

# Trials of the heart

From a vision to an international institution, TIMI trials continue to push cardiology's boundaries and save lives

TIMI investigators (from left) Eugene Braunwald, MD, Christopher Cannon, MD, and Stephen Wiviott, MD



**T**HE YEAR WAS 1984. Ronald Reagan was president. The summer Olympics were held in Los Angeles. And a clinical trial was getting under way that would revolutionize the care of cardiac patients.

"At that point, we did not think that we were going to be talking about TIMI 42," admits Eugene Braunwald, MD, chairman of the BWH-based TIMI Study Group.

TIMI, which stands for Thrombolysis in Myocardial Infarction, began as a single clinical trial of a new clot-busting drug for heart attack patients. The name reflects the study's original intent: dissolving clots, or thrombolysis, in cases of heart attack, which physicians call myocardial infarction.

Braunwald had been searching for ways to reduce heart attack deaths since the 1960s, and his work led to the discovery that heart attacks could be managed with drugs. His research also helped lay the groundwork for the use of beta-blockers as

a treatment for coronary artery disease. By 1984, after years of pre-clinical testing, the National Institutes of Health threw its support behind TIMI to test the efficacy of a "designer" clot-buster known as tPA for the treatment of heart attack. The trial showed tPA was superior to streptokinase, which had been the drug of choice.

Now, 21 years later, TIMI has grown into an enormous international endeavor with trials taking place in more than 50 countries and 1500 hospitals. So far, 40 trials have been completed, eight are enrolling patients and at least five more are in the planning stages. "It used to be a joke," says Christopher Cannon, MD, a principal investigator for the TIMI Study Group. "People would say TIMI 50 or TIMI 99. But we're going to get there."

Cannon joined the TIMI trials as a cardiology fellow in 1990. He had been researching some of Braunwald's editorial

comments concerning the classification of patients with coronary disease. After boldly offering his own findings to Braunwald, Cannon was asked to join the group, which was starting TIMI 3. Since then, he has played an instrumental role in organizing the trials.

"It's been great to be a part of it," says Cannon. "In the last 15 years, there's been a remarkably rapid evolution in care." Another long-term member of the group, Carolyn McCabe, has been TIMI's director since the program began in 1984.

## Bettering clinical practice

The prolific nature of TIMI is a testament to a study infrastructure that has become the gold standard. For each trial, the group spends years conceptualizing, organizing and gathering data. Then it works with medical organizations to update guidelines for use by practicing physicians. "Our goal is not to write papers," says Braunwald, chairman of Medicine at BWH from 1972 to 1996. "It's to improve clinical practice."

Since TIMI began, mortality from heart attacks has dropped almost in half. The trials have provided data on virtually every nonsurgical treatment of coronary artery disease, and have branched out to include procedures like angioplasty, which opens blocked blood vessels. Among the highlights:

- Establishing a universal coronary flow grading system to assess heart function
- Showing that early angioplasty is superior to "watchful waiting" in patients with worsening chest pain or small heart attacks
- Proving that "lower is better" for cholesterol after a heart attack, thus setting a new standard for national cholesterol guidelines
- Revealing that lowering a marker of inflammation called high sensitivity C-reactive protein, or hsCRP, may be just as important as lowering cholesterol
- Demonstrating that minutes matter when delivering clot-busting drugs to heart attack sufferers, making treatment in an ambulance very useful.

One serious problem for those who've suffered a major heart attack is that they have a 25 percent chance of having another blockage or a second heart attack. But recently released data from

CLARITY-TIMI 28 show that adding clopidogrel, available commercially as Plavix, to standard treatment reduces the chance of a blocked artery by 36 percent and the risk of a second heart attack—or death—by 20 percent. As a short-term therapy, clopidogrel is an inexpensive, potentially life-saving option, particularly for centers that don't perform coronary angioplasty.

"Most patients in the United States, and the vast majority worldwide, don't have access to centers that do catheterization," says Braunwald. "That's why we're very excited about the CLARITY-TIMI 28 trial."

Another trial that's currently changing cardiac care is PROVE IT-TIMI 22. It followed patients with heart attacks or new chest pain. Those who aggressively lowered LDL, or "bad" cholesterol, with high-dose statin therapy reduced the risk of death and heart attack, as well as the need for angioplasty or bypass surgery. Many doctors now advise patients to reduce LDL below 100 mg/dl, the current guideline. An LDL below

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70mg/dl now appears beneficial for patients with serious coronary artery disease.

"Being more aggressive in lowering cholesterol could improve the lives of 100 million people," says Cannon. "To do a study that can affect this many people is a pretty humbling thought."

On the horizon: the TIMI Study Group is exploring the genetic risk factors of heart disease. Building on work first done by Brigham and Women's Elliott Antman, MD, the group has already begun one of the largest blood marker studies ever undertaken. Markers for heart disease may indicate who is at higher risk and allow doctors to better tailor treatments.

Braunwald's new vision is to reach a point where the threat of heart attack can be managed more akin to diabetes. "It's a very exciting time to be working on this," he adds. "Although deaths from heart attacks have been reduced, there's much more work to do." ■