can prevent one.



When you were born, your arteries were clean, smooth pipes, through which your blood flowed unobstructed to reach your vital organs, i.e., the brain, heart, lungs, and kidneys.

In this blood are red blood cells to carry oxygen, white blood cells to fight infection and remove foreign particles, and platelets to stop any bleeding in case you cut yourself. Then as you started to consume food (e.g., dairy products of milk, eggs, cheese, etc.), your body needed a safe way to move the fat in these foods through your blood to your muscle to be used as energy. It could not simply secrete fat into your blood because fat is not soluble in blood (think of adding drops of oil to a cup of water). Therefore, your body developed a way of packaging the fat in your blood. Soluble fat particles consisting of protein and cholesterol surrounding the fat globule

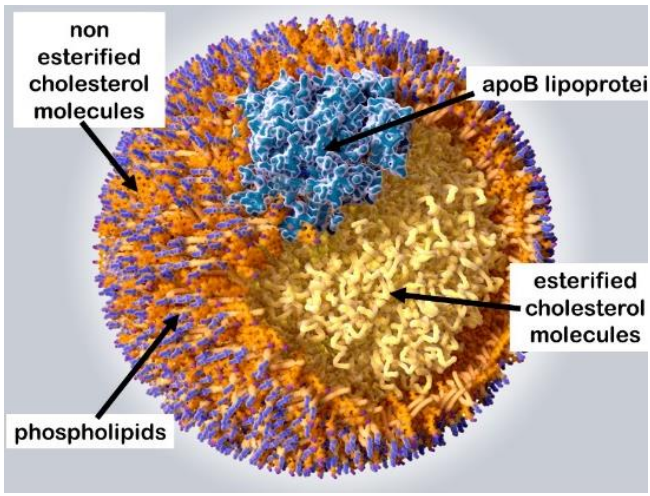


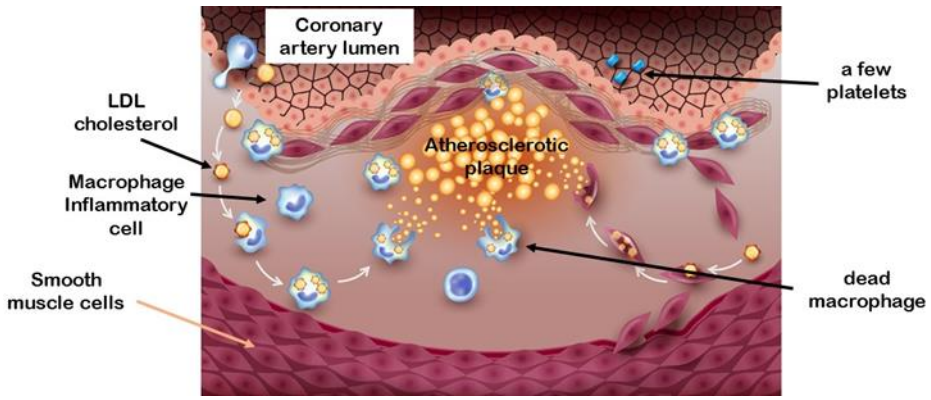
worked well. This turned out to be an excellent solution, and your muscles (including your heart) received all the fat energy they needed.

The problem then arose as to what to do with the leftover protein and cholesterol after the fat was used for energy. Unfortunately, your body has no way of breaking down the cholesterol, so your body developed an ingenious solution. It constructed specific cholesterol removers (called LDL receptors) on the liver which take up the cholesterol and excrete it into the intestine for ultimate elimination in the stool.

This approach worked very well until you consumed too much fat and the liver's LDL receptors were overwhelmed with cholesterol removal. The remaining excess cholesterol then moved passively into the walls of the arteries and formed atherosclerotic plaques that result in heart attacks.

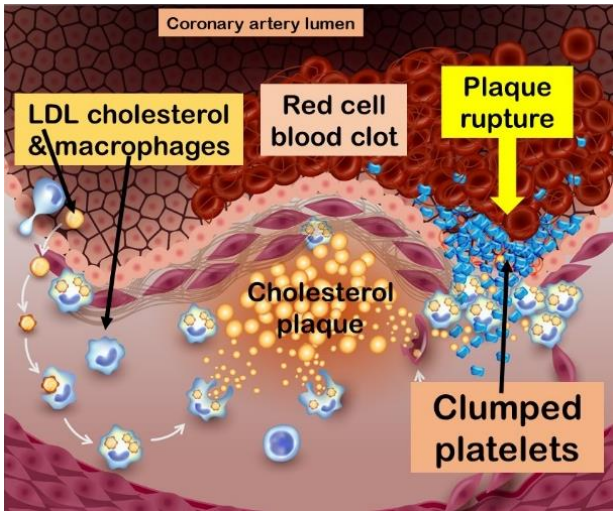
The leftover particles of cholesterol and protein are called lipoproteins (lipo = lipid = fat). The specific lipoprotein left over when the fat is removed is called "low density lipoprotein" because it is not very heavy when spun in a centrifuge. This is the specific particle that is taken up by the liver's LDL cholesterol receptors (LDL cholesterol particles = LDLc for short). These particles circulate in the blood, waiting to be taken up by the liver or to move into the wall of your arteries. Whether they do the former or the latter activity is dependent on several conditions in the artery. The primary barrier to movement of LDLc particles into the walls of the artery is the thin, one cell thick, inside lining of the artery called the "endothelium" (shown in the first figure above). If this endothelium lining is healthy, very few LDLc particles get through. But if it gets damaged by an "insult", such as smoking, hypertension, or diabetes, then the LDL particle easily gets through.



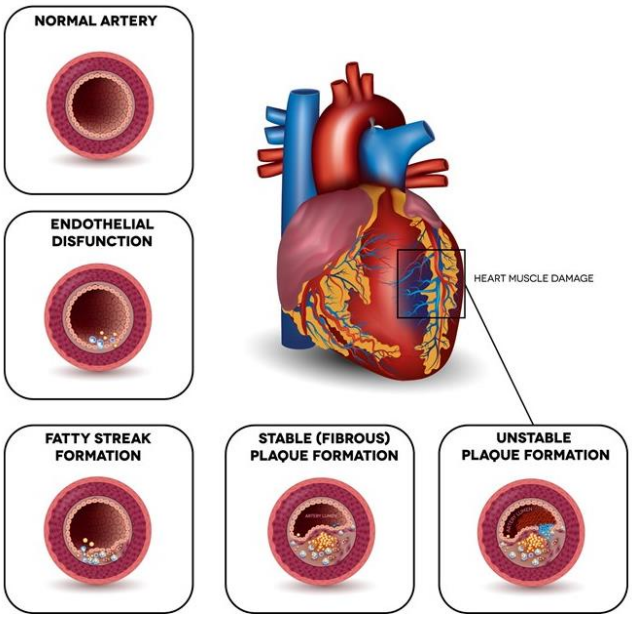


Once through the endothelium, the LDL particle needs to join with other LDL particles to form a plaque. This is where the white blood cell called the "macrophage" (big eater) comes in. Normally, there are very few macrophages in the artery wall. However, when the endothelium is damaged, macrophages easily get through the endothelium and can engulf the LDL particles

in the artery wall. Unfortunately, the macrophage cannot digest the LDLc particle, so it becomes engorged with cholesterol and dies. When several macrophages die in close proximity, they form a fatty streak. This streak becomes the beginning of an atherosclerotic

