Too Close for Comfort: Heart Disease & Diabetes

by Sona Iyengar | photography by Raj Chawla

(Above) BARI 2D study participant Pete Schoch meets with his cardiologist, David Schneider, M.D., one of the researchers working on the study. (Right) BARI 2D researcher and diabetologist Richard Pratley, M.D.
Physician-researchers at the University of Vermont are on the leading-edge of international research that seeks to understand the link between heart disease and diabetes — with the goal of developing new treatments to reduce the risk of death. A newly published, ground-breaking study fuels these efforts.

It was a beautiful fall day when Pat Schoch got in the car with her husband Pete to drive to the health center in Ticonderoga, New York. Three days before, Pete, a volunteer fireman and a diabetic, had returned from an accident scene feeling exhausted, and he’d felt rotten ever since.

“I had a feeling that something wasn’t right,” Pat says. “I remember him saying ‘Don’t drive too fast.’”

At the health center, the physician assistant took an EKG and found out Pete, 63, had had a heart attack. He was transported to Fletcher Allen Health Care in Burlington and ultimately recovered from the attack.

Four years later, Pete returned to Fletcher Allen for triple bypass surgery. It was then that his physician, David Schneider, M.D., UVM professor of medicine and director of cardiology at Fletcher Allen, asked if he wanted to participate in a research study called Bypass Angioplasty Revascularization Investigation 2 Diabetes — or BARI 2D. The study looked at ways to treat patients with type 2 diabetes and stable coronary artery disease.

“I thought it would be a good idea,” Pete says. And it was. Over the next six years, doctors, nurses and dieticians closely monitored his condition, helping him manage his diabetes and treating his coronary symptoms effectively. Schoch was fortunate to come to UVM/Fletcher Allen for his treatment, since Vermont’s academic medical center is one of 49 sites around North America participating in the monumental BARI project, and is the home of Burton Sobel, M.D., principal investigator of the fibrinolysis and coagulation core laboratory component of the study and one of the key figures behind its conception. The BARI 2D results, published in the New England Journal of Medicine in June, indicated that type 2 diabetes patients with clinically stable coronary disease benefitted equally from medical therapy alone, as opposed to medical therapy plus intervention. It also pointed to increased benefit of insulin sensitizing medication for diabetics stratified as suitable candidates for coronary bypass grafting. In addition, a group of higher-risk patients had more favorable outcomes with coronary artery surgery compared with medical management alone. “So we need to do a better job of identifying those kinds of patients going forward,” says Sobel. In addition to BARI 2D, UVM is participating in several additional clinical trials focused on understanding and controlling cardiovascular risk in people with diabetes. (See page 23.)
“All these studies we’ve participated in help guide us in the development of new studies of diabetes and cardiovascular disease,” says Richard Pratley, M.D., professor of medicine and a UVM/Fletcher Allen endocrinologist and principal investigator on the BARI 2D trial. “There are going to be a lot more diabetes and cardiovascular disease trials and I think diabetes specialists and cardiologists are going to be working together more and more.”

**Preventing the risk of cardiovascular disease**

Today in the United States, 23.6 million people — approximately 8 percent of the population — have diabetes. Patients with this chronic disease, which is characterized by high blood sugar levels and linked to obesity — are more likely to develop high blood pressure, plaque in their arteries and have at least twice the risk of heart failure. An additional 57 million people have pre-diabetes, in which blood glucose levels are above normal and likely to pass the threshold for diabetes. At least two-thirds of all deaths in people with diabetes are caused by cardiovascular disease. In addition, heart attacks occur at an earlier age in people with diabetes and often result in premature death. BARI 2D was designed to compare the effectiveness of various therapeutic regimens in reducing the number of deaths from coronary artery disease among people with type 2 diabetes.

Coordinated by the University of Pittsburgh’s Graduate School of Public Health, with funding from the National Heart, Lung and Blood Institute, the National Institute of Diabetes and Digestive & Kidney Disease and GlaxoSmithKline, the BARI 2D study enrolled 2,368 patients between 2001 and 2005 at 49 clinical sites in North America, South America and Europe.

