A myocardial infarction (MI), or heart attack, is caused by a sudden blockage in the arteries that supply the heart muscle, known as the coronary arteries. Most of these blockages occur as a result of atherosclerosis, a process by which cholesterol and white blood cells accumulate in the wall of the artery (Figure).

Atherosclerosis leads to the build up of plaque, which is composed of a fibrous cap and a lipid (fatty) core, and grows slowly over years. The fibrous cap is comprised mostly of a thick, strong material called collagen that functions as a barrier between the blood stream and the lipid core. The lipid core is a collection of fats, cholesterol, white blood cells, and proteins that activates clot formation.

The fibrous cap prevents the lipid core from becoming exposed to the blood. Direct contact between the lipid core and the blood stream triggers a chain reaction that can become fatal: accumulation of platelets, clotting factors, and other cells leads to rapid obstruction of the coronary artery. Thus, if the fibrous cap ruptures, sudden blockage ensues leading to an MI.

The degree of coronary artery blockage or size of the lipid core does not necessarily predict the occurrence of MI or a short lifespan. Some people can live long and apparently healthy lives with large plaques in the coronary arteries as long as the fibrous cap remains intact.

So, if the size of the plaque does not matter, what does increase the risk of developing an MI?

**Inflammation: A True Predictor of Plaque Rupture**

Inflammation is now thought to play a major role in the risk of plaque rupture. Inflammation describes the body’s reaction to injury and infection. The inflammatory response includes white blood cells and the signals they send throughout the blood stream and can cause cardiovascular disease. Inflammation thins the fibrous cap and leaves it vulnerable to breakage or injury. Inflammation also interferes with the normal repair process, specifically the synthesis of new collagen, that is necessary to fix a damaged fibrous cap. Once the cap thins too much, it ruptures, and the coronary artery becomes obstructed.

Inflammation is increased by diverse stimuli and disease processes. Inflammation may be present in high levels even when there is no injury or infection in the body. Environmental or lifestyle causes of inflammation are important to recognize, because they lend themselves to modification (Table). Limiting or removing these triggers with lifestyle changes can decrease the risk of developing an MI. Health care providers and patients should pay particular attention to cigarette smoking, alcohol use, obesity, hypertension, diabetes mellitus, and metabolic syndrome, a condition composed of obesity, abnormal lipids, and abnormal glucose metabolism that often leads to diabetes mellitus. If these risk factors can be reduced, eliminated, or treated, then the level of inflammation and the risk of MI can be lowered.

Identifying those with elevated levels of inflammation requires an accurate diagnostic test. There are many markers of inflammation in the blood. High-sensitivity C-reactive protein (hsCRP) is 1 of the most thoroughly studied and best-known inflammatory markers. Patients with elevated hsCRP have an increased risk of cardiovascular disease, including stroke and MI, compared with those with a normal hsCRP, regardless of cholesterol levels. Levels of hsCRP <1 mg/L, 1 to
3 mg/L, and >3 mg/L indicate lower, average, and higher relative risks for future cardiovascular events, respectively. It is important to make sure that the units are mg/L, not mg/dL. If your CRP test is reported as mg/dL, then you did not have the correct test performed.

Statin, a class of medications used to lower cholesterol levels, help prevent MI. They decrease levels of bad cholesterol, called low-density lipoprotein, but also decrease hsCRP. Statins are thus 2-for-1 medications that combine lipid-lowering and anti-inflammatory mechanisms, making them especially important for preventing cardiovascular disease.

One major study, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), investigated the anti-inflammatory property of statins. The investigators enrolled almost 18,000 apparently normal subjects who had normal lipid profiles but high hsCRP levels. These patients would not ordinarily have qualified for statin therapy because they already had low levels of cholesterol. However, they were at significantly increased cardiac risk, because they had elevated levels of hsCRP. The JUPITER results showed that a statin medication called rosuvastatin, when compared with placebo, lowered hsCRP levels and reduced cardiovascular events such as MI and stroke by nearly 50% and the overall risk of death by 20%. Because both hsCRP and cholesterol levels were reduced with this medication, it is uncertain whether the inflammation-lowering or cholesterol-lowering effect was primarily responsible for the markedly lower rate of MI, stroke, and cardiovascular death.

Additional evidence for the potential cardiovascular benefits of anti-inflammatory medications comes from observational studies of patients with rheumatoid arthritis and psoriatic arthritis. These studies compared those taking low dose methotrexate (LDM), an anti-inflammatory medication, with those who were not. Patients with inflammatory disorders such as rheumatoid arthritis are at increased cardiac risk. However, the results suggested that these same patients who took LDM had lower rates of heart attack and stroke compared with those who did not take LDM. These observations require further study.
Reduction Trial (CIRT). The study is called the Cardiovascular Inflammation Reduction Trial: a test of the inflammatory hypothesis of atherothrombosis. 

Rationale and design


Cardiovascular Inflammation Reduction Trial website. www.theCIRT.org.


American Heart Association website. www.heart.org.

Disclosures

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Ongoing Research:
Do Anti-Inflammatory Medications Prevent MI?

Whether reducing inflammation alone will lower vascular event rates is a major public health question. The National Heart, Lung, and Blood Institute is sponsoring a 7000-patient randomized trial called the Cardiovascular Inflammation Reduction Trial (CIRT). The study is enrolling patients in the United States and Canada at >300 centers to determine whether patients without arthritis but with known coronary disease might also benefit from LDM. CIRT is designed to test whether lowering inflammation can prevent MI and other cardiovascular events, such as stroke.

The study tests the effects of treating cardiovascular inflammation by using LDM, a safe and effective anti-inflammatory medication that does not reduce cholesterol or decrease blood pressure. LDM is a generic drug that has been widely used to treat arthritis for 40 years and has been taken safely by hundreds of thousands of adults.

CIRT is currently enrolling adults who within the past 5 years have had an MI or were diagnosed with coronary artery disease in >1 coronary artery. Patients must also have either diabetes mellitus or metabolic syndrome, 2 conditions with a high inflammatory state. For more information about the study, visit the trial website at www.theCIRT.org.

Additional Resources


Cardiovascular Inflammation Reduction Trial website. www.theCIRT.org.


American Heart Association website. www.heart.org.
Inflammation and Myocardial Infarction
Kathryn H. Melamed and Samuel Z. Goldhaber

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