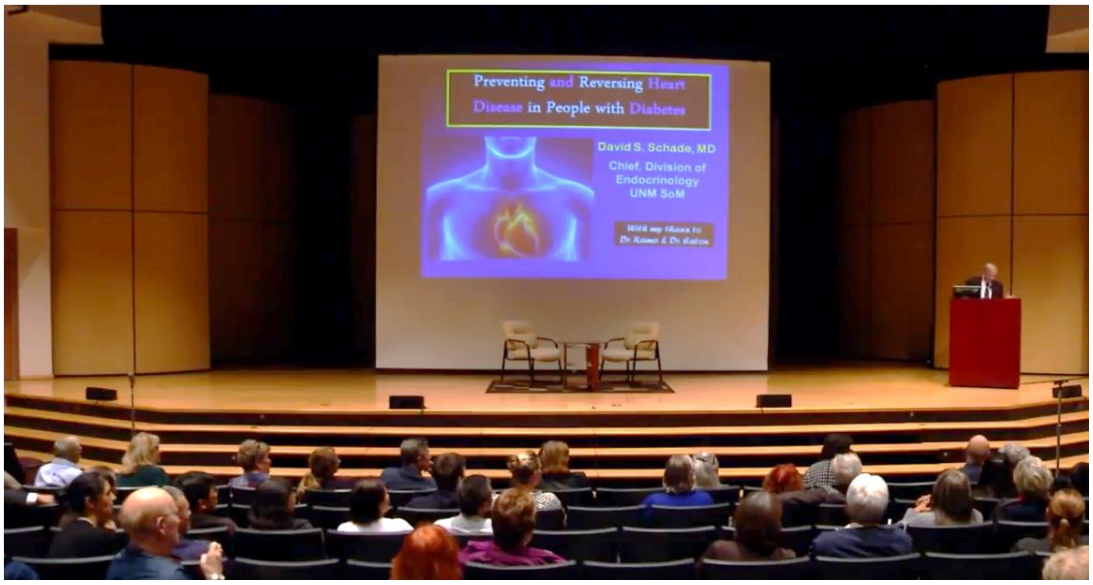


plaque. As the fatty streak matures, it collects many other substances, including calcium, smooth muscles cells, and molecules called proteinases. These proteinases collect on the side of the atherosclerotic plaque and eventually dissolve the cap covering the plaque. In other words, the plaque ruptures into the lumen of the artery (the opening in the artery through which the blood flows). This rupture is detected by platelets circulating in the blood that is flowing through the artery. The platelets act as small plugs in an attempt to repair the rupture. They also activate a blood clot to further plug the rupture. Unfortunately, this blood clot may become large enough to totally obstruct the artery. If the artery is in the heart, a heart attack results. Preventing a heart attack is not rocket science. It involves protecting the endothelium, lowering the LDLc to levels that the liver can safely remove, and limiting the number of macrophages that can move into the artery wall. This book will explain how to achieve all three of these goals. It may well save your life!



The good news is that you also have a method to remove the plaque once it has formed called “HDL cholesterol”. It carries LDL-derived cholesterol from the plaque in the wall of the artery to the liver for disposal. But it too can be overwhelmed if you don’t limit your food cholesterol ingestion. That is why we say “Eat smart and live long.”

Q2: Interview with the Author



Dr. Barry Ramo (below, left), a well-known cardiologist and television commentator, periodically holds interviews with physicians in Albuquerque on topics of interest to the public. One topic that he moderated was *Preventing and Reversing Heart Disease* with Dr. David S. Schade, who presented the current thinking on preventing the number 1 cause of death in the United States. This presentation and subsequent interview is shown in this video.

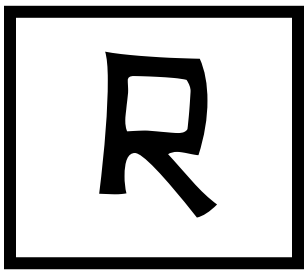
Instructions: Go to Youtube.com, type in City of Albuquerque GOVTV, Search Dr. Schade or type the link below into your computer browser:

https://www.youtube.com/watch?v=MXQtNxrp0ZE&feature=youtube

Number Zero

Q3: <50 Achievement Club

Join the winners – who have achieved an LDL cholesterol level of less than 50 mg/dl for at least one year. Receive a certificate of achievement, a <50 lapel pin, and a "50 Ways to Save Your Heart" Book".



INDEX & CITATIONS

R1. Index & Dictionary

Bold numbers indicate the word was mentioned more than 5 times on that page.

The VLA (very large array) is a world class radio telescope on the Plains of St. Augustine near Socorro, New Mexico. It is studying the black hole at the center of our galaxy.

Contributed by: E. Speegle

Albuquerque, New Mexico in the winter. The 10,500 foot Sandia mountain includes a ski slope, a tram to the top, and multiple hiking trails.

R.
CITATIONS

R2. Citations- Alphabetical by Author

1. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34(2):154-156.

2. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008; 358(24):2545-2559.

3. Agarwal S, Cox AJ, Herrington DM, Jorgensen NW, Xu J, Freedman BI, et al. Coronary calcium score predicts cardiovascular mortality in diabetes: diabetes heart study. Diabetes Care. 2013; 36(4):972-977.

4. AIM-HIGH Investigators. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. N Engl J Med 2011; 365:2255-2267.

5. Akram ON, Bernier A, Petrides F, et al. Beyond LDL cholesterol, a new role for PCSK9. Arterioscler Thromb Vasc Biol 2010; 30:1279-1281.

6. Aliev G., Burnstock G. Watanabe rabbits with heritable hypercholesterolaemia: a model of atherosclerosis. Histol Histopathol; 1998(3):797-817.

7. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, Keeble T, et al. on behalf of the ORBITA Investigators. Percutaneous coronary intervention instable angina (ORBITA): a double-blind, randomized controlled trial. 2017; doi:10.1016/S0140-6736(17)32714-9 Last accessed 11-2-17.

8. Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, et al. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. JAMA 2014; 311(5):490-497. doi:10.1001/jama.2013.285122

9. Altmann SW et al. Niemann-Pick C1 Like 1 Protein is critical for intestinal cholesterol absorption. Science 2004; 303(5661):1201-1204.

10. Ansell B et al. Inflammatory/Anti-inflammatory Properties of High-Density Lipoprotein Distinguish Patients From Control Subjects Better Than High-Density Lipoprotein Cholesterol Levels and Are Favorably Affected by Simvastatin Treatment. Circulation 2003; 108:2751-2756.

11. Appleby PN, Thorogood M, Mann JI, Key TJ. The Oxford Vegetarian Study: an overview. Am J Clin Nutr. 1999; 70(3 Suppl):525S-531S.

12. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol. 2000; 36(4):1253-1260.

13. Alexopoulos N, Raggi P. Calcifaction in atherosclerosis. Nat Rev Cardiol. 2009;6(11):681-688.

14. Bacha F, Edmundowicz D, Sutton-Tyrell K, Lee S, Fjayli H, Arslanian SA.Coronary Artery Calcification in Obese Youth: What Are the Phenotypic and Metabolic Determinants? Diabetes Care 2014; 37:2632–2639 | DOI: 10.2337/dc14-0193

15. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R and the Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Lancet 2005; Oct 8; 366(9493):1267-1278. Epub 2005 Sep 27.

16. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomized placebo-controlled trial. Lancet. 2011; 377(9784):2181-2192.

17. Baker JL, Olsen LW, Sorensen TI. Childhood body mass index and the risk of coronary heart disease in adulthood. Ugeskr Laeger 2008; 170(33):2434-2437.

18. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP, for the Ezetimibe Study Group. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. Circulation 2003; 107:2409-2415.

19. Bao W, Srinivasan SR, Wattigney WA, Bao W, Berenson GS. Usefulness of childhood low-density lipoprotein cholesterol level in predicting adult dyslipidemia and other cardiovascular risks: The Bogalusa Heart Study. Arch Intern Med 1996; 156(12):1315-1320. doi: 10.1001/archinte.1996.00440110083011

20. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009 Jun 11; 360(24):2503-2515.

21. Barnard ND, Cohen J, Jenkins DJA, Turner-McGrievy G, Gloede L, Jaster B, et al. A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 2006; 29:1777-1783.

22. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, et al. for the Treating to New Targets Investigators. HDL Cholesterol, Very Low Levels of LDL Cholesterol, and Cardiovascular Events. N Engl J Med 357:1301-1310.

23. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, Knopp RH, Lipka LJ, LeBeaut AP, Yang B, Mellars LE, Cuffie-Jackson C, Veltri EP, Ezetimibe Study Group. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001; 23(8):1209-1230.

24. Bedi U, Singh M, Singh P, Molnar J, Khosla S, Arora R. Effects of statins on progression of coronary artery disease as measured by intravascular ultrasound. J Clin Hypertens (Greenwich) 2011; 13:492-496.

25. Berenson GS. Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The Bogalusa Heart Study. Am J Cardiol. 2002; 90(10C):3L-7L.

26. Berry JD, Dyer A, Cai X, Garside DB, Ning N, Thomas A, et al. Lifetime risks of cardiovascular disease. N Engl J Med 2012; 366:321-329.

27. Bilheimer DW, Goldstein JL, Grundy SM, Starzl TE, Brown MS. Liver transplantation to provide low-density-lipoprotein receptors and lower plasma cholesterol in a child with homozygous familial hypercholesterolemia. N Engl J Med 1984; 311:1658-1664.

28. Blaha M, Budoff MJ, Shaw LJ, Khosa F, Rumberger JA, Berman D, et al. Absence of coronary artery calcification and all-cause mortality. JACC Cardiovasc Imaging. 2009; 2(6):692-700.

29. Blaha MJ, Blumenthal RS, Budoff MJ, Nasir K. Understanding the utility of zero coronary calcium as a prognostic test: a Bayesian approach. Circ Cardiovasc Qual Outcomes 2011; 4:253-256.

