





Whether it's a sudden  
crisis or an ongoing illness,  
outcome-driven  
comparative effectiveness  
research helps physicians  
determine the best  
course of care.

# Critical Distinctions

BY NANCY ROSS-FLANIGAN

Sudden, staggering chest pains, nausea, cold sweats — the symptoms are instantly recognizable. But not every patient who arrives at the ER with these classic signs of a heart attack is actually in the throes of myocardial infarction. A rare few may be suffering from aortic dissection — a tear in the lining of the aorta that can lead to rupture of the vessel and death, as it did in the widely publicized case of actor John Ritter in 2003.

Similar symptoms, yet the treatments for these two conditions differ in important ways: clot-busting drugs and artery-opening procedures for heart attack; urgent surgery for aortic dissection. Mistaking the rarer disease for the more common cardiac emergency can result in measures that actually worsen the condition and hasten death, so distinguishing between the two and making sure patients get the appropriate treatment is crucial, says Kim Eagle, M.D., the Albion Walter Hewlett Professor of Internal Medicine and a co-director of the Cardiovascular Center. That's becoming more and more likely, not just at the U-M, but throughout the world, thanks to work by Eagle and others using comparative effectiveness research.

Asked to define the term, Eagle deconstructs it. "There are two words in there: *compare* and *effective*. This whole field is about examining the ways we care for patients and/or individual problems, learning from that examination and striving to make care better."

With aortic dissection, for instance, comparative effectiveness research has taken the form of a worldwide collaborative project: the International Registry of Acute Aortic Dissection (IRAD). Through IRAD, researchers evaluate treatments and track patients at 33 hospitals in the U.S., Spain, Israel, Italy, France, Japan, Germany, Austria and Switzerland.

"We're comparing the care that we're giving, and we're learning what is the best practice for early diagnosis, how to properly manage the patients surgically and non-surgically, and what's the most effective means of follow-up," says Eagle, who was recruited to the U-M in 1994 to develop a comparative effectiveness research program in cardiovascular care.

Over the years, U-M researchers have applied the approach to a range of questions, from how best to care for heart attack patients to how to combat obesity in middle school students. Along the way, they've been reassured to learn that many common health care practices are sound. But they've also had to re-think a few, such as across-the-board administration of anticoagulants to patients with irregular heartbeat and widespread use of blood transfusions after angioplasty.

## WHAT IT IS, WHAT IT ISN'T, AND WHY WE NEED IT

Comparative effectiveness research is different from the kind of medical research that usually makes headlines. Those studies typically are clinical trials, in which questions are narrowly defined, and patients are studied in carefully controlled settings, says James Froehlich, M.D. (Fellowship 1996), associate professor of internal medicine and director of the Michigan Cardiovascular Outcomes Research and Reporting Program (MCOORP), which oversees IRAD and other comparative effectiveness research projects.

In clinical trials, "patients get a very different level of care and attention than patients outside clinical trials," says Froehlich. "Someone is making sure they take their medication, someone is watching them for side effects, someone is seeing them more frequently than they normally would be seen."

Comparative effectiveness research, on the other hand, takes place in the messy, unpredictable real world that patients actually inhabit and involves observations rather than experiments.

"We observe and record treatments given and outcomes obtained in a world where things are not so well-controlled," Froehlich explains. "By studying what happens in the real world, we learn things about who actually receives medications and treatments. Are medications and treatments being given to people for whom benefit isn't proven? Or is it that treatments *aren't* being given to people who *would* benefit?"

"What we get with comparative effectiveness research," he says, "is answers to questions that physicians and patients ask every day: Does it make any difference if I take this drug or that drug? Does it make a difference if I have surgery for this problem or not?"

Comparative effectiveness research also covers territory that clinical trials don't touch. Most clinical trials are funded by drug or device companies that must demonstrate the safety and effectiveness of their products before they can be approved for public use. There's no such requirement for medical procedures, and thus no incentive to test the safety and effectiveness of procedures in clinical trials. The two approaches are complementary, not mutually exclusive, Eagle emphasizes.

"We can't afford to do clinical trials for every little question," he says. "We also understand that simply observing care doesn't necessarily offer the study design to ask, does the new therapy really add value? And so we need both. We absolutely need both."



Kim Eagle



James Froehlich



Hitinder Gurm

That’s truer than ever today, with mounting pressures to improve health care while containing costs.

“Americans want and deserve better health care, and the sentiment of our nation right now is that we need to be sure we’re getting the best health care product for the dollar,” Eagle says. “Comparative effectiveness research takes us in this direction, telling us how care delivery can improve, how we can make it more efficient and affordable, and how we can effect real improvement in the health of our population.”