The trial sought to determine in patients with type 2 diabetes whether initial treatment with angioplasty or bypass surgery is better than initial treatment with medical therapy. At the same time, it compared two approaches to controlling blood sugar: providing insulin-stimulating medication, or providing medication that sensitizes the body to the available insulin. UVM played a major role in
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—Burton Sobel, M.D.

the study, enrolling patients from Vermont and Northern New York in the trial, and playing a key role overall as one of the core laboratories for the effort. As a participant in BARI 2D, Schoch, a former college administrator who developed diabetes at the age of 60, had to keep close watch of his blood sugar levels. Every day for six years, he kept a careful record of his finger sticks and checked his blood pressure on a daily basis. He traveled to Burlington every few months to visit the diabetes clinic, where he met with Linda Tilton, dietician and research coordinator, and Ann Gotham, N.P., diabetes nurse practitioner. He also met with Dr. Schneider every six months. “It kept me straight, kept my weight down,” he says. “I learned a lot. It gave me the information I needed to better control my situation.”

The science behind the link
Schoch wasn’t the only one learning from BARI 2D. The scientists behind the study made many preliminary discoveries along the way, as they focused on specific systems at the root of the diabetes–heart disease link.

Dr. Sobel, who is a professor of medicine, director of the Cardiovascular Research Institute and a primary driver of the BARI 2D study, became interested in the connection between heart disease and diabetes in the mid-1990s. He was the director of cardiology at Washington University and Barnes Jewish Hospital in St. Louis at the time, and had been studying the fibrinolytic system — the system in the blood that works to dissolve potentially destructive blood clots.

Sobel and his colleagues decided to test the hypothesis that the breakdown of the fibrinolytic system might be a contributing factor to the link between diabetes and heart disease.

His work focused on a heart protein called plasminogen activator inhibitor type-1 (PAI-1). It had previously been shown that an excess of this protein in the fibrinolytic system could predispose people to accelerated coronary disease. When this happened, tiny blood clots in the vessels were not dissolved and instead propagated and caused coronary events. Previous studies had looked at this in coronary artery disease in general; Sobel asked the question specifically about diabetes.

A dangerous connection
Sobel and his colleagues found that there was an excess of the PAI-1 protein in people with type 2 diabetes. They also showed that in people with type 2 diabetes — the form of the disease that is caused not by too little insulin production, but by a person’s developed insulin resistance — high levels of insulin can trigger the increased synthesis of PAI-1. This in turn leads to inhibition of the fibrinolytic system, and a greater risk of coronary events.

The next thing the researchers did was to look at the blood vessel walls. There they found a greater level of PAI-1 in cases of insulin resistance. They also discovered that PAI-1 in the vessel walls led to the production of unstable plaque that was prone to rupture and block the vessel. Ultimately, Sobel and his colleagues discovered that increased PAI-1 in the blood can cause thrombosis — while increased
PAI-1 in the vessel walls can produce vulnerable plaque in diabetes patients. Both of those circumstances can lead to harmful and life-threatening cardiac events.

In 1998, four years into his twelve-year tenure as chair of medicine and physician leader at the academic medical center, Sobel had the opportunity to work with a group of researchers who had also focused on heart disease and diabetes. Together they teamed up to create the BARI 2D trial. The fibrinolytic system became one of the central components of the trial, with Sobel running a core laboratory at UVM coordinated by research nurse Michaelanne Rowen, R.N. UVM researcher Dagnija Neimane conducted testing and analysis in the lab, which processed approximately 23,300 samples.

In March of this year, Sobel, Schneider, and their colleagues published results of their work in Experimental Biology and Medicine. “Our team’s work indicated that down-regulating PAI-1 expression in the heart may be protective in patients with type 2 diabetes who sustain heart attacks,” Sobel says. “It opens up a novel and potentially important pathway for potential development of improved therapies to help reduce heart failure associated with diabetes.”