30. Blaha MJ, Budoff MJ, DeFilipppis AP, Blankstein R, Rivera JJ, Agatston A, et al. Associations between C-reactive protein, coronary artery calcium, and cardiovascular events: implications for the JUPITER population from MESA, a population-based cohort study. Lancet 2011; 378:684-692.

31. Blair SN, Kohl III HW, Barlow CE, Paffenbarger, Jr. RS, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: A prospective study of healthy and unhealthy men. JAMA 1995; 273:1093-1098.

32. Bloomfield HE, Koeller E, Greer N, MacDonald R, Robert Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet with No Restriction on Fat Intake. Ann Intern Med. 2016; 165(7):491-500. DOI: 10.7326/M16-0361

33. Boden W and the AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. A Systematic Review and Meta-analysis. Ann Intern Med 2016; 165:491-500. doi: 10.7326/M16-0361.

34. Boden WE, O'Rourke RA, Teo KT, Hartigan PM, Maron DJ, Kostuk WJ, et al, for the COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007; 356:1503-1516.

35. Boekholdt SM, Arsenault BJ, Mora S, Pedersen TR, LaRosa JC, Nestel PJ, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. 2012; 307(12):1302-1309.

36. Braunwald (not author) Zoler ML. Internal Medicine News. 2016 (Sept 20): http://www.mdedge.com/internalmedicinenews/article/113821/cardiology/escs-new-lipid-guidelines-keep-ldl-cholesterol. Accessed 1-18-17.

37. Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. 1990; 323(19):1289-1298.

38. Brown MS et al. Lowering LDL – not only how low, but how long? Science 2006; 311:1721-1723.

39. Brown MS, Anderson RG, Goldstein JL. Recycling receptors: The round-trip itinerary of migrant membrane proteins. Cell 1983; 32:663-667.

40. Brugts JJ, Yetgin T, Hoeks, SE, Gotto AM, Shepherd J, Westendorp RGJ,

Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: meta-analysis of randomized controlled trials. BMJ. 2000; 321(7253):73-77.

41. Budoff MJ, McClelland RL, Nasir K, Greenland P, Kronmal RA, Kondos GT, Shea S, Lima JA, Blumenthal RS. Cardiovascular events with absent or minimal coronary calcification: The Multi-Ethnic Study of Atherosclerosis (MESA). Am Heart J 2009; 158:554-561.

42. Budoff MJ, Hokanson JE, Nasir K, et al. Progression of coronary artery calcium predicts all-cause mortality. J Am Coll Cardiol Img 2010; 3:1229 –36.

43. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, Detrano RC, Bild DE, Guerci AD, Liu K, Shea S, Szklo M, Post W, Lima J, Bertoni A, Wong ND. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-ethnic study of atherosclerosis). J Am Coll Cardiol 2013; 61:1231-1239

44. Budoff MJ, Young R, Burke G, Carr JJ, Detrano RC, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: The multi-ethnic study of atherosclerosis (MESA). Eur Heart J. 2018; 0, 1-10. Doi:10.1093/eurheartj/ehy217.

45. Budoff MJ, Yu D, Nasir K, Mehrotra R, Chen L, Takasu J, Agrawal N, Liu ST, Blumenthal RS. Diabetes and progression of coronary calcium under the influence of statin therapy. Am Heart J 2005; 149:695-700.

46. Burge MR, Eaton RP, Comerci G, Cavanaugh B, Ramo B, Schade DS. Management of asymptomatic patients with positive coronary artery calcium scans. J Endo Society 2017; 1(6):588-599. doi: 10.1210/js.2016-1080

47. Burge MR, Eaton RP, Schade DS. The role of a coronary artery calcium scan in type 1 diabetes. Diabetes Technol Ther 2016; 18(9):594-603.

48. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA. 2007; 297(18):2018-2024.

49. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; IMPROVE-IT Investigators. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015; 372(25):2387-2397. doi: 10.1056/NEJMoa1410489.

50. Carr JJ, Jacobs DR, Jr, Terry JG, Shay CM, Sidney S, Liu K, et al. Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death. JAMA Cardiol. 2016; doi:10.1001/jamacardio.2016.5493 Published online February 8, 2017.

51. Chaikriangkrai K, Velankar P, Schutt R, Alchalabi S, Nabi F, Mahmarian J, et al. Additive prognostic value of coronary artery calcium score over coronary computed tomographic angiography stenosis assessment in symptomatic patients without known coronary artery disease. Am J Cardiol. 2015; 115(6):738-744.

52. Chambless LE, Folsom AR, Davis V, Sharrett R, Heiss G, Sorlie P, et al. Risk factors for progression of common carotid atherosclerosis: the Atherosclerosis Risk in Communities Study, 1987-1998. Am J Epidemiol. 2002; 155(1):38-47.

53. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. 1997; 146(6):483-494.

54. Cheng VY, Lepor NE, Madyoon H, Eshaghian S, Naraghi AL, Shah PK. Presence and Severity of Noncalcified Coronary Plaque on 64-Slice Computed Tomographic Coronary Angiography in Patients With Zero and Low Coronary Artery Calcium. Am J Cardiol 2007; 99:1183-1186.

55. Cho I, Shim J, Chang HJ, Sung JM, Hong Y, Shim H, et al. Prognostic value of multidetector coronary computed tomography angiography in relation to exercise electrocardiogram in patients with suspected coronary artery disease. J Am Coll Cardiol. 2012; 60(21):2205-2215.

56. Cholesterol Treatment Trialists' (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. Lancet. 2012; 380(9841):581-590. doi: 10.1016/S0140-6736(12)60367-5.

57. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials. Lancet 2010; 376:1670-1681 http://dx.doi.org/10.1016/S0140-6736(10)61350-5.

58. Clausss S, Wai K-M, Kavey W, Kuehl K. Ezetimibe treatment of pediatric patients with hypercholesterolemia. J Pediatr 2009; 154:869-872.

59. Cleary PA, Orchard TJ, Genuth S, Wong ND, Detrano R, Backlund J-Y C, Zinman B, Jacobson A, Sun W, Lachin JM, Nathan DM for the DCCT/EDIC Research Group. The Effect of intensive glycemic treatment on coronary artery calcification in type diabetic participants of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) Study. Diabetes 2006; 55:3556-3565.

60. Colhoun HM. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicenter randomized placebo-controlled trial. Lancet 2004; 364:685-696.

61. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. Lancet. 2001; 357:89–95

62. Connor WE, Cerqueira MT, Connor RW, Wallace RB, Malinow MR, Casdorph HR. The plasma lipids, lipoproteins, and diet of the Tarahumara Indians of Mexico. Am J Clin Nutr.1978 (7):1131-1142.

63. Connor WE, Hodges RE, Bleiler RE. The serum lipids in men receiving high cholesterol and cholesterol-free diets. Journal of Clinical Investigation. 1961; 40(5):894-901.

64. Connor WE, Lin DS. The intestinal absorption of dietary cholesterol by hypercholesterolemic (type II) and normocholesterolemic humans. J Clin Invest. 1974; 53(4):1062-1070.

65. Couzin-Frankel J. LIPID BIOLOGY. Why high 'good cholesterol' can be bad news. Science. 2016; 351(6278):1126. doi: 10.1126/science.351.6278.1126.

66. Cromwell WC, Otvos JD, Keyes MJ, et al. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study – Implications for LDL Management. Journal of clinical lipidology. 2007; 1(6):583-592.

67. Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. Am J Clin Nutr. 2013; 97(3):597-603.

68. Cushman WC, Goff DC. More HOPE for prevention with statins. N Engl J Med 2016; 374:2085-2087

69. Daniels SR. Cardiovascular disease risk factors and atherosclerosis in children and adolescents. Current atherosclerosis reports. 2001; 3(6):479-85.

70. Davidson M et al. Comparison of effects on low-density lipoprotein cholesterol and high-density lipoprotein cholesterol with rosuvastatin versus atorvastatin in patients with type IIa or IIb hypercholesterolemia. Am J Cardiol 2002; 89:268-275.

71. Davidson MH. Reducing residual risk for patients on statin therapy: The potential role of combination therapy. Davidson Reducing residual risk for patients on statin therapy. Am J Cardiol 2005; 96[suppl]:3K–13K.

72. Davignon J and Dubuc G. Statins and Ezetimibe Modulate Plasma Proprotein Convertase Subtilisin Kexin-9 (PCSK9) Levels. Transactions of the American Clinical and Climatological Association. 2009;120:163-173.

73. Dayspring T, Dall T, Abuhajir M. Moving beyond LDL-C: incorporating lipoprotein particle numbers and geometric parameters to improve clinical outcomes. Research Reports in Clinical Cardiology. 2010; 2010(1):1-10.

