Antiplatelet Therapy

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Blood clots can be especially dangerous for patients with heart disease. The present article presents information about how blood clots form, how they are treated, and how they might be prevented.

Platelets, Blood Clotting, and Heart Disease

Platelets, small elements that circulate normally in the bloodstream, help the body defend itself against bleeding and blood loss. They do this by sticking together and helping in the formation of a clot at the site of bleeding. Although this process of creating a blood clot, which is called thrombosis, is beneficial in a person with severe bleeding, it can also cause problems, particularly when a blood clot forms in the circulation of the heart or brain. A heart attack (myocardial infarction) results when a blood clot interrupts or blocks blood flow to the heart, which starves the heart muscle of oxygen and causes heart muscle cells to die; the same process in the brain causes a stroke (cerebral infarction).

Under normal healthy conditions, the different parts of flowing blood (such as red and white blood cells and platelets) are unable to stick to the inner lining of blood vessels and cause a blockage that disrupts blood flow. However, when there is a buildup of fatty deposits (atherosclerosis) within blood vessels, the lining of the vessels (the endothelium) is less resistant to blood clotting.

A variety of stimuli, including high blood pressure, high blood sugar, and poisonous chemicals like tobacco components may make atherosclerotic fat deposits (plaques) unstable. This is particularly true when plaques are rich in fat (cholesterol) and white blood cells (inflammatory cells). An unstable plaque may crack or rupture and expose its contents to flowing blood. In its own defense, the body attempts to heal this injury by forming a blood clot over the damaged area.

The formation of a blood clot occurs in several steps (see Movie). First, platelets adhere to the plaque surface. They then begin to stick together in a process known as aggregation. The growing platelet aggregate forms a surface on which the process of coagulation can occur: Through a series of enzymatic reactions, red strands that mesh together to become a net-like substance (fibrin) form, linking platelets together, red blood cells are trapped within the fibrin meshwork, and a blood clot results.

Thus, platelets play a key role in the body's response to injury in an artery and in beginning the process of forming a blood clot. Interrupting that process has become an important part of the battle against heart disease and stroke.

Antiplatelet Therapies

Drugs that interfere with platelet function can be classified into 3 categories: Those that prevent cardiovascular disease (primary prevention), those that treat an acute disease, and those that treat a chronic disease (secondary prevention) (Table). There are both oral (taken by mouth) and intravenous (given through a vein) drugs that inhibit platelet function and are used to treat patients with cardiac and cerebrovascular diseases.

Aspirin

Aspirin is the cornerstone of treatment for patients with any vascular disease,[1] having been used as a medical product for over 100 years. Although it is not advised for most healthy people to prevent a first heart attack or stroke, it does offer some protection for older (>50 years of age) individuals at high risk, including smokers or those with diabetes or a family history of atherosclerotic disease at an early age. In

From the Duke Clinical Research Institute, Durham, NC.

The Movie is available as an online-only Data Supplement at http://www.circulationaha.org.

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Roles of Antiplatelet Therapies in Preventing and Treating Heart Diseases

Antiplatelet Therapy	Primary Prevention	Acute Indications	Secondary Prevention
Aspirin	Patients at high risk of heart attack or stroke (including those with an older age, history of early heart disease, diabetes, etc)	Heart attack Unstable angina Stroke Coronary angioplasty Coronary bypass surgery	Heart attack Unstable angina Stroke Coronary angioplasty Coronary bypass surgery
Clopidogrel	Studies currently underway	Heart attack Unstable angina Coronary angioplasty	Heart attack Unstable angina Coronary stenting
Glycoprotein IIb/IIIa Inhibitors	Not appropriate	Heart attack Unstable angina Coronary angioplasty	Not appropriate

studies involving more than 100 000 patients, aspirin has been shown to reduce the risk of dying from a heart attack or stroke when it is given in the early hours after symptoms begin. Patients who undergo invasive procedures such as coronary angioplasty/stenting or coronary artery bypass surgery also benefit from aspirin (for more information about coronary artery bypass surgery, please see the Cardiology Patient Page by Mullany [Coronary artery bypass surgery. *Circulation*. 2003;107:21–22]; for more information about angioplasty, please see the Cardiology Patient page by Michaels and Chatterjee [Angioplasty versus bypass surgery for coronary artery disease. *Circulation*. 2002;106:187–190]). Given before and after these procedures, it reduces the risk of heart attack and stroke. Once a patient has had a heart attack, a stroke, or an episode of chest pain (angina), daily treatment with aspirin substantially reduces the risk of a second heart attack or stroke. Aspirin is also extremely economical, costing only pennies a day for generic brands.

