MAYO CLINIC

Treating Coronary Artery Disease in Diabetic Patients With Balloons and Stainless Steel: What Is the Role of Percutaneous Coronary Intervention?

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"The doctor of the future will give no medicine but will interest her or his patients in the care of the human frame, in a proper diet, and in the cause and prevention of disease."
Thomas A. Edison (1847-1931)

In this issue of *Mayo Clinic Proceedings*, Singh et al[1] present a thoughtful analysis of the long-term results of percutaneous coronary intervention (PCI) in a large, nonrandomized, consecutive series of patients with diabetes mellitus (DM) and coronary artery disease (CAD) (N=6908) treated at a single institution (Mayo Clinic) over an extended period (1979-2008).

That study is important because it encompasses the development of interventional cardiology techniques from the earliest days of percutaneous transluminal coronary angioplasty (PTCA) through bare-metal stenting to the current era of drug-eluting stents. The study reports an impressive improvement over time in success rates and much lower complication rates for PCI, exemplified by the striking reduction in the need for emergency coronary artery bypass grafting (CABG) after unsuccessful PCI (down a relative 93% from an 8.2% incidence in the early years of PTCA to 0.6% in the most recent patient cohort). In-hospital mortality declined by nearly 50% (from 4.9% to 2.5%), and long-term major adverse cardiovascular events and long-term mortality improved in each successive patient cohort.

While it is reassuring that the in-hospital outcomes of PCI in patients with DM are now broadly similar to those in patients without DM, it remains worrisome that, compared with patients without DM, patients with DM continue to have a worse long-term survival rate and survival free of major adverse cardiovascular events. Coronary artery bypass grafting is also less successful in patients with DM, as validated by decreased long-term survival when compared with patients without DM.

A lingering debate (initially ignited by publication of the BARI [Bypass Angioplasty Revascularization Investigation] trial in 1996) was whether PTCA or CABG should be the preferred strategy for coronary revascularization in patients with DM and multivessel CAD.[2] The BARI trial reported that patients with DM (a subgroup not prespecified in the original trial protocol) had better 5-year survival after CABG compared with PTCA: 80.6% for the CABG group compared with 65.5% for the PTCA group (P=.003).[2]

The recently reported FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, a large, multicenter, randomized trial that enrolled 1900 patients, may finally settle the PCI vs surgical revascularization controversy in patients with DM and multivessel disease.[3] Coronary artery bypass grafting was broadly superior to a PCI revascularization strategy that incorporated current-era drug-eluting stents. This conclusion was driven by a reduction in 5-year all-cause mortality (10.9% in the CABG group vs 16.3% in the PCI group; P=.049), but at the cost of a greater number of strokes (5-year stroke rate, 5.2% in the CABG group and 2.4% in the PCI group; P=.03).[3]

Why is multivessel coronary revascularization less successful in patients with DM than in those without DM? Probably several factors are involved: smaller-caliber coronary vessels, more diffuse disease, and greater likelihood of native coronary and graft disease progression in patients with DM compared with those without DM. Diabetes mellitus is frequently associated with an atherogenic lipid profile: low concentration of high-density lipoprotein cholesterol and high concentration of triglycerides, with an elevation in the concentration of small, dense, low-density lipoprotein (LDL) particles. The plasma LDL cholesterol concentration is often within normal limits; however, this is falsely

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reassuring because patients with DM tend to have higher atherogenic LDL particle numbers than do those without DM, for an equivalent LDL concentration. Individual LDL particles may also be more atherogenic in the presence of a high insulin concentration, typical of type 2 DM.

In our opinion, PCI or CABG affords critical time for the patient and physician to address the underlying metabolic disorder, which in turn is fueling progression of CAD. The following goals must be achieved: hemoglobin A_{1c} concentration less than 7.0%, although some suggest 6.5%; body mass index (calculated as the weight in kilograms divided by the height in meters squared) less than 25 or weight loss of greater than 10% of body weight if body mass index is greater than 30; daily exercise of 10,000 steps or more; blood pressure less than 140/90 mm Hg; and LDL less than 70 mg/dL, with small LDL particles less than 800 nmol/L. In practice, this means aggressive lifestyle changes, which can be hard to achieve, and use of medications, which are easy to take, but long-term adherence is often poor.

Sigwart,[4] in the 1996 Gruntzig Lecture, described stents as a mechanical solution for a biological problem, much like false teeth as a mechanical solution for dental caries, artificial joints for osteoarthritis, or prosthetic heart valves for valve stenosis. The difference is that CAD in patients with DM will inevitably progress after PCI unless the underlying metabolic disturbance is adequately treated. A PCI can be performed to treat myocardial ischemia and alleviate angina; however, there is no convincing scientific evidence that PCI by itself substantially alters progression of CAD in patients with DM.