74. De Bruyne B, Pijls NH, Kalesan B, Barbato E, Tonino PAL, Piroth Z, et al. for the FAME 2 Trial Investigators. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012; 367:991-1001.

75. de Craen AJM, Knopp RH, Nakamura H, Ridker P, van Domburg R, Deckers JW. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomized controlled trials. BMJ 2009; 338:b2376

76. Dedic A, Genders TS, Ferket BS, Galema TW, Mollet NR, Moelker A, et al. Stable angina pectoris: head-to-head comparison of prognostic value of cardiac CT and exercise testing. Radiology. 2011; 261(2):428-436.

77. DeGoma EM, Martin SS, Smith DA. Review: Statins are not associated with cognitive impairment, Alzheimer disease, or dementia. Ann Intern Med 2014; 160(10) doi: 10.7326/0003-4819-160-10-201405200-02010

78. Dubuc G, Chamberland A, Wassef H, Davignon J, Seidah NG, Bernier L, Prat A. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated concertase-1 implicated in familial hypercholesterolemia. Arterioscler Thromb Vasc Biol 2004; 24:1454-1459. doi: 10.1161/01.ATV.0000134621.14315.43

79. Dykun I, Lehmann N, Kälsch H, Möhlenkamp S, Moebus S, Budde T, et al. Statin Medication Enhances Progression of Coronary Artery Calcification: The Heinz Nixdorf

Recall Study. J Am Coll Cardiol. 2016; 68(19):2123-2125. doi: 10.1016/j.jacc.2016.08.040.

80. Eaton RP, Burge MR, Comerci G, Cavanaugh B, Ramo B, Schade DS. Abnormal coronary artery calcium scans in asymptomatic patients Am J Med 2016; http://dx.doi.org/10.1016/j.amjmed.2016.10.006

81. Eidelman R, Hebert P, Weisman S, Henekens C. An Update on Aspirin in the Primary Prevention of Cardiovascular Disease. Arch Intern Med. 2003;163:2006-2010.

82. Elias-Smale SE, Proenca RV, Koller MT, et al. Coronary artery calcium score improves classification of coronary heart disease risk in the elderly: the Rotterdam study. J AM Coll Cariol,. 2010;56(17):1407-1414.

83. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA, Flack JM. Effect of Long-Term Exposure to Lower Low-Density Lipoprotein Cholesterol Beginning Early in Life on the Risk of Coronary Heart Disease: A Mendelian Randomization Analysis. J Am Coll Cardiol 2012; 60(25):2631-2639.

84. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: Executive Summary. Circulation 2012; 126:3097-3137.

85. Fleg JL, Mete M, Howard BV, Umans JG, Roman MJ, Ratner RE, et al. Effect of statins alone versus statins plus ezetimibe on carotid atherosclerosis in type 2 diabetes: the SANDS (Stop Atherosclerosis in Native Diabetics Study) trial. J Am Coll Cardiol. 2008; 52(25):2198-2205.

86. Fuchs VR, Milstein A. The $640 billion question – Why does cost-effective care diffuse so slowly? N Engl J Med 2011; 364(21):1985-1987.

87. Funabashi N, Misumi K, Ohnishi H, Asano M, Komoro I. Characterization and morphology of atherosclerotic plaque of coronary arteries: utility of electron-beam tomography to detect non-calcified plaque: a comparison with conventional coronary angiography and intravascular ultrasound. International journal of cardiology. 2007; 115(1):108-113.

88. Fuster V. The CVD paradox: mortality vs. prevalence. Nature Reviews Cardiology. 2009; 6:669 doi:10.1038/nrcardio.2009.187

89. Gæde P, Vedel P, Larsen N, Jensen GVH, Parving H-H, Pedersen Oluf. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348:383-393.

90. Gagné C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, Cho M, Musliner TA, Gumbiner B., for the Ezetimibe Study Group. Efficacy and safety of Ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002; 90:1084-1091.

91. Gagné C, Gaudet D, Bruckert E. for the Ezetimibe Study Group. Efficacy and safety of ezetimibe coadministered with atorvastatin in patients with homozygous familial hypercholesterolemia. Circulation 2002; 105:2469-2475.

92. Gidding SSRJ, Rana JS, Prendergast C, et al. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) risk score in young adults predicts coronary artery and abdominal aorta calcium in middle age: the CARDIA Study. Circulation. 2016; 133(2):139-146.

93. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med. 1987; 316(22):1371-1375.

94. Goldstein JL, Anderson, RGW, Brown MS. Coated pits, coated vesicles, and receptor-mediated endocytosis. Nature 1979; 279:679-685.

95. Goldstein JL, Brown MS. History of discovery: The LDL Receptor. Arteroscler Thromb Vasc Biol 2009; 29:431-438.

96. Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart disease events. JAMA. 2003; 290(7):891-897.

97. Greenland P, Blaha M, Budoff M, Erbel R, Watson K: Coronary Calcium Score and Cardiovascular Risk. J Am Coll Cardiol. 2018 Jul 24;72(4):434-447. doi: 10.1016/j.jacc.2018.05.027.

98. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004; 14; 291(2):210-215.

99. Grundy SM. Primary prevention of coronary heart disease: Integrating risk assessment with intervention. Circulation 1999; 100:988-998.

100. Hannan EL, Samadashvili Z, Cozzens K, Walford G, Holmes DR, Jacobs AK, et al. Appropriatensss of diagnostic catheterization for suspected coronary artery disease in New York State. Circ Cardiovasc Interv 2014; 7:19-27.

101. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 2005; 352:1685-1695.

102. Hansson L, Zanchetti A, Carruthers G, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowing and low-dose aspirin in patients with hypertension: Principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet. 1998;351:1755-1762.

103. Havel RJ, Yarnada N, Shames DM. Watanabe heritable hyperlipidemic rabbit: animal model for familial hypercholesterolemia. Arteriosclerosis Supplement I (1989; 9:1-33 – I-38.

104. Havel RJ. The formation of LDL: mechanisms and regulation J Lipid Res 1984; 25:1570-1576.

105. Hayward RSA. Clinical practice guidelines on trial. CMAJ. 1997; 156(12):1725-1727.

106. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the Society of Cardiovascular Computed Tomography. J Cardiovasc Comput Tomogr. 2017; 11(2):157-168.

107. Hecht HS, Narula J. Coronary artery calcium scanning in asymptomatic patients with diabetes mellitus: a paradigm shift. J Diabetes 2012; 4:342-50.

108. Hecht HS. Coronary artery calcium scanning: past, present, and future. JACC Cardiovasc Imaging 2015 May; 8(5):579-596 doi: 10.1016/j.jcmg.2015.02.006.

109. Hermiller JB, Tenaglia AN, Kisslo KB, Phillips HR, Bashore TM, Stack RS, et al. In vivo validation of compensatory enlargement of atherosclerotic coronary arteries. Am J Cardiol 1993(Mar15); 71(8):665-668.

110. Hiro T, Kimura T, Morimoto T, Miyauchi K, Nakagawa Y, Yamagishi M, Ozaki Y, Kimura K, Saito S, Yamaguchi T, Daida H, Matsuzaki M. Effect of statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome: A multicenter randomized trial evaluated by volumetric intravascular ultrasound using

pitavastatin versus atorvastatin (JAPAN-ACS [Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome] study). J Am Coll Cardiol 2009; 54:293-302.

111. Ho M, Garnett SP, Baur L, Burrows T, Stewart L, Neve M, et al. Effectiveness of lifestyle interventions in child obesity: systematic review with meta-analysis. Pediatrics. 2012; 130(6):e1647-1671. doi: 10.1542/peds.2012-1176.

112. Horton JD, Cohen JC, and Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J. Lipid Res. 2009;50:S172-S177

113. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, et al. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med 1997; 337(21):1491-1499.

114. Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. JAMA. 2002; 288(20):2569-2578.

115. Jarcho JA et al. Proof that lower is better - LDL cholesterol and IMPROVE-IT. N Engl J Med 2015; 372(25):2448-2450.

116. Jensen LO, Thayssen P, Pedersen KE, Stender S, Haghfelt T. Regression of coronary atherosclerosis by simvastatin: a serial intravascular ultrasound study. Circulation. 2004; 110(3):265-270.

117. Jia H, Abtahian F, Aguirre AD, Lee S, Chia S, Lowe H, et al. In vivo diagnosis of plaque erosion and calcified nodule in patients with acute coronary syndrome by intravascular optical coherence tomography. J Am Coll Cardiol. 2013; 62(19):1748-1758. doi: 10.1016/j.jacc.2013.05.071.