### SOLUTIONS SOMETIMES SIMPLE

**T**he observations and analyses of Eagle, Froehlich and their colleagues don’t necessarily lead to seismic shifts in practice patterns. But even slight adjustments can have significant impact, as illustrated by a project initiated soon after Eagle’s arrival at the U-M to evaluate the care of heart attack patients.

“When a patient is admitted with a heart attack, there’s a certain group of medications that we should always administer unless there’s a contraindication,” says Eagle. “Similarly, at the point of discharge, patients should go home with a particular set of medications and preventive strategies unless there’s a contraindication. What we saw in our analysis of our own practices was that there was a lot of variation, and sometimes we forgot.”

From those findings came a program called Guidelines Applied in Practice with the simple mission of standardizing admission orders and the discharge process for heart attack

patients. “When we did that, we got a lot better at doing what we were supposed to do, and patients got better care as a result,” Eagle says. The U-M researchers went on to lead a statewide initiative involving 33 hospitals, aimed at improving heart attack care by making sure everyone followed the same guidelines. “We all improved, and the mortality of patients improved, both in the hospital and a year after discharge.”

Another statewide initiative, now funded by Blue Cross Blue Shield of Michigan and headed by Hitinder Gurm, M.D., assistant professor of internal medicine, focuses on the safety and quality of coronary artery angioplasty (a procedure used to open blocked or narrowed heart arteries and improve blood flow to the heart) and stenting (inserting a tiny, mesh tube inside the artery to keep it open).

“For anyone in the state of Michigan who gets a stent in their heart, we follow their in-hospital outcome,” says Gurm. “We look at who these patients are, what kind of medical problems they have, what medications they’re on. And then we look at what happens with them: Do they survive? Do they develop kidney problems? Do they develop bleeding problems? We ask what kind of stents were used, what medications were given during the procedure, and whether, when they were sent home, someone talked to them about diet, smoking and cardiac rehab.”

After analyzing the data, Gurm and colleagues can compare hospitals and individual physicians. Based on their findings, the collaboratives’ advisory group, made up of physicians from participating hospitals, sets goals and works to reduce any problems.

## CONSIDERING COMMON PRACTICES

One such problem was kidney failure after coronary artery angioplasty. “This is a very rare event, so a practitioner might see it only once every three or four years and chalk it up to bad luck,” says Eagle. “But if you’re studying it in 35 hospitals, and you have all the details of how angioplasty is performed, you may discover preventable processes that actually cause the problem.”

That’s exactly what researchers discovered. During angioplasty, special dye, visible on an X-ray, is used to reveal the location and extent of blockages. The dye is essential to the procedure, but too much can be toxic to the kidneys.

“We found that we could calculate, based on a patient’s body weight and pre-procedure kidney function, the maximum amount of dye that should be used,” says Eagle, “and we demonstrated a six-fold increase in the incidence of dialysis-dependent renal failure if that amount was exceeded.”

Another revelation: Hospitals across the state varied widely in their use of blood transfusions after angioplasty, with some performing four to five times more transfusions than others. Transfusions can be lifesaving, but they also can cause allergic reactions and suppress the immune system, opening the door to infections. Couple those concerns with the limited resource of banked blood, and there’s a strong argument that only patients who really need transfusions should get them.

U-M was one of the hospitals on the high end of the transfusion spectrum. After evaluating its practices and reviewing the literature, the research team recommended adopting more conservative guidelines published by the American College of Physicians. “We went from being one of the highest users of transfusion to one of the lowest by discovering the problem, evaluating what we were doing, and creating a system to improve,” says Eagle.

Discover, evaluate, improve. That’s also the mantra for another collaborative project sponsored by Blue Cross Blue Shield of Michigan: the Michigan Anticoagulation Quality Improvement Initiative. In this project, Froehlich and colleagues are studying the use of the anti-clotting drug warfarin in patients with atrial fibrillation. The condition puts people at risk for developing blood clots in the heart, and if a clot breaks free and travels to the brain, it can cause stroke.

Warfarin prevents clots from forming. But the drug carries its own risks — most notably severe, life-threatening bleeding — and patients who take it must have frequent blood tests to make sure they’re taking just the right amount.

Based on their research, Froehlich’s group recently reported that some 10 to 15 percent of atrial fibrillation patients taking warfarin may be at low enough risk for blood clots to stop taking the drug altogether.

## INSIGHTS, NOT EDICTS

A key part of all of these projects is sharing information and conclusions through publications, presentations and face-to-face meetings with health care teams at participating hospitals in Michigan.

