

STAYING ALIVE

Two Schulich Heart Centre doctors work to keep the beat for cardiac patients

DR. JACK TU INVALIDATES A DEAL-BREAKER FOR HEART SURGERY DEVICE WITH EVIDENCE THAT IMBUES IT WITH RENEWED CREDIBILITY

The car was late and Dr. Jack Tu was starting to panic. Tu, a senior scientist at Sunnybrook Research Institute, was bound for Bloomberg TV, a business network whose Toronto office was awaiting the stock-shaking news this science-minded guest promised to deliver. But with the car lost and the clock ticking, Tu found he was reduced to a race into the financial district as a passenger in a Sunnybrook media relations officer's car. Just under the wire he arrived, with time only to get outfitted with an earpiece and installed in a studio before setting about turning the lucrative and closely watched world of cardiac surgical devices on its head.

The news that Tu, who's also a practising internist at Sunnybrook and holder of the Canada Research Chair in Health Services Research, shared with the world that 2007 September day was that drug-eluting stents—once the darlings of the cardiac surgery set but dismissed when their safety was thrown into doubt—were darlings once more.

Before stents revolutionized this arm of medicine 20 years ago, 30% to 40% of angioplasty patients' arteries relogged within one year of the procedure. With no interventional fix available, the patient had to undergo emergency bypass graft surgery. "It was the biggest problem with angioplasties," says Tu. "Scar tissue would form and chest pain would return."

A stent is a metal tube that's inserted into the coronary artery after balloon angioplasty (the technique of widening a narrowed or totally obstructed blood vessel; tightly folded balloons are passed into the narrowed locations and inflated) to stop the once-blocked artery from closing again. In France in 1986, the first stent was put into a human

coronary artery. Eight years later, the Food and Drug Administration (FDA) approved stents for use. In response, the rate of postsurgery blockage there dropped to 20%.

The first stent was bare metal. Its fine wire mesh allows blood to pass through but prevents scar tissue from forming and jamming the artery. Drug-eluting stents were introduced to Ontario hospital rooms in 2003. An improvement on their predecessors, they were a departure from the purely mechanical approach to postsurgery therapy, and capitalized on pharmacologic advances. Drug-eluting stents are coated with drugs that leach into the patient's bloodstream over the three months following a surgical procedure.

In the U.S., physicians embraced the improved stents, and had increased by 2004 their use to about 90% of all stent procedures. Encouraged by their promise but concerned about their price (about \$3,000, compared with \$600 for bare-metal stents), the Ontario Ministry of Health and Long-Term Care nominated a 60-40 split for stent coverage, favouring the bare-metal variety, in September 2003. Cardiologists were to use the more expensive version for their high-risk patients: those with diabetes, longer-duration blockages of the arteries or smaller vessels. This determination of eligibility made for some "difficult conversations with patients," says Tu, but doctors here nevertheless joined the world in their enthusiasm for this innovation, and the international market for them exploded.

Then came the crash.

At a European Society of Cardiology meeting in September 2006, a group of Swiss scientists presented a paper that claimed drug-eluting stents increased patients' risk of postoperative heart attacks from blood clots forming around the sticky metal in the artery. With some six million drug-eluting stents implanted in patients at the time, this revelation incited a kind of panic. In December 2006, the FDA convened a hearing to which they invited international experts. A group of Swedish scientists presented data there that showed a 30% higher risk of dying with these new models than with the bare-metal variety. The mood among cardiologists, Tu says, remained "scared."



Dr. Gerald Cohen and Dr. Jack Tu

In Ontario, the government makes it a condition of funding that data be collected on every patient outfitted with either type of stent. These data, housed in the Cardiac Care Network of Ontario, could provide the means for a real-world evaluation of the effectiveness of drug-eluting stents, Tu realized. Using a tool he developed called the propensity score-matching technique, Tu paired bare-metal-stent with drug-eluting-stent patients according to identifying characteristics, including age, sex, cardiac history and other medical conditions. These statistical methods, he says, were superior to those used in the Swedish study.

But more than comprehensive and sophisticated, Tu's study was groundbreaking. For drug-eluting-stent patients who were given blood thinners for one year after surgery, the risk of postop heart attacks was the same as for patients with bare-metal stents. What's more, Tu found that the mortality rate was lower for drug-coated-stent patients.

The response was immediate. The media jumped on it, and in the markets, where stents are a \$6-billion-a-year business, the freefall among drug-eluting stent manufacturers' stocks halted and started the climb back. Other scientists have published studies confirming Tu's research since, and neither of the cart-tipping original studies' findings has been duplicated. In the U.S., a resurgence in drug-eluting stents' usage now puts this segment of the market at almost 70%. "They've come back into vogue as a result of our work," says Tu, whose study was named one of the American Heart Association's top 10 research advances in the field of cardiology in 2007. "It's exciting to be doing science that affects practice."