Despite technologic advances in interventional cardiology, we may be in danger of missing the forest for the trees. What do we mean? Intellectually, it is helpful to consider type 2 DM as an epidemic disease, remembering that no epidemic disease in humans has ever been stopped by a surgical or interventional procedure alone. The current DM epidemic is likely no exception. Although the term "epidemic" is usually associated with infectious diseases, its literal meaning derives from the ancient Greek *epi*, meaning above, and *demos*, meaning people; thus, an epidemic is a disease that is occurring at a much higher rate than expected in the population. The facts speak for themselves: DM affects 347 million persons worldwide, including 25.8 million in the United States alone, a prevalence of about 8.3% in the US population.[5,6]

Epidemics are stopped using 3 methods. First, a clear scientific understanding of the pathogenesis of the disease is needed, both in terms of basic molecular and cellular disease mechanisms and of individual and societal human behaviors that promote the disease. Second, measures that block the key steps in the pathogenesis of the disease must be instituted. These can include vaccination (eg, for polio prevention), drug prophylaxis (eg, against malaria), or personal and/or societal hygiene measures (eg, water chlorination to prevent cholera transmission). Historically, this type of individualized disease-focused strategy has worked well. Smallpox was eradicated by use of the *Vaccinia* vaccine. Plague in Europe was stopped by control of rats that carried fleas, the vector for *Yersinia pestis*. Scurvy, an epidemic condition in sailors in the 19th century, was stopped by ingestion of fresh fruits and lime juice. Insofar as epidemic disease causation in type 2 DM, we need to focus as a society on our profligate consumption of sugars and processed carbohydrates. Third, and probably the most difficult measure to implement in epidemic prevention, is compliance with sensible preventive public health measures by the at-risk population.

How do we stop the current diabetes epidemic? We need to ask, "What factors have led to the current epidemic, and why has it occurred at this moment in history"? Type 2 DM, which accounts for greater than 90% of DM in the United States and Europe, is a disease with a genetic predisposition that is promoted by ecologic factors typically associated with modern civilization: an abundance of inexpensive, easily available food that is dense in sugar, processed carbohydrates, and fats, and energy-saving devices that have obviated the need for almost all occupational heavy physical exercise. The corn hybrid revolution that dramatically increased corn yield per acre resulted in an abundance of inexpensive high-fructose corn syrup that has entered our food supply in large amounts. (*Corn sugar*, the preferred term of the Corn Refiners Association, was recently rejected as an alternate label by the US Food and Drug Administration.)

The linking of human biology, diseases, and evolution is generally credited to several famous evolutionary biologists including Theodosius Dobzhansky,[7] an Eastern Orthodox Christian, who wrote a famous essay entitled "Nothing in Biology Makes Sense Except in the Light of Evolution," and the Catholic Jesuit priest Pierre Teilhard de Chardin,[8] who wrote *The Phenomenon of Man*. Human biology has evolved over millennia in which food scarcity was the norm, death by starvation was widespread, and daily heavy physical exercise was a requisite for hunting, gathering, and farming. To this end, we developed taste receptors that served an evolutionary function to help humans identify ripe fruit as a valuable sugar-rich source of food. Humans possess specific taste receptors, TAS1R2 and TAS1R3, located on the tongue and palate, that bind sugars and send pleasure signals to the brain. However, sugar receptors that were valuable to primitive man are probably detrimental in a modern society awash with sugar-laden food and drinks. We are trapped in bodies whose biology evolved in a world far different from modern life.

What is the answer to the current DM epidemic? There is no easy solution. However, part of the answer may lie in the diets of other developed countries that have comparatively low rates of type 2 DM and CAD, such as the European Mediterranean countries of Spain, France, Italy, and Greece. In 2008, these countries had age-adjusted DM mortality per 100,000 population of 9.4, 8.1, 4.3, and 5.0, respectively, compared with 15.2 in the United States, despite much lower absolute and gross domestic product percentage expenditure on health care.[9] Mortality due to ischemic heart disease in these Mediterranean countries is also a relative 25% to 64% lower than in the United States.[9]

The English satirist George Orwell may have best summed up our dilemma about PCI in DM in a completely different context in his novella *Animal Farm* when referring to Benjamin the donkey: "Benjamin was the oldest animal on the farm, and the worst tempered. He seldom talked, and when he did, it was usually to make some cynical remark—for instance, he would say that God had given him a tail to keep the flies off, but that he would sooner have had no tail and no flies."

A much better and much less expensive strategy for health care in America is to prevent type 2 DM in the first place by eating a healthier diet that is lower in sugar, animal fat, and processed carbohydrates. This strategy has worked in limited clinical trials and is characteristic of the diet of European Mediterranean countries. This strategy will require dramatic changes in societal eating and exercise habits. The alternative is continuation of the DM epidemic and reversal of declining CAD mortality observed in recent years due to the successful public health campaign for smoking cessation combined with better pharmacologic treatment of hypertension and hyperlipidemia.

Perhaps then PCI revascularization to treat DM-associated CAD will become redundant (much like Benjamin's tail in the absence of flies), if we can address the root cause of DM in our society. A note of caution: if we thought the health benefits of smoking cessation were difficult to promote in society, we may have seen nothing yet compared with the challenge of changing deeply ingrained American societal eating habits!

Joseph G. Murphy, MD
Thomas G. Allison, PhD, MPH
Division of Cardiovascular Diseases
Mayo Clinic
Rochester, MN

Correspondence: Address to Joseph G. Murphy, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (murphy.joseph@mayo.edu).

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