Although the benefits of prolonged aspirin use are now well known by healthcare providers, the best dose of aspirin is unknown. There is evidence to support dosages that range from a baby aspirin or less (81 mg) through a full standard aspirin (325 mg). Because there are no definite dosing data, most cardiologists recommend 160 to 325 mg as a daily dose and accept a dose of 81 mg/d as probably enough for patients who have side effects with higher doses (see Risks of Antiplatelet Therapies below).

Clopidogrel

Clopidogrel is a fairly new drug that reduces the risk of vascular events when it is given with aspirin to patients who have unstable chest pain or angina or certain types of heart attacks.[2] When taken regularly after a heart attack or stroke, its benefits are similar to those of aspirin. Clopidogrel works by interfering with one of the ways that platelets stick together. Although no conclusions have yet been reached about the benefits of clopidogrel for patients with other heart ailments, more extensive studies are underway to examine its effect among patients with stroke and those at high risk of heart attack or stroke.

Glycoprotein IIb/IIIa Inhibitors

By studying families who have an inherited disorder of their platelets, investigators have learned that platelets stick together by binding a protein in the blood (fibrinogen), to a certain site on the surface of the platelet, the glycoprotein IIb/IIIa receptor complex. Blocking fibrinogen's ability to bind to the glycoprotein IIb/IIIa receptor dramatically interferes with what platelets typically do, thus decreasing blood clotting. The drugs that do this are the glycoprotein IIb/IIIa inhibitors, and they are a wonderful example of drugs that are designed to interfere with a specific biological process (in this case, platelet function).[3] The glycoprotein IIb/IIIa inhibitors are given intravenously to patients who are undergoing coronary angioplasty/stenting or to high-risk patients with unstable angina or a particular type of heart attack. Their benefits have been especially noteworthy with coronary angioplasty, where they reduce the occurrence of acute complications (death, heart attack, or the need for an urgent second procedure, such as bypass surgery). Unfortunately, efforts to find an oral form of these drugs have been unsuccessful; it had been hoped that they would be another oral wonder drug, similar to aspirin, but clinical trials have all been negative.

Risks of Antiplatelet Therapies

Because all antiplatelet drugs interfere with normal blood clotting, the most common side effect or risk associated with using them is bleeding. Bleeding risks range from the very minor (such as nose bleeds) to major, life-threatening events (such as bleeding into the brain). Fortunately, most of the bleeding risk is mild, is non-life–threatening, and does not require a blood transfusion. Among patients being treated with antiplatelet therapies for acute heart attacks and strokes, the most common sites of bleeding are locations where vascular catheters, like intravenous catheters, have been inserted, including the site (usually in the groin) used for access during coronary angioplasty. Less common is

bleeding from the stomach or urinary tract. When there is bleeding from these locations after treatment with antiplatelet drugs, a careful evaluation of the source is needed, as frequently such bleeding comes from previously undetected disease like peptic ulcers or cancer. Other important risks associated with antiplatelet drugs are unusual, such as allergy or hives with aspirin or low platelet count (thrombocytopenia) with the glycoprotein IIb/IIIa inhibitors.

Summary

Blood clotting is an important method the body uses to respond to tissue injury and to prevent blood loss. Clotting at the site of an atherosclerotic plaque, however, can have dire consequences, including heart attacks and strokes. Because platelets play a critical role in the clotting process, therapies directed against platelets are some of the most important in the battle against vascular diseases of the heart and brain. Although the benefits of antiplatelet drugs are well known, there are also bleeding risks that need to be considered. Most of this risk is manageable with careful attention to the patients who are selected for antiplatelet therapy, to the doses they receive, and to monitoring these patients for side effects.

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References

1. US National Library of Medicine and National Institutes of Health. MEDLINE plus health information: aspirin. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a682878.html. Accessed July 18, 2003.
2. US National Library of Medicine and National Institutes of Health. MEDLINE plus health information: clopidogrel. Available at: http://www.nlm.nih.gov/medlineplus/druginfo/medmaster/a601040.html. Accessed July 18, 2003.
3. Yale New Haven Health. Glycoprotein IIb/IIIa inhibitors for heart attack and unstable angina. Available at: http://yalenewhavenhealth.org/library/healthguide/IllnessConditions/topic.asp?hwid=tx4284. Accessed July 18, 2003.