"Blood Thinners" Coumadin, Heparin, and Coagulation Laboratory Testing

Coumadin® and Heparin are Anticoagulants

"Blood thinners" don't really thin the blood. They are *anticoagulants*, prescription drugs that either keep existing blood clots from growing larger or prevent new clots from forming. Normal clotting is essential to stop blood loss after an injury. But abnormal clotting or *thrombosis* is clotting that happens when there is no apparent injury. An abnormal clot in a blood vessel is called a *thrombus*, and it may completely plug the vessel. For example, a thrombus may plug an artery that provides blood to the heart muscle, causing a heart attack, or *acute myocardial infarction*. Or a clot may plug a large leg vein, causing *deep venous thrombosis*. Pieces of venous clots may break off, travel to the lungs or brain, and plug an artery. These pieces are called *emboli*. An *embolus* that travels to the brain causes a stroke. One that goes to the arteries in the lungs is called a *pulmonary embolism*, often fatal.

Anticoagulants are prescribed after a *thrombotic event*. They are also prescribed to *prevent* thrombotic events in high-risk situations. Table 1 lists typical thrombotic events and situations that require anticoagulant therapy.

Table 1: Thrombotic events that require anticoagulant therapy

Peripheral artery disease	PAD	A clot forms in an artery other than arteries of the heart such as a *carotid* artery in the neck, reducing the blood supply to that region.
Acute myocardial infarction	AMI	A clot forms in an artery of the heart, called a *coronary* artery, cutting off the blood supply to a portion of the heart muscle. This is usually called a heart attack.
Cerebrovascular accident	CVA	A clot forms in an artery of the brain, reducing the blood supply and causing the loss of brain tissue. This is usually called a stroke.
Transient ischemic attack	TIA	A small clot in an artery of the brain causes a temporary loss of memory, loss of balance, unconsciousness, or other temporary *neurological* symptoms.
Deep venous thrombosis	DVT	A clot forms in a large vein in the calf or the leg, causing pain, swelling, a sensation of heat, and redness. Some DVTs cause a long-term disability called *post-phlebitic syndrome*.
Pulmonary embolism	PE	A clot forms in a large vein in the leg, a portion breaks off and travels to the lung, causing death of lung tissue and shortness of breath. May be rapidly fatal.
Atrial fibrillation	AFIB	A mild irregularity in the heartbeat causes the formation of clots in the *atria* of the heart that travel to the brain to cause a CVA.
Orthopedic surgery and other major surgery		Doctors prescribe anticoagulants to people who are *at risk* of a thrombotic event, such as people who have had hip or knee replacement surgery

A Typical Case Requiring Anticoagulant Therapy

John arrives in the emergency department with severe chest pain. The nurse immediately gives him an aspirin. A technician performs an EKG and a laboratory scientist draws blood for laboratory tests. The results soon show that John has an AMI. The doctor treats him with an intravenous *thrombolytic* "clot buster" drug to reopen the clogged artery.

Soon, John is started on intravenous *heparin* and on *Coumadin*® pills. About three days after he is admitted he goes to the catheterization laboratory where a *stent* is placed in the artery to keep it open. He suffers no complications, the heparin is discontinued in five days, and he is discharged on the sixth.

John must continue to take oral Coumadin® for six months. Although a typical dose is one 5-milligram tablet a day, the dosage varies by individual and it varies over time. Once a month he comes to the hospital laboratory or an outside laboratory to have a blood test called a prothrombin time ("protime," PT), and he has to adhere to a "Coumadin® diet" until the end of the therapy.

John also takes *antiplatelet* drugs; aspirin and Plavix®. He will discontinue the Plavix® after one year but will continue taking one baby aspirin a day for the rest of his life.

What Is Heparin For?

Heparin is an immediate-acting anticoagulant that has been used successfully since 1945. It is administered intravenously, so it is convenient only for inpatients. Also, heparin actually *causes* thrombosis in about 1% of patients, so it has to be carefully monitored by daily laboratory testing.

How Does the Laboratory Test for Heparin?

During the first day that John was getting his IV heparin, his blood was drawn every six hours. During days two through four, his blood was collected every 24 hours. The specimen went to the laboratory, where scientists performed the *activated partial thromboplastin time* (APTT or PTT) test.