“We want to make sure that the clinicians and care teams have an opportunity to compare themselves to their colleagues across the state, and potentially make changes in their practices,” says Paul Michael Grossman, M.D., an associate professor of internal medicine who directs a Blue Cross Blue Shield of Michigan-funded initiative focused on evaluating peripheral vascular intervention — treatments designed to reopen blocked vessels in parts of the body other than the heart. “We send out the reports, but we also travel to hospitals and meet with the teams that take care of the patients — not just the physicians, but also the technicians and nurses and administrators.”

The point is not to deliver edicts, but to offer insights.

“We try not to prescribe how patients should be cared for, but we set a standard, set a bar,” says Grossman. “We’ve seen significant improvement across the consortium in many of the areas on which we’ve focused attention.”

Physicians and other caregivers welcome the shared wisdom and guidance, says Froehlich. “Every physician wants to do the best job for their patients, and arming them with information is often all you need to do to see changes. Through these Blue Cross Blue Shield initiatives, we empower caregivers to seek self-improvement, rather than try to impose someone else’s idea of improvement. It’s very much a carrot, rather than a stick, approach to quality improvement.”

But wait a minute — if physicians and hospitals everywhere are standardizing procedures and conforming to the same guidelines, isn’t there a danger of one-size-fits-all patient care? That’s a fair question, Gurm says, and it’s important to keep in mind that even the most thorough research may not show a clear advantage to doing things one way versus another. Some aspects of medical practice will always be less black-and-white than shaded in gray, and there should be room for physicians to exercise judgment based as much on interactions with patients as on results of studies. The hope is that comparative effectiveness research offers another

tool to help physicians cope with the complexities of caring for human beings, with their many and varied needs, physical differences and combinations of conditions.

Another concern that's often voiced is that comparative effectiveness findings could lead to health care rationing — those scary scenarios of elders being denied treatment and insurers refusing to pay for lifesaving therapies.

To that assertion, Eagle has a ready response: "We're already rationing, but it's what I call irrational rationing: People who have insurance get care, and people who don't have

insurance, don't," he says. "We have two choices at this moment in our medical heritage: one is to continue what we're doing now; the other is to move toward 'rational rationing.' Using things like comparative effectiveness research, we decide as a society how much we can afford for health care, what is the best buy for the amount of benefit to individuals and populations, and what is discretionary. We haven't gotten there yet, but we need to get to that. Americans deserve better, and comparative effectiveness research is one tool that we can use to try to begin to do things rationally." [M]

## Comparing Effectiveness, Changing Lives

A number of other comparative effectiveness research projects are under way at the U-M, under the auspices of the Michigan Cardiovascular Outcomes Research and Reporting Program (MCORRP).

### **Fibromuscular Dysplasia (FMD) International Registry**

FMD is an extremely rare, poorly studied vascular disease. Some patients have no symptoms at all. Others have complaints that range from abdominal pain to headache. But all have similar stories: It took too long for the condition to be diagnosed, and once it was, their doctors didn't know much about the disease or how to treat it. At the request of the Fibromuscular Dysplasia Society of America, MCORRP created an international registry that now includes almost 350 patients. Researchers are comparing approaches to managing the condition,

and they're in the process of collecting blood samples from patients in order to investigate the genetic basis of the disease.

### **Project Healthy Schools**

This university-community collaboration aims to address the problem of childhood obesity by providing middle school students and their families and teachers with information and activities directed at healthy lifestyle changes. Students are encouraged to exercise at least 150 minutes per week, increase consumption of fruits and vegetables, reduce or eliminate consumption of sugary beverages and fast or fatty food, and reduce "mindless screen time," substituting

physical activity for TV, computer use and video games. In a pilot project at Ann Arbor's Clague Middle School, researchers showed that students' cholesterol levels, blood sugar and measures of fitness improved after the 10-week curriculum. Students surveyed after the program said that their attitudes toward healthy habits had changed. The curriculum is now being used in some 20 middle schools in southeast Michigan.

### **Project My Heart Your Heart**

In many low-income countries, a pacemaker costs more than the average person's annual income. As a result, about one million people die each year for

lack of the device. At the same time, many Americans die with still-functional pacemakers that could give life to another human being. Through this project, pacemakers from deceased patients are sterilized, checked for battery life and distributed to teaching hospitals in other parts of the world for implantation. In collaboration with World Medical Relief, a pilot study in the Philippines provided 12 patients with pacemakers. Now the project has been expanded to include 300 patients in the Philippines, Nicaragua, Vietnam and possibly Pakistan. Comparative effectiveness research is being used to study every aspect of the program. —NR-F