118. Jia L, Betters JL, Yu L. Niemann-Pick C1-Like 1 (NPC1L1) Protein in intestinal and hepatic cholesterol transport. Annu Rev Physiol 2011; 73:239-259. Doi:10.1146/annurev-physiol-012110-142233

119. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, MD, Cain VA, Blasetto JW, for the STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR Trial). Am J Cardiol 2003; 92(2):152-160.

120. Joy TR, Monjed A, Zou GY, Hegele RA, McDonald CG, Mahon JL. N-of-1 (Single-patient) trials for statin-related myalgia. Ann Intern Med 2014; 160(5):201-210 doi: 10.7326/M13-1921.

121. Kalia NK, Miller LG, Nasir K, et al. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis 2006; 185(2):394-399. Epub 2005 Jul 26 PMID: 16051253

122. Kamari Y, Bitzur R, Cohen H, Shaish A, Harats D. Should All Diabetic Patients Be Treated With a Statin? Diabetes Care. 2009; 32(Suppl 2):S378-S383.

123. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ. Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. JAMA 1990; 264(23):3007-3012.

124. Katritsis DG, Ioannidis JPA. Percutaneous coronary intervention versus conservative therapy in nonactute coronary artery disease: A meta-analysis. Circulation 2005; 111:2906-2912.

125. Kavousi M, Desai CS, Ayers C, Blumenthal RS, Budoff MJ, Mahabadi A-A, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: A meta-analysis. JAMA 2016; 316(20):2126-2134. Doi:10.1001/

126. Keelan PC et al. Long-term prognostic value of coronary calcification detected by electron-beam computed tomography in patients undergoing coronary angiography. Circulation 2001; 104:412-417.

127. Kelley GA, Kelley KS, Franklin B. Aerobic Exercise and Lipids and Lipoproteins in Patients With Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials. Journal of cardiopulmonary rehabilitation. 2006; 26(3):131-144.

128. Keraliya A, Blankstein R. (2017) Regression of coronary atherosclerosis with medical therapy. NEJM 2017; 376(14):1370.

129. Key TJ, Fraser GE, Thorogood M, Appleby PN, Beral V, Reeves G, et al. Mortality in vegetarians and nonvegetarians: detailed findings from a collaborative analysis of 5 prospective studies. Am J Clin Nutr. 1999; 70(3 Suppl):516S-524S.

130. Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT, et al. Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years. J Am Coll Cardiol. 2016; 67(9):1013-1022.

131. Lambert G, Sjouke B, Bhoque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. J Lipid Res 2012; 53:2515-2524.

132. LaRosa JC et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352:1425-1435.

133. Lauridsen et al. Genetic variation in the cholesterol transporter NPC1L1, ischaemic vascular disease, and gallstone disease. Eur Heart J 2015; 36:1601-1608.

134. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326:1423 doi: 10.1136/bmj.326.7404.1423

135. Law MR, Wald NJ. Risk factor thresholds: their existence under scrutiny. BMJ. 2002; 324(7353):1570-1576.

136. Lazar LD, Pletcher MJ, Coxson PG, Bibbins-Domingo K, Goldman L. Cost-effectiveness of statin therapy for primary prevention in a low-cost statin era. Circulation. 2011; 124(2):146-153.

137. Leening MJG, Berry JD, Allen NB. Lifetime perspectives on primary preventon of atherosclerotic cardiovascular disease. JAMA 2016; 315(4):1449-1450.

138. Leening MJ, Elias-Smale SE, Kavousi M, et al. Coronary calcification and the risk of heart failure in the elderly: the Rotterdam Study. JACC Cardiovasc Imaging. 2012;5(9):874-880.

139. Leibowitz M, Karpati T, Cohen-Stavi CJ, Feldman BS, Hoshen M, Bitterman H, et al. Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment. JAMA Intern Med. 2016; 176(8):1105-1113.

140. Libby P, Theroux P. Pathophysiology of Coronary Artery Disease. Circulation 2005; 111:3481-3488.

141. Libby P. Atherosclerosis: The new view. Sci Am 2002 May; 286(5):46-55.

142. Libby P. Inflammation in atherosclerosis. Nature 2002; 420:868-874.

143. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013; 368:2004-2013 doi: 10.1056/NEJMra1216063

144. Libby P. The forgotten majority: unfinished business in cardiovascular risk reduction. J Am Coll Cardiol 2005; 46(7):1225-1228.

145. Lin GA, Dudley RA, Redberg RF. Cardiologists' use of percutaneous coronary interventions for stable coronary artery disease. Arch Intern Med. 2007; 167(15):1604-1609.

146. Lloyd-Jones DM, Wilson PW, Larson MG, Beiser A, Leip EP, D'Agostino RB, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol 2004; 94(1):20-24.

147. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. Adverse effects of statin therapy: perception vs. the evidence – focus on glucose homeostasis, cognitive, renal and hepatic function, hemorrhagic stroke and cataract. Ear Heart J 2018; 0:1-18 doi:10.1093/eurheartj/ehy182

148. Maher JE, Raz JA, Bielak LF, Sheedy PF 2nd, Schwartz RS, Peyser PA. Potential of quantity of coronary artery calcification to identify new risk factors for asymptomatic atherosclerosis. Am J Epidemiol. 1996; 144(10):943-953.

149. Mamudu HM, Paul TK, Veeranki SP, Budoff M. The effects of coronary artery calcium screening on behavioral modification, risk perception, and medication adherence among asymptomatic adults: a systematic review. Atherosclerosis. 2014; 236(2):338-350.

150. Mark DB, Hlatky MA, Harrell FE Jr, Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. Ann Intern Med. 1987; 106(6):793-800.

151. Maron DJ, Hartigan PM, Neff DR, Weintraub WS, Boden WE, COURAGE Trial Investigators. Impact of adding ezetimibe to statin to achieve low-density lipoprotein cholesterol goal (from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] trial). Am J Cardiol. 2013(Jun 1); 111(11):1557-62. doi: 10.1016/j.amjcard.2013.02.005. Epub 2013 Mar 25.

152. Mattson FH, Erickson BA, Kligman AM. Effect of dietary cholesterol on serum cholesterol in man. Am J Clin Nutr. 1972; 25(6):589-594.

153. McMahan CA, Gidding SS, Malcom GT, Tracy RE, Strong JP, McGill HC Jr, et al. Pathobiological determinants of atherosclerosis in youth risk scores are associated with early and advanced atherosclerosis. Pediatrics. 2006; 118(4):1447-1455.

154. McMurry MP, Connor WE, Cerqueira MT. Dietary cholesterol and the plasma lipids and lipoproteins in the Tarahumara Indians: a people habituated to a low cholesterol diet after weaning. Am J Clin Nutr 1982; 35:741-744.

155. Meek C et al. Daily and intermittent rosuvastatin 5 mg therapy in statin intolerant patients: an observational study. See comment in PubMed Commons below Curr Med Res Opin 2012(Mar); 28(3):371-8 doi: 10.1185/03007995.2012.657302

156. Mehta SR. Aspirin for prevention and treatment of cardiovascular disease. Ann Intern Med 2009; 150:414-416.

157. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb. 1992; 12(8):911-919.

158. Mensink RP, Zock PL, Keater ADM, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003; 77(5):1146-1155.

159. Miedema MD, Duprez DA, Misialek JR, Blaha MJ, Nasir K, Silver MG, et al. Use of coronary artery calcium testing to guide aspirin utilization for primary prevention: Estimates from the multi-ethnic study of atherosclerosis. Circ Cardiovasc Qual Outcomes 2014; 7:453-460.

160. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. Lancet. 2012; 380(9841):581-590.

161. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009; 119(7):931-939.

162. Mori H, Torii S, Kutyna M, Sakamoto A, Finn AV, Virmani R. Coronary artery calcification and its progression: What does it really mean? JACC Cardiovasc Imaging. 2018; 11(1):127-142. doi: 10.1016/j.jcmg.2017.10.012.

163. Morris ZS Wooding S, Grant J. The answer is 17 years, what is the question: Understanding time lags in translational research. J R Soc Med 2011; 104:510-520.

164. Morrison KM, Dyal L, Conner W, Helden E, Newkirk L, Yusuf S, et al. Cardiovascular risk factors and non-invasive assessment of subclinical atherosclerosis in youth. Atherosclerosis. 2010; 208(2):501-505. doi: 10.1016/j.atherosclerosis.2009.07.034.

165. Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: A systematic review and meta-analysis of randomized controlled trials. PLoS Med 2010; 7(3), e10000252. Doi:10.1371/journal.pmed.1000252

166. Müller H, Lindman AS, Brantsaeter AL, Pedersen JI. The serum LDL/HDL cholesterol ratio is influenced more favorably by exchanging saturated with unsaturated fat than by reducing saturated fat in the diet of women. J Nutr. 2003; 133(1):78-83.

167. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002; 346(11):793-801.

168. Nabel EG, Braunwald E. A tale of coronary artery disease and myocardial infarction. N Engl J Med 2012; 366:54-63.

169. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D et al. From vulnerable plaque to vulnerable patient – Part III: Executive summary of the screening for Heart Attack Prevention and Education (SHAPE) Task Force Report. AM J Cardiol. 2006 Jul 17; 98(2A):2H-15H.

170. Nakamura T, Obata JE, Kitta Y, Takano H, Kobayashi T, Fujioka D, Saito Y, Kodama Y, Kawabata K, Mende A, Yano T, Hirano M, Sano K, Nakamura K, Kugiyama K et al. Rapid stabilization of vulnerable carotid plaque within 1 month of Pitavastatin treatment in patients with acute coronary syndrome. J Cardiovasc Pharmacol 2008; 51:365-371.

171. Nakanishi R, Li D, Blaha MJ, Whelton SP, Matsumoto S, Alani A, et al. The relationship between coronary artery calcium score and the long-term mortality among patients with minimal or absent coronary artery risk factors. International Journal of Cardiology 2015; 185:275–281. Doi: 10.1016/j.ijcard.2015.03.146

172. Nasir K, Bittencourt MS, Blaha MJ, Blankstein R, Agatson AS, Rivera JJ, Miedema MD, Sibley CT, Shaw LJ, Blumenthal RS, Budoff MJ, Krumholz HM. Implications of coronary artery calcium testing among statin candidates according to American College of Cardiology/American Heart Association cholesterol management guidelines. J Am Coll Cardiol 2015; 66:1657-1668.

173. Nasir K, Rubin J, Blaha MJ, Shaw LJ, Blankstein R, Rivera JJ, Khan AN, Berman D, Raggi P, Callister T, Rumberger JA, Min J, Jones SR, Blumenthal RS, Budoff MJ. Interplay of coronary artery calcification and traditional risk factors for the prediction of

all-cause mortality in asymptomatic individuals. Circ Cardiovasc Imaging 2012; 5:467-473.

174. Newman AB, Naydeck BL, Ives DG, et al. Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcome sin adults 70 to 99 years old. Am J Cardiol. 2008;101(2):186-192.

175. Newman CB, Tobert JA. Statin Intolerance – Reconciling clinical trials and clinical experience. JAMA 2015; 313(10):1011-1012 doi:10.1001/jama.2015.1335.

176. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman J, Erbel RM, Libby P, Raichlen JS, Uno K, Borgman M, Wolski K, Nissen SE. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011; 365:2078-87.

177. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, Wolski K, Crowe T, Desai MY, Hazen SL, Kapadia SR, Nissen SE. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. JAMA 2007; 297:499-508. doi:10.1001/jama.297.5.499.

178. O'Keefe JH, Jr., Cordain L, Harris WH, Moe RM, Vogel R. Optimal low-density lipoprotein is 50 to 70 mg/dl: Lower is better and physiologically normal. J Am Coll Cardiol 2004; 43(11):2142-2146 doi: 10.1016/j.jacc.2004.03.046.

179. Odden MC,Pletcher MJ, Coxson PG, et al. Cost-Effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States. Ann Intern Med. 2015;162(8):533-541.

180. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008; 300(18):2134-2141. doi: 10.1001/jama.2008.623.

181. Ohman EM, Chronic stable angina. N Engl J Med 2016; 374:1167-1176.

182. Olson JC, Edmundowicz D, Becker DJ, Kuller LH, Orchard TJ. Coronary calcium in adults with Type 1 diabetes: A stronger correlate of clinical coronary artery disease in men than in women. Diabetes 2000; 49:1571-1578.

183. Olsson AG, Pears J, McKellar J, Mizan J, Raza A. Effect of rosuvastatin on low-density lipoprotein cholesterol in patients with hypercholesterolemia. Am J Cardiol 2001; 88:504-508.

184. Ong P, Athanasiadis A, Hill S, Vogelsberg H, Voehringer M, Sechtem U. Coronary artery spasm as a frequent cause of acute coronary syndrome: The CASPAR (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) Study. J Am Coll Cardiol. 2008; 52(7):523-527.

185. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010; 362(10):886-895.

186. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med. 2005; 353(22):2373-2383.

187. Phillips RL, Lemon FR, Beeson WL, Kuzma JW. Coronary heart disease mortality among Seventh-Day Adventists with differing dietary habits: a preliminary report. Am J Clin Nutr. 1978; 31(10 Suppl):S191-S198.

188. Pijls NH, van Schaardenburgh P, Manoharan G, Boersma E, Bech JW, van't Veer M, et al. Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER Study. J Am Coll Cardiol. 2007; 49(21):2105-2111.

189. Pitt B, Waters D, Brown WV, van Boven AJ, Schwartz L, Title LM, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. N Engl J Med. 1999; 341(2):70-76.

190. Rawshani A, Rawshani A, Franzen S, Sattar N, EliassonB, Svensson A, et al. Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2018;379(7):633-644.

191. Redberg RF. What is the prognostic value of a zero calcium score? Am Coll Cardiol 2010; 55(7):635-636.

192. Reid FDA, Cook DG, Whincup PH. Use of statins in the secondary prevention of coronary heart disease: is treatment equitable? Heart 2002;88:15-19.

193. Rewers M, Ehrlich J, Jensen L, Siegel R, Barriga K, Garg S, et al. High Prevalence of Asymptomatic Coronary Atherosclerosis Detected by Electron Beam Computed Tomography in Young Adults With IDDM. Diabetes. 1998; 47(1S):12A.

194. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE et al. Statins and cognitive function Ann Intern Med 2013; 159:688-697.

195. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. for the Pravastatin or Atorvastatin evaluation and infection therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352:20-28.

196. Ridker PM, Cook NR. Cholesterol Evaluation in Young Adults: Absence of Clinical Trial Evidence Is Not a Reason to Delay Screening. Ann Intern Med. 2017; 166(12):901-902. doi: 10.7326/M17-0855.

197. Ridker P, Cook N, Lee M, Gordon D, Gaziano M, Manson J, et al. A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women. N Engl J Med. 2005;352(13):1293-1304

198. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med. 1997; 336(14):973-979.

199. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, Kastelein JJP, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd JD, Willerson, JT, Glynn RJ. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008(21); 359:2195-2207 doi 10.1056/NEJMoa0807646.

200. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017; 377(12):1119-1131. doi: 10.1056/NEJMoa1707914. Epub 2017 Aug 27.

201. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012; 380:565-571.

202. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto Jr AM, et al. for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. 2001; 344(26):1959-1965.

203. Ridker PM, Rifai N, Pfeffer MA, Sacks FM, Moye LA, Goldman S et al. for the Cholesterol and Recurrent Events (CARE) Investigators. Inflammation, Pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Circulation 1998; 98:839-844.

204. Ridker PM. High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation 2001; 103:1813-1818.

205. Roberts ET, Horne A, Martin SS, Blaha MJ, Blankstein R, Budoff MJ, et al. Cost-Effectiveness of Coronary Artery Calcium Testing for Coronary Heart and Cardiovascular Disease Risk Prediction to Guide Statin Allocation: The Multi-Ethnic Study of Atherosclerosis (MESA). PLoS ONE 2015; 10(3):e0116377. Doi:10.1371/journal.pone.0116377

206. Robinson JG, Rosenson RS, Farnier M, Chaudhari U, Sasiela WJ, Merlet L, et al. Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab: Pooled Data From Randomized Trials. J Am Coll Cardiol. 2017; 69(5):471-482. doi: 10.1016/j.jacc.2016.11.037.

207. Rodrigues TC, Veyna AM, Haarhues MD, Kinney GL, Rewers M, Snell-Bergeon JK. Obesity and coronary artery calcium in diabetes: The coronary artery calcification in type 1 diabetes (CACTI) Study. Diabetes Technol Ther 2011; 13(10):991-996. Doi:10.1089/dia.2011.0046

208. Rohatgi A, Khera A, Berry JD, Givens EG, Ayers CR, Wedin KE, et al. HDL cholesterol efflux capacity and incident cardiovascular events. N Engl J Med 2014; 371:2383-2393.

209. Rosenson RS, Brewer HB Jr, Ansell BJ, Barter P, Chapman MJ, Heinecke JW, et al. Dysfunctional HDL and atherosclerotic cardiovascular disease. Nat Rev Cardiol. 2016; 13(1):48-60.

