Inflammation and Myocardial Infarction
Kathryn H. Melamed, MD; Samuel Z. Goldhaber, MD

Myocardial Infarction: More Complex Than Plumbing
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.

Figure. Formation of an atherosclerotic plaque in the coronary arteries. This is a cross-sectional view (horizontal slice) of a coronary artery with an atherosclerotic plaque. The fibrous cap is made up of a strong material called collagen that is protecting the blood stream from the lipid core. In addition to cholesterol and fats, the lipid core contains white blood cells, which are the inflammatory cells in the body. If the fibrous cap breaks, these inflammatory cells are exposed to the blood stream. A chain reaction then occurs that results in accumulation of platelets, clotting factors, and other cells, leading to rapid obstruction of the coronary artery and subsequent MI.

Statins, 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 rosvastatin, 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.

### Table. Causes of Inflammation and Strategies to Modify Their Risk

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<th>Cause</th>
<th>Modifiable Action</th>
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<tr>
<td>Cigarette smoking</td>
<td>- Smoking cessation groups or group therapy&lt;br&gt;- Telephone quit lines (eg, 1-800-QUIT-NOW)&lt;br&gt;- Text message or web-based computer assistance programs (eg, SmokefreeTXT, QuitSTART App, Smokefree.gov)&lt;br&gt;- Over-the-counter nicotine replacement therapy: gum, patch, lozenges, sublingual tablet, inhaler, nasal spray, mouth spray&lt;br&gt;- Prescription medications*: bupropion, varenicline&lt;br&gt;- Electronic cigarettes (highly controversial)</td>
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<tr>
<td>Excessive alcohol use</td>
<td>- Alcohols Anonymous or other 12 step programs&lt;br&gt;- Behavioral therapy&lt;br&gt;- Detoxification programs†&lt;br&gt;- Rehabilitation programs (inpatient or outpatient)†&lt;br&gt;- Prescription medications*: naltrexone, acamprosate, disulfiram</td>
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<td>Obesity</td>
<td>- Exercise: at least 30 min per day for 6 days per week&lt;br&gt;- Dietary changes: eg, low-carbohydrate, low-fat, portion control&lt;br&gt;- Weight loss and diet program: eg, Weight Watchers, Jenny Craig, South Beach&lt;br&gt;- Advice from a nutritionist or dietician&lt;br&gt;- Individual or group therapy&lt;br&gt;- Prescription medications*: orlistat, lorcaserin&lt;br&gt;- Weight reduction surgery (often called gastric bypass surgery)‡</td>
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<td>Immobility</td>
<td>- Exercise: at least 30 min per day for 6 days per week&lt;br&gt;- Take the stairs instead of the elevator&lt;br&gt;- Take a walk while talking on the phone&lt;br&gt;- Walk around a mall if no other space is available&lt;br&gt;- Join the Fitbit Challenge</td>
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<tr>
<th>Cause</th>
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| Metabolic syndrome or prediabetes | Strategies to prevent diabetes mellitus:  
- Weight loss and diet as described above  
- Prescription medications*: metformin |
| Hypertension                 | Strategies to reduce blood pressure:  
- Weight loss and diet as described above, with particular attention to a low salt and high fiber diet and limited alcohol intake  
- Prescription medications*: your primary care physician or cardiologist should select the correct blood pressure lowering medication among the many available choices |
| Obstructive sleep apnea      | Strategies to combat obstructive sleep apnea:  
- Weight loss and diet as described above  
- Avoid sleeping on the back  
- Avoid alcohol and sedating medications (eg, benzodiazepines, opiates), particularly at night  
- CPAP or BiPAP machine§  
- Corrective upper airway surgery¶  
- Dental appliances |
| Anxiety or depression        | - Psychosocial support from family and friends  
- Support groups  
- Individual or group psychotherapy  
- Prescription medications*: see your internist or mental health professional |
| Autoimmune diseases (eg, rheumatoid arthritis, systemic lupus erythematosus) | - Prescription medications*: see your primary care physician or rheumatologist, treatment varies based on disease |
| Periodontal disease          | - Daily flossing and twice daily teeth brushing  
- Visit the dentist every 6 months for teeth cleaning  
- Follow recommendations from your dentist for further oral hygiene |
| Infection                    | - Seek medication attention if you are concerned that you have a serious infection that may require antibiotics  
- Signs of infection often include temperature >100.4°F, heart rate >90 bpm, muscle aches, generalized fatigue |

*The use of prescription medications should be decided on by your primary care physician or other health care providers.  
†† If addicted to alcohol, complete cessation should be done in an observed medical setting because of the risks of alcohol withdrawal. If concerned, please contact your doctor.  
‡ Gastric bypass surgery requires consultation from a multidisciplinary team to determine whether a patient qualifies for and would benefit from weight loss surgery.  
§ Diagnosis of sleep apnea and prescription for a CPAP or BiPAP machine requires a sleep study or consultation with a Sleep Medicine specialist.  
¶ Corrective surgery may not be appropriate for all patients with sleep apnea and requires consultation with a head and neck surgeon.

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.the-CIRT.org.


American Heart Association website. www.heart.org.

Disclosures

Dr Goldhaber reports the following disclosures: Research grants: BMS, Daiichi Sankyo, BTG, NHLBI, Thrombosis Research Institute (London, UK); Consultant: Ariad, Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Merck, Pfizer, Portola. Dr Melamed reports no conflicts.
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Circulation. 2014;130:e334-e336
doi: 10.1161/CIRCULATIONAHA.114.010614
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/130/24/e334

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