1986 Cleveland Clinic observational study showed that coronary artery bypass grafting with the left internal thoracic artery anastomosed to the left anterior descending artery provided better 10-year survival and graft patency than saphenous vein bypass grafts. Subsequently, it was demonstrated that use of both left and right internal thoracic arteries further improved survival. However, when Taggart and colleagues conducted a 28-site phase III randomized trial of using a single internal thoracic artery graft versus both internal thoracic arteries (ART [Arterial Revascularization Trial]), no survival difference was evident even at 10 