A closer look at blood clots

Schneider, also a principal investigator on the BARI 2D trial, followed another path with the research and looked at platelets, the cellular components of blood clots — an area he has focused on for the past 12 years. His work looked specifically at platelet function in people with diabetes. It was known that people with diabetes had more active platelets — which can cause blockages in the vessels. He wanted to understand what factors caused this reactivity in platelets, and whether insulin may be a trigger. The patients enrolled in the medical arm of BARI 2D were a perfect group to test this hypothesis.

Schneider developed a separate NIH-sponsored project within the BARI 2D study that sought to answer whether insulin is one of the drivers of platelet reactivity in patients with diabetes. Through this work — a baseline study was recently published in Diabetes Care — Schneider and his colleagues hypothesized that insulin resistance and platelet reactivity appear to be tied together, and that improved glycemic control using as little insulin as possible may help reduce platelet reactivity. A related research study conducted by Dr. Sobel focused on identifying markers for thrombosis in patients with diabetes.

“This helps us expand our understanding of how the treatment of diabetes influences thrombosis,” Schneider says.
The end of the beginning

While the full implications of BARI 2D are not yet understood, it could change the whole approach to how we treat diabetes, Schneider said. It will likely influence the type of medicines we use and whether or not we use revascularization procedures, he said.

For example, if a patient with diabetes comes in with angina and has a stress test that shows a blockage, cardiologists may avoid doing a coronary intervention in the catheterization lab — often the current practice — but instead treat the patient with medical therapy, Schneider said.

“This trial could tell us that’s not an option, don’t go to the cath lab,” says Schneider. “It may turn out that by going in there and doing this procedure, you’re accelerating the process. It could be like giving a little match to the kindling.”

The trial may also have a significant impact from an economic standpoint, Schneider says.

“Over the next several years, much data will be analyzed,” Sobel says. “We are forming writing groups as we speak that will go over all this information and put it in a format that can be digested by the scientific and clinical communities.”

Quoting Winston Churchill, he says, “This isn’t the end. It’s not the beginning of the end. … It’s the end of the beginning.”

UVM Brings Major Diabetes/Cardiovascular Studies to Vermont

Researchers at the University of Vermont are participating in a number of international diabetes drug trials that seek to prevent and reduce cardiovascular risk in diabetes patients. The University plays a global leadership role in diabetes drug development due to its expertise in this area, with researchers often tapped to advise national efforts and design trials, said Richard Pratley, M.D., professor of medicine and director of the Diabetes & Metabolism Translational Medicine Unit.

The development of diabetes drugs took a turn recently following new regulations from the Food and Drug Administration, Pratley said. The FDA now requires that companies developing new drugs for type 2 diabetes must show that the drugs do not increase the risk of cardiovascular events.

“This is a sea change in how we develop drugs for diabetes,” says Pratley, a lead investigator of several national drug trials now underway. “It’s good because we’ll get a better assessment of safety for treatments of diabetes and how they impact cardiovascular disease.”

Major diabetes drug trials underway at UVM include:

1. NAVIGATOR study (sponsored by Novartis): A multi-center, multi-national trial conducted over 30 countries and involved 7,500 participants and 700 investigative centers. This study, the largest diabetes prevention clinical trial to date, looks at whether two medications are effective at reducing progression to type 2 diabetes and cardiovascular disease in people with impaired glucose tolerance (IGT). Results of the trial, which will close in 2009, are expected to be published next year.

2. ORIGIN study: A multi-center international trial studying the effects of insulin glargine — a medication produced by Sanofi-Aventis — versus standard care in reducing cardiovascular morbidity and mortality in high-risk people who have either impaired fasting glucose, impaired glucose tolerance or early type 2 diabetes. The trial is expected to enroll 12,500 participants and conclude in 2012.

**Other Studies**

Pratley is a lead investigator on several additional studies of diabetes drugs, including one developed by Japanese drug company Takeda Pharmaceuticals that belongs to a new class of diabetes drugs called DPP-4 inhibitors. DPP-4 is an enzyme that prevents the activation of hormones known to lower glucose levels in people with type 2 diabetes. Pratley is also involved in other drug studies sponsored by Novartis and Novo Nordisk looking at development of new drugs that boost those same hormones — known as incretins — and thus help regulate blood sugar.