210. Rosqvist F, Iggman D, Kullberg J, Cedernaes J, Johansson HE, Larsson A, Johansson L, Ahlström H, Arner P, Dahlman I, Risérus U. Overfeeding Polyunsaturated and Saturated Fat Causes Distinct Effects on Liver and Visceral Fat Accumulation in Humans. Diabetes 2014; 63:2356–2368 DOI: 10.2337/db13-1622

211. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med. 1999; 340(2):115-126.

212. Sabatine MS Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, Ballantyne CM, Somaratne R, Legg J, Wasserman SM, Scott, R, Michael J. Koren MJ, Stein EA, incl Open-label study of long-term evaluation against LDL cholesterol (OSLER) Investigators. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events N Engl J Med 2015 [PMID: 25773607].

213. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SAKuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376:1713-1722. DOI: 10.1056/NEJMoa1615664.

214. Sabatine MS, Wiviott SD, Im K, Murphy SA, Giugliano RP. Efficacy and safety of further lowering of low-density lipoprotein cholesterol in patients starting with very low levels: A meta-analysis. JAMA Cardiol. Doi:10.1001/jamacardio.2018.2258

215. Sachdeva A, Cannon CP, Deedwania PC, LaBresh KA, Smith SC, Jr, Dai D, et al. Lipid levels in patients hospitalized with coronary artery disease: An analysis of 136,905 hospitalizations in Get with the Guidelines. Am Heart J 2009; 159:111-117.e2

216. Saleheen D, Scott R, Javad S, Zhao W, Rodrigues A, Picataggi A, et al. Association of HDL cholesterol efflux capacity with incident coronary heart disease events: a prospective case-control study. Lancet Diabetes Endocrinol. 2015; 3(7):507-513.

217. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalcifying methodology. J Am Coll Cardiol Jan 1998; 31(1):126-33.

218. Schade DS, Cavanaugh B, Ramo B, Eaton RP. The application of the LDL principle. World J of Cardiovascular Diseases 2016; 6:109-125.

219. Schade DS, Eaton RP. Residual Cardiovascular Risk—Is Inflammation the Primary Cause? World Journal of Cardiovascular Diseases 2018; 8:59-69. https://doi.org/10.4236/wjcd.2018.81007

220. Schade DS, Helitzer D, Eaton P. Evidence that low density lipoprotein is the primary cause of atherosclerotic cardiovascular disease: A Bradford-Hill approach. WJCD 2017; 7:271-284.

221. Schade DS, Murphy S, Exil V, Eaton P. A Pediatric Opportunity in Adolescents to Prevent Adult Heart Attacks" WJCD 2018; 8(2):85-101 DOI: 10.4236/wjcd.2018.82009

222. Sedlis SP, Hartigan PM, Koon KT, Maron DJ, Spertus JA, Mancini GBJ, Kostuk W, Chaitman BR, Berman D, Lorin JD, Dada M, Weintraub WS, Boden WE, for the Courage Trial Investigators. Effect of PCI on Long-term survival in patients with stable ischemic heart disease. N Engl J Med 2015; 373:1937-1946.

223. Shaw L, Giambrone AE, Blaha MJ, Knapper JT, Berman DS, Bellam N, Quyyumi A, Budoff MJ, Callister TQ, Min JK. Long-term prognosis after coronary artery calcification testing. Ann Intern Med 2015; 163:14-21 doi: 10.7326/M14-0612

224. Shaw LJ, Min JK, Budoff M, Gransar H, Rozanski A, Hayes SW, et al. Induced cardiovascular procedural costs and resource consumption patterns after coronary artery calcium screening: results from the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) study. J Am Coll Cardiol. 2009; 54(14):1258-1267.

225. Shepherd J, Barter P, Carmena R, Deedwania P, Fruchart J-C, Haffner S, et al. Effect of lowering LDL cholesterol substantially below currently recommended levels in patients with coronary heart disease and diabetes. Diabetes Care 2006; 29:1220-1226.

226. Silbernagel G et al. High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis. J Am Coll Cardiol 2013; 62:291-299.

227. Silverman MG, Blaha MJ, Krumholz HM, Budoff MJ, Blankstein R, Sibley CT. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of atherosclerosis. Eur Heart J 2014; 35(33):2232-2241. doi: 10.1093/eurhrtj/eht508. Epub 20313 Dec 23

228. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, Braunwald E, Sabatine MS. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: A systematic review and meta-analysis. JAMA 2016; 316(12):1289-1297. doi:10.1001/jama.2016.13985

229. Singh IM1, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. JAMA. 2007; 298(7):786-798.

230. Starkman HS, Cable G, Hala V, Hecht H, Donnelly CM. Delineation of prevalence and risk factors for early coronary artery disease by electron beam computer tomography in young adults with type 1 diabetes. Diabetes Care 2003; 26(2):433-436.

231. Stary HC. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. Arteriosclerosis Supplement I 1989; 9:I19 – I32

232. Steinberg D. Earlier Intervention in the Management of Hypercholesterolemia. JACC. 2010;56(8):627-629.

233. Steinhubl SR, Bhatt DL, Brennan DM, Montalescot G, Hankey GJ, Eikelboom JW, Berger PB, Topol EJ, on behalf of the CHARISMA Investigators. Aspirin to prevent cardiovascular disease: The association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med 2009; 150:379-386.

234. Stergiopoulos K, Boden WE, Hartigan P, Möbius-Winkler S, Hambrecht R, Hueb W, et al. Percutaneous coronary intervention outcomes in patients with stable obstructive coronary artery disease and myocardial ischemia: a collaborative meta-analysis of contemporary randomized clinical trials. JAMA Intern Med. 2014; 174(2):232-240. doi: 10.1001/jamainternmed.2013.12855.

235. Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, et al and the Myocardial infarction genetics consortium investigators.et al. Myocardial infarction genetics consortium investigators. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med 2014; 371:2072-2082.

236. Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011; 364(3):226-35.

237. Sudhop T, Lütjohann D, Kodal A, Igel M, Tribble DL, Shah S, et al. Inhibition of intestinal cholesterol absorption by Ezetimibe in humans. Circulation 2002; 106:1943-1948.

238. Swiger KJ, MD; Manalac RJ, Blumenthal RS, Blaha MJ, Martin SS. Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. Mayo Clin Proc 2013; 88(11):1213-1221.

239. Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: assessment by optical coherence tomography study. Atherosclerosis. 2009; 202(2):491-497. doi: 10.1016/j.atherosclerosis.2008.05.014.

240. Taylor AJ, Bindeman J, Feuerstein I, Cao F, Michael Brazaitis M, O'Malley PG. Coronary Calcium Independently Predicts Incident Premature Coronary Heart Disease Over Measured Cardiovascular Risk Factors Mean Three-Year Outcomes in the Prospective Army Coronary Calcium (PACC) Project. J Am Coll Cardiol 2005; 46:807-814.

241. Taylor AJ, Bindeman J, Feuerstein I, Le T, Bauer K, Byrd C, Wu H, O'Malley PG. Community-Based Provision of Statin and Aspirin After the Detection of Coronary

Artery Calcium Within a Community-Based Screening Cohort. J Am Coll Cardiol 2008; 51(14):1337-1341.

242. Temel RE, Tang W, Ma Y, Rudel LL, Willingham MC, Ioannou YA, et al. Hepatic Niemann-Pick C1-like 1 regulates biliary cholesterol concentration and is a target of ezetimibe. J Clin Invest. 2007; 117(7):1968-1978.

243. The Medical Research Council's General Practice Research Framework: Thrombosis prevention trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet. 1998; 351: 233–41.

244. Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. Lancet. 2003; 361(9356):477-485.

245. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. JAMA 2003; 289(13):1681-1690. doi: 10.1001/jama.289.13.1681

246. Tirosh A, Shai I, Afek A, Dubnov-Raz G, Ayalon N, Gordon B, et al. Adolescent BMI Trajectory and Risk of Diabetes versus Coronary Disease. N Engl J Med 2011; 364:1315-1325.

247. Topol EJ, Nissen SE. Our preoccupation with coronary luminology: the dissociation between clinical and angiographic findings in ischemic heart disease. Circulation 1995; 92: 2333-2342 doi:10.1161/01.CIR.92.8.2333

248. Tota-Maharaj R, Blaha MJ, McEvoy JW, Blumenthal RS, Muse ED, Budoff MJ, et al. Coronary artery calcium for the prediction of mortality in young adults <45 years old and elderly adults >75 years old. Eur Heart J 2012; 33:2955-2962.

249. Tuzcu EM, Kapadia SR, Tutar E, Ziada KM, Hobbs RE, McCarthy PM, Young YB, Nissen SE. High prevalence of coronary atherosclerosis in asymptomatic teenagers and young adults. Circulation 2001; 103:2705-2710.

250. Twig G, Yaniv G, Levine H, Leiba A, Goldberger N, Derazne E, et al. Body-Mass Index in 2.3 Million Adolescents and Cardiovascular Death in Adulthood. N Engl J Med. 2016; 374(25):2430-2440.