HEART ATTACK PATIENTS LIVE LONGER IN REGIONS WHERE MEDICINE IS A FIRST RESORT OVER SURGERY — BUT CARE ISN'T DELIVERED AS DISCRIMINATELY AS IT MIGHT BE

The question of how successfully a person will rise from his misfortune, it turns out, has much to do with where he was when he fell.

Drs. Dennis Ko and Jack Tu explored this premise in a widely cited 2007 *Circulation* paper that compares quality of care and outcomes of heart attack patients in the U.S. and Ontario. At the end of this, the most comprehensive study ever conducted on the subject, they concluded that it's better to be stricken in Ontario or the northeastern U.S. than anywhere else.

Taking advantage of the clinical data available to them through the Canadian Enhanced Feedback for Effective Cardiac Treatment project (one of the largest initiatives in the world looking at quality of cardiac care), and the Department of Health and Human Services in the U.S., the researchers looked at the medical experience of a person felled by an acute myocardial infarction (AMI), including occurrence of surgery and prescription of drugs. With their American counterparts, Ko and Tu collected data over two years, culling stats from almost every hospital in Ontario. Their objectives were clear: to determine, first, whether one country uses more procedures than the other; and, second, to consider its effect on the outcomes.

That there are higher rates of procedure use in the U.S. was no surprise to the scientists. Recent research had suggested that American practitioners are fonder of invasive procedures—like angiograms, angioplasties and bypass surgeries—for treating AMI patients than are Canadian physicians. But in Ontario and the northeastern U.S., it's

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Drs. Jack Tu and Dennis Ko

a different story. There, clinicians were revealed to engage in relatively low use of invasive procedures and high use of evidence-based medication, like beta blockers, cholesterol drugs and aspirin.

The outcome of these treatments was the punctuation to Ko and Tu's research: patients treated for AMI in Ontario and the northeastern U.S. fared much better than those treated in the rest of the U.S. Elsewhere in the U.S. doctors are doing more invasive surgery and, say the scientists, more patients are dying.

The connection between higher rates of invasive surgery and death from AMI is as important as it is tricky to explain. Ko—a scientist at Sunnybrook Research Institute and interventional cardiologist at Sunnybrook's Schulich Heart Centre, and Tu—a senior scientist at the research institute, practising internist and holder of the Canada Research Chair in Health Services Research—speculate on possible reasons, including better access to medication and outpatient care in Canada, healthier lifestyles among the older citizens of Canada, and increased exposure to the risk of death that comes with every surgery. What's more, says Ko, centres that do a lot of procedures tend to underemphasize medication use.

The clinical revelations to be extracted from this research are revolutionary. After all, says Ko, he and his colleagues have proven that the impact of medication on mortality is probably greater than the impact of surgery. "It's an argument against doing lots of procedures," he says. "It gets to questions of efficiency. Invasive therapies like angiograms are very expensive. Medication is cheap and easy."

Curious about the details of such revolution, Ko followed up with "Regional variation in cardiac catheterization appropriateness and baseline risk after acute myocardial infarction," published in 2008 in the *Journal of the American College of Cardiology*. Here, he sought to understand the specifics of the regional variation his earlier research identified. "If you're using it a lot, are you using it appropriately and on the patients who would benefit the most?"

The answer surprised him. Patients at higher risk for problems, and those with more appropriate indications for surgery (positive enzymes in their blood or limited life expectancy, for example) are the ones who might benefit the most from an invasive strategy after having an AMI. But they aren't the focus of clinical attention on this front. When Ko looked at geographic regions where highly invasive procedures are the norm, he found that physicians don't discriminate among their patients when determining candidates for surgery. Procedure selection, he says, "is not based on whether a patient will benefit; it's likely based on availability. Physicians aren't performing the procedures according to the needs of the patient."

From a policy angle, says Ko, this news is big. "We need to examine physician practice to ensure that procedures are performed appropriately." In the U.S., spurred by money-focused health maintenance organizations, a movement has begun to create guidelines on appropriateness (first for diagnostic procedures like echocardiograms and stress testing; up next is cardiac revascularization). "I hope Canada will follow suit," Ko says, because despite Canada's lower utilization of invasive procedures, "the field is changing rapidly, and as the volume of procedures goes up, the potential for inappropriateness also increases. It's simple. Appropriateness criteria are linked to benefits. If the medical community is performing more appropriate procedures, outcome is better." ■

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