Heparin affects everyone differently, so there is no standard dose. The doctor or nurse must repeatedly adjust the heparin dosage to achieve and maintain a *therapeutic* PTT result. In John's hospital, the therapeutic PTT value was *65 to 95 seconds*, but this varies by the hospital.

If the PTT shortens to below the therapeutic range, John would be in danger of having a second heart attack. Often second attacks are fatal. PTT results that are longer than the high limit indicate a risk of bleeding.

What is Coumadin® For?

Coumadin® is the only anticoagulant that can be taken orally, so it is used for long-term anticoagulant therapy. It is one of the top twenty most prescribed drugs in the United States and comes in at least four forms as are listed in table 2.

Table 2: Names of the various forms of oral anticoagulants

- Coumadin (most common brand)
- Warfarin (oldest brand name)
- Coumarin
- Dicumarol

The various forms of Coumadin all work the same and are reliable, although the required dosage may vary by brand. It takes Coumadin about five days to become effective and therapy

usually lasts for six months or longer, depending upon the patient's condition. For example, people with atrial fibrillation may take Coumadin their whole lives to prevent a stroke, people with an AMI are usually treated for six months.

Coumadin is Dangerous and Hard to Control

Coumadin prevents a new clot from forming or an existing clot from growing. If a patient is taking too little Coumadin, it will not provide this protection and a new clot may form. Conversely, too much Coumadin causes bleeding, often severe enough to require hospitalization.

The Coumadin dosage is hard to control. There are at least 100 drugs (table 3) that affect Coumadin, either by increasing or decreasing its effect. Further, green vegetables decrease Coumadin, and some dietary supplements may either decrease or increase Coumadin, so careful dosage adjustments are needed (tables 4 and 5). Some drugs and supplements affect *platelets*, blood cells that help in blood clotting, thereby increasing the risk of bleeding.

Table 3: Classes of drugs that may either increase or decrease the effect of Coumadin

- Antibiotics of many types
- Anti-inflammatory drugs including aspirin and ibuprofen
- Anti-malarial drugs such as quinidine
- Anti-seizure drugs such as Dilantin®
- Chemotherapy for cancer
- Drugs for treatment of gout
- Drugs for treatment of stomach disorders
- Lipid lowering drugs such as Pravachol® or Lipitor®
- Psychiatric drugs like Thorazine®

Table 4: Foods and dietary supplements that reduce the effect of Coumadin

- Coenzyme-Q, a free radical scavenger
- Ginseng and green tea
- Green leafy vegetables and salads
- Green tea
- Liver

Table 5: Dietary supplements that appear to increase the effect of Coumadin or that contribute to bleeding by disabling platelets

- Angelica root
- Anise
- Chamomile
- Dong quai
- Feverfew
- Garlic
- Ginger
- Ginkgo biloba
- Meadowsweet (aspirin-like substance from Spirea shrub)
- Papain (papaya-based tenderizer)
- Vitamin E, an antioxidant

How Does the Laboratory Test for Coumadin? The INR

Let's return to our case. When John started getting his IV heparin, he also started taking Coumadin. The same blood specimens that went to the laboratory for a PTT to monitor heparin were used to perform a second test, the prothrombin time (PT). The PT is similar to the PTT, but it is more sensitive to Coumadin and the result is reported not in seconds but as an international normalized ratio (INR).

The INR is the ratio between the time it takes normal blood to clot and Coumadin blood to clot. The more Coumadin, the higher the INR. Most people taking Coumadin should have an INR between 2 and 3. An INR below 2 signals the danger of a new clot, whereas an INR over 4 means a risk of dangerous bleeding. The INR, as the name implies, is international, so it should be comparable no matter where the test is performed.

While he was in the hospital, John's PT was tested once a day until it reached an INR between 2 and 3. Then it was tested once every two weeks for the first three times, and then once a month for as long as he took Coumadin. Why once a month? Coumadin dosages need constant adjustment as we change our diet, our habits, or our other medicines. If John waits two months to have his PT performed, his INR could drift out of control.

Doctors and patients would prefer to use substitutes for heparin and Coumadin that are safer and require less laboratory testing, and researchers everywhere are looking for these new drugs. Until they are successful, however, regular laboratory testing is the only answer.

For more information, contact the UAB Coagulation Service

George A. Fritsma MS MT (ASCP)
Coordinator, UAB Coagulation Service
P: 205-934-1348; F: 205-975-4468