251. Van der Wal AC, Becker AE, van der Loos CM, Das PK. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an

inflammatory process irrespective of the dominant plaque morphology. Circulation. 1994; 89(1):36-44.

252. Verma S, Wang CH, Li SH, Dumont AS, Fedak PW, Badiwala MV, et al. A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis. Circulation. 2002; 106(8):913-919.

253. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcifction improves cardiovascular risk prediction in the elderly. Circulation. 2005;112(4):572-577.

254. Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child–Parent Familial Hypercholesterolemia Screening in Primary Care. N Engl J Med 2016; 375:1628-1637.

255. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003; 326(7404):1419.

256. Waters DD, Guyton JR, Herrington DM, McGowan MP, Wenger NK, Shear C, and the TNT Steering Committee Members and Investigators. Treating to New Targets (TNT) Study: does lowering low-density lipoprotein cholesterol levels below currently recommended guidelines yield incremental clinical benefit? Am J Cardiol 2004; 93:154-158. doi:10.1016/j.amjcard.2003.09.031

257. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. Am J Clin Nutr. 2001; 73(5):885-891.

258. Weintraub WS, Spertus JA, Kolm P, Maron DJ, Zhang Z, Jurkovitz C, et al. Effect of PCI on quality of life in patients with stable coronary disease. N Engl J Med. 2008; 359(7):677-687. doi: 10.1056/NEJMoa072771.

259. Weis U, Turner B, Gibney J, Watts GF, Burke V, Shaw KM, et al. Long-term predictors of coronary artery disease and mortality in type 1 diabetes. QJ Med 2001; 94:623-630.

260. Weissler AM. Traditional risk factors for coronary heart disease. JAMA. 2004; 291(3):299-300.

261. Welder G, Zineh I, Pacanowski MA, Troutt JS, Cao G, Konrad RJ. High-dose atorvastatin causes a rapid sustained increase in human serum PCSK9 and disrupts its correlation with LDL cholesterol. J Lipid Res 2010 Sept; 51(9):2714-2721. doi:10.1194/jlr.M008144

262. Whelton SP, Silverman MG, McEvoy JVV, Budoff MJ, Blankstein R, Eng J, et al. Predictors of long-term healthy arterial aging: Coronary artery calcium non development in the MESA study. J Am Coll Cardiol Img 2015 Dec; 8(12):1393-1400. doi: 10.1016/j.jcmg.2015.06.019 Epub 2015 Nov 11.

263. Whisler RL, Proctor VK, Downs EC, Mortensen RF. Modulation of human monocyte chemotaxis and procoagulant activity by human C-reactive protein (CRP). Lymphokine Res. 1986; 5(3):223-228.

264. Wiegman A, Hutten BA, deGroot E, Rodenburg J, Bakker HD, Büller HR, Sijbrands EJG, Kastelein JJP. Efficacy and safety of statin therapy in children with familial hypercholesterolemia: A randomized controlled trial. JAMA 2004; 292(3)331-337.

265. Wikipedia editors. Cholesterol. https://en.wikipedia.org/wiki/cholesterol#biosynthesis. Accessed 1-23-17.

266. Wilson PWF, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, O'Leary D, Wolf PA. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. N Engl J Med 1997; 337:516-522.

267. Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E, et al for the PROVE-IT-TIMI 22 Investigators. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy – a PROVE IT-TIMI 22 sub study. J Am Coll Cardiol 2005; 46:1411-1416 doi: 10.1016/j.jacc.2005.04.064

268. Xaplanteris P, Fournier S, Pijls N, Fearon W, Barbato E, Tonino P, et al: Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. N Engl J Med. 2018; 379:250-259 DOI: 10.1056/NEJMoa1803538

269. Yano Y, O'Donnell CJ, Kuller L, Kavousi M, Erbel R, Ning H, et al. Association of Coronary Artery Calcium Score vs Age With Cardiovascular Risk in Older Adults: An Analysis of Pooled Population-Based Studies. JAMA Cardiol. 2017. doi: 10.1001/jamacardio.2017.2498.

270. Yeste D, Chacon P, Clemente M, Albisu MA, Gussinye M, Carrascosa. Ezetimibe as monotherapy in the treatment of hypercholesterolemia in children and adolescents. J Pediatr Endocrinol Metab 2011; 22(6): 487–492. DOI: https://doi.org/10.1515/JPEM.2009.22.6.487.

271. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomized open-label, blinded endpoint analysis. Lancet 2007; 369:1090–1098.

272. Yonetsu T, Kakuta T, Lee T, et al. In vivo critical fibrous cap thickness for rupture-prone coronary plaques assessed by optical coherence tomography. European Heart Journal 2011; 32:1251–1259. doi: http://dx.doi.org/10.1093/eurheartj/ehq518 1251-1259 First published online: 27 January 2011

273. Yoon H-C, Emerick AM, Hill JA, Gjertson DW, Goldin JG. Calcium begets calcium: Progression of coronary artery calcification in asymptomatic subjects. Radiology 2002; 224:236-241. Doi: 10.1148/radiol.2241011191

274. Yusuf S, Bosch J, Dagenais G, Zhu J, Xavier D, Liu L, et al. for the HOPE-3 Investigators. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. N Engl J Med 2016; 374:2021-2031. http://www.nejm.org/doi/full/10.1056/NEJMoa1600176

275. Yusuf S, Phil D, Lonn E, Pais P, Bosch J, Lopez- Jaramillo P, et al. for the HOPE-3 Investigators. Blood pressure and cholesterol lowering in persons without cardiovascular disease. N Engl J Med 2016; 374:2032-2043.

276. Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F, Dailing C, Karlsberg RP, Budoff M. Effect of statin treatment on coronary plaque progression - A serial coronary CT angiography study. Atherosclerosis 2013; 231:198-204.

277. Zhang YX, Cliff WJ, Schoefl GI, Higgins G. Coronary C-reactive protein distribution: its relation to development of atherosclerosis. Atherosclerosis. 1999; 145(2):375-379.

Carlsbad Caverns in southeast New Mexico housing enormous colonies of Mexican free-tailed bats.

Billy the Kid, born in 1859, also known as William H. Bonney, was an outlaw and gunfighter who killed eight men before he was shot and killed at age 21 by Sheriff Pat Garrett. He took part in New Mexico's Lincoln County War, during which he allegedly took part in three murders.

An Opportunity for you to Save a Life!

Have you enjoyed reading this book? Do you want other folks to enjoy it?

As you know, we never charge money for this book. We have no sponsors. The book is downloadable at no charge on the internet. However, a downloaded version is never as good as reading a real hard copy. *You can make this possible.*

Make a tax deductible donation of $50 to “50 ways to save your heart” to the University of New Mexico Foundation at, 700 Lomas Blvd NE, Albuquerque, NM, 87102. This donation will purchase two books to be distributed to other “at risk” people. Hopefully, they in turn will also donate. You will save someone’s life!

Here is how you make the donation. From your computer’s browser go to https://www.unmfund.org/ and enter the name of the fund – “**50 ways to save your heart**” and follow the step by step instructions. Alternatively, it can be sent to the UNM Foundation at 700 Lomas Blvd NE. Albuquerque, NM 87102. Please reference the name “**50 ways to save your heart**” when making a gift.

David S. Schade, MD and R. Philip Eaton, MD thank you.

What Readers Are Saying About This Book

“This book has changed my life. My family and I are making a real change in what we eat and our exercises to take care of our hearts.” –John Smith, New York

“This information is thought provoking and useful for people in need of help with health issues.” –Karen Martinez, Texas

“After reading this book I am living healthier. I never knew of all the dangers I was putting myself in, this book helped me realize I needed to make a change.” –Michelle Robinson, South Dakota

“Written in a way I can appreciate. Heart disease runs in my family and now I feel lucky to come across this book so I can understand it.” –Tom Jones, California

“A book made not only to inform but to also heal.” –Scott Burns, Virginia

“Dr. Schade and Dr. Eaton are extraordinary physicians and they’ve created an invaluable book to anyone who reads it.” –Richard Greene, Arkansas

“Now I know I don’t have to die of a heart attack like my father and my brothers” – Robert Morton, New Mexico

“The explanations throughout the book are terrific! It helps explain all things cardiac to patients.” –Judy Ford, Alabama

“A revolutionary plan to prevent heart disease.” –Mary Norris, Nevada

“This book includes more information than how to eat better. It also informs you on new treatments to keep you healthy.” –Jack Foster, Ohio

Contributed by: E. Fondino

Sandia Mountains overlooking the Rio Grande river
bosque Albuquerque, New Mexico