THROMBOTIC THREAT

VASCULAR CLOTTING CALLS FOR A COLLABORATIVE RESPONSE

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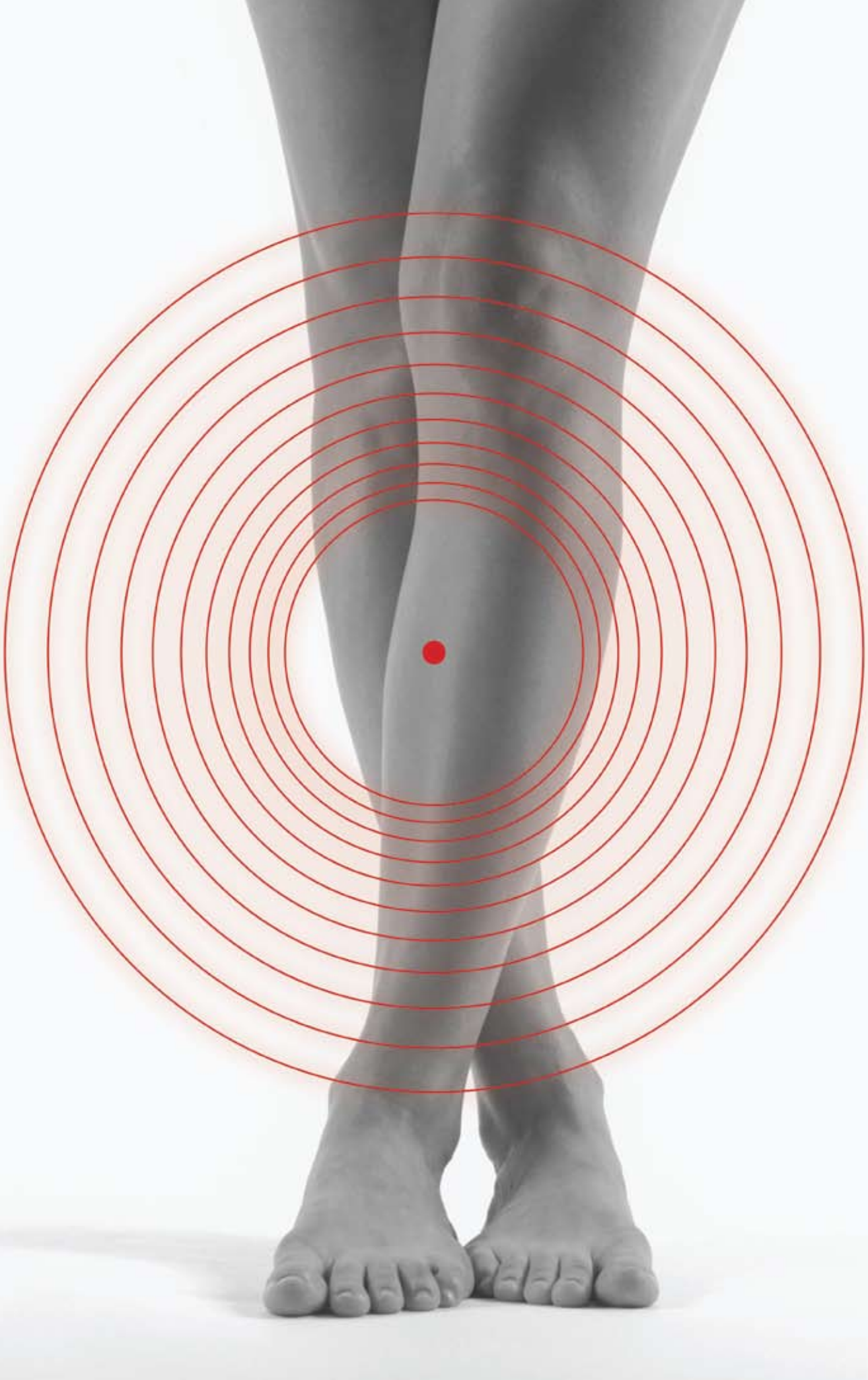

A little leg pain, no big deal. Or so the 15-year-old tennis champ thought. It was early summer, and Elizabeth Baiardi had just won a state singles title and helped her Birmingham, Michigan, high school team clinch the Division 3 state championship. All the hours of practice that went into those victories were bound to result in some muscle aches, Baiardi told herself as she settled into her family's Harbor Springs summer home on Lake Michigan for a few months of swimming, sunning and, of course, more tennis. When the pain kept dogging her, she saw a local physician who diagnosed a pulled hamstring and assured her ibuprofen should take care of it.

It didn't.

Eight days later, Elizabeth was in the emergency room at Northern Michigan Regional Hospital with pain that had traveled from her left thigh to behind her knee. After examining her, the ER team ran tests to rule out a blood clot. To the shock of Elizabeth and her parents, the results came back positive, and ultrasound subsequently revealed extensive clotting from hip to ankle.

"We'd never heard of anything like this in such a young woman," her mother, Cindy Baiardi, recalls. "It was completely unexpected." Later, the family would learn that an anatomical anomaly put Elizabeth at risk for deep-vein problems, including clot formation, and that the condition is not uncommon in young women. But that weekend, they were blindsided by the news and stunned at the prospects. As with any blood clot in a deep vein, there's a danger that the clot will break free and travel through the heart into the lungs, resulting in pulmonary embolism — a condition that kills some 300,000 Americans every year.

When initial treatment failed to dissipate the clot, the U-M-trained vascular surgeon who was caring for Elizabeth sent her to the U-M Cardiovascular Center (CVC) for the coordinated, multi-specialty care that is its hallmark.

With the opening of the CVC's new Venous Disease Clinic this fall, integrated care has become even easier to provide, and the experience is more seamless for patients.

"The clinic is designed specifically to facilitate a collaborative, multidisciplinary approach, with vascular surgeons, vascular medicine specialists, interventional radiologists and nurse practitioners sharing clinic space, diagnostic facilities and waiting rooms," says James Froehlich, M.D. (Residency 1996), M.P.H., who heads the clinic. "Any patient with venous disease can be seen here. Whether it's a mild, cosmetic venous problem or a limb-threatening, disabling condition, we can offer complete care without the patient having to go to other facilities to see other specialists or practitioners for further diagnostic or therapeutic interventions."

Few, if any, other centers offer such a complete venous disease treatment program, says James Shields, M.D. (Residency 1978), assistant professor of radiology and director of the Division of Vascular and Interventional Radiology.

The center is notable not only for the breadth of medical expertise represented, but also for the depth. "The physicians who are involved have a lot of experience," says Shields. "The other thing that's unique is the willingness on the part of the people who do interventions to take on very complex cases. The surgical or interventional corrections for these complex problems are often procedures that require four hours at a time and two or three visits to the operating room over the course of a few days, along with care in the intensive care unit, and there just aren't very many people who are willing to take this on."

In addition to improving patient care, the one-stop clinic makes it easier for referring physicians to figure out where to send patients, no matter what type of vein problem they have. "They don't have to choose which provider is appropriate for which patient," says Froehlich. "They don't even have to know what provider is here doing this sort of work. And in addition to referral services, we also plan to offer consultative or even educational services to help physicians — especially those who are some distance from Ann Arbor — manage these problems themselves."

The clinic's opening is timely: In September, the Office of the U.S. Surgeon General announced a Call to Action

to focus attention on venous thrombosis as a serious public health threat. The campaign is similar to those launched in the 1960s to discourage cigarette smoking and in the 1980s to raise awareness of AIDS, says Thomas Wakefield, M.D. (Residency 1984, Fellowship 1986), professor of surgery and head of the Section of Vascular Surgery, who was an invited speaker at the 2006 conference that set the stage for the current Call to Action.

"It was gratifying to hear the surgeon general recognize this national health problem," Wakefield said after returning from this year's conference. "We need such a public awareness campaign, and we also need new research in order to improve the care that we currently give."

THE SURGEON GENERAL HAS ANNOUNCED A CALL TO ACTION TO FOCUS ATTENTION ON VENOUS THROMBOSIS, SIMILAR TO CAMPAIGNS LAUNCHED IN THE 1960S TO DISCOURAGE SMOKING AND IN THE 1980S TO RAISE AWARENESS OF AIDS.

In Elizabeth Baiardi's case, coordinated care meant that she could undergo a series of treatments and surgical procedures over a three-day period and be monitored during her recovery in one place, by a team of physicians working closely to deliver the most appropriate therapy.

The root of her problem, the team determined, was a condition known as May-Thurner syndrome. It's not a disease, but an anatomical variation that can lead to narrowing of the left iliac vein, which snakes up from the left leg into the vena cava (the large vein that returns blood from the legs and abdomen to the heart). The left iliac vein is overlain by the right iliac artery, which supplies the right leg with blood. Usually that arrangement is not a problem, but in May-Thurner syndrome, pressure from the artery causes the vein to narrow, obstructing blood flow and causing swelling and pain in the left leg. Clots can also form in the narrowed vein, as happened in Elizabeth's case.

May-Thurner syndrome is especially common after pregnancy, when the expanding uterus adds to the pressure on the vein, but it's also seen in young women who never have been pregnant, and physical fitness is no insurance policy. While Elizabeth was undergoing treatment, her grandmother researched the condition online and learned that 25-year-old Olympic cross-country skier Kikkan Randall had

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been diagnosed with May-Thurner syndrome a few months earlier, after a clotting episode much like Elizabeth's.

The venous disease team at the U-M has more than a decade's experience treating patients with May-Thurner syndrome and published a paper in the *Journal of Vascular Surgery* last year on their approach. Elizabeth's treatment, which was typical, involved an aggressive attack with a combination of clot-dissolving medication and catheter-guided devices to mechanically remove clots. In addition, interventional radiologist David Williams (M.D. 1979, Residency 1983) inserted a stent to widen the narrowed portion of the vein, and Wakefield performed a surgical procedure in which a branch of the vein is temporarily connected to the side of an artery in order to push more blood through the vein and prevent re-clotting.

The decision about how aggressively to treat a patient with a clot isn't an easy one. The traditional, conservative approach — using only blood-thinning medication — is quite effective in preventing the clot from breaking off and causing pulmonary embolism, but doesn't forestall the suite of distressing and sometimes disabling physical problems that often occur some time after a clotting incident.

"There's a 30-50 percent incidence of what we call the post-thrombotic syndrome after somebody's had a clot, which means pain and swelling in the leg and even ulcerations in hard-to-heal areas on the extremities," says Wakefield. "We know that if you get rid of the clot, you can decrease the incidence of that problem, but the treatment for getting rid of the clot is more extensive than just giving the patient blood-thinning medicine."

Sometimes a patient's age and health status dictate how aggressive the treatment should be, but in other cases, it's not as clear whether the benefits outweigh the costs. A large-scale study aimed at clarifying the issue began this fall, and the U-M is one of about 50 participating institutions nationwide. The study will compare standard treatment — blood thinners, compression stockings and reliance on the body's own methods of breaking down clots — with newer, catheter-based methods of directly dissolving and removing the clot. Patients will be evaluated at the end of the study on both medical and quality-of-life outcomes.

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As for the teenage tennis champ, who now tosses around terms like "thrombolysis" as handily as she returns a serve, she couldn't be more pleased with the outcome of her treatment.

"I'm pretty much back to normal," she reported midsummer. "I'm playing tennis a lot — an hour to an hour and a half every day — and I'm swimming and working at a tennis club."

While stories like Elizabeth's aren't unusual, young women certainly aren't the only people at risk for developing deep vein thrombosis (DVT) — abnormal clotting in a deep vein, most commonly in the lower leg or thigh. Being over age 60, using hormone-based contraceptives or hormone therapy for menopause, having certain chronic illnesses such as cancer or heart disease, undergoing lengthy surgery or hospitalization or having an inherited clotting disorder such as Factor V Leiden ups the odds. Smoking, obesity and sitting for hours at a time, as on long flights, also increase clotting risk, and the factors are additive — the more you have, the greater the threat.

"As our understanding of risk has gotten more refined," says Froehlich, "we've come to realize that some risk factors, namely age and obesity, are increasing in our population rather dramatically."

The Health System has a number of efforts underway to help prevent DVT. One such study involves risk-assessment for every patient admitted to the hospital, determining who may benefit from anti-clotting medications (known as anticoagulants or blood thinners) to reduce their risk for DVT. Not everyone who undergoes surgery or a long hospital stay will develop a clot, so treating everyone with blood thinners isn't a good idea, especially given the side effect of increased risk for excessive bleeding.

"Currently, only broad guidelines exist for this risk stratification process," says vascular surgeon Peter Henke, M.D. (Residency 2000), who is involved in the research. "We're working on a way to assign patients to risk categories in a standardized and validated fashion, based on a scoring system devised by a surgeon at Northwestern." If preliminary results hold true, it appears that the scoring system is a reliable tool for making decisions about preventive use of blood thinners.

Other research projects are delving even further into DVT — all the way to the molecular level. Wakefield's lab is homing in on a molecule called P-selectin that's known to be involved in inflammation. Inflammation and clot formation are interrelated — typically clotting occurs in a vein after the vein's inner lining becomes activated and inflamed — and Wakefield's group is looking at ways of squelching clot formation by inhibiting P-selectin. This approach leaves the hemostatic process intact, reducing the risk of excessive bleeding, but discourages the formation of troublesome clots in veins by damping down inflammation.

In September, Wakefield, Henke, Jobst Vascular Research Laboratories Director Daniel Myers, D.V.M., and Medical School colleagues received a five-year, $3.6 million grant, to be shared with researchers at Harvard University and the biopharmaceutical company Archemix Corp., to develop inhibitors of P-selectin and von Willebrand factor, a protein involved in clotting.

Wakefield's research is still in early stages, but in the meantime, new blood thinners are being developed that attack the clotting system in different ways. They are easier to administer and require less monitoring than traditional blood thinners, says Froehlich, and the Venous Disease Clinic offers the most up-to-date medications available.

On a shelf in Wakefield's office, alongside snapshots and awards, is a note card decorated with a summery design of flip-flops and bright flowers on a sand-colored background with a wavy edge like surf on a northern Michigan beach. The message inside praises Wakefield not only for his surgical skill, but also for his bedside manner.

"He's probably one of the nicest doctors I ever met," Elizabeth Baiardi says in explaining what prompted her to write the note. "He took really good care of me." [M]

ABOUT VENOUS DISEASE

Deep vein thrombosis (DVT) is abnormal clotting of the blood in a vein deep in the body, usually the lower leg or thigh.

Pulmonary embolism (PE) occurs when a clot breaks free from its original site in a vein and travels through the heart and into the lungs. PE can damage the lungs and other organs and may result in death.

Venous thromboembolism (VTE) is an umbrella term that includes DVT and PE.

- VTE affects nearly 1 million Americans every year, many of whom are hospitalized as a result.
- About 300,000 Americans die of PE every year.
- Deaths from PE are five times more common than deaths from breast cancer, car crashes and AIDS combined.
- VTE is the third most common vascular disease, after heart disease and stroke.
- VTE affects men, women and children; however, women are more likely than men to develop VTE. The use of oral contraceptives and hormone therapy accounts for some of that discrepancy.
- The risk of VTE increases with age.
- VTE is potentially life-threatening, but treatable and largely preventable.

What causes deep vein thrombosis?
Blood clots can form in the body's deep veins when:

- Damage occurs to a vein's inner lining. Surgery, serious injury, inflammation or an immune response can cause such damage.
- Blood flow is sluggish or slow. This can happen when a person's movement is restricted after surgery, during illness or on long trips.
- Blood is thicker or more likely to clot than usual. Certain inherited conditions, such as Factor V Leiden, increase the blood's tendency to clot, as does treatment with hormone therapy or birth control pills.

Sources: National Heart Lung and Blood Institute, Venous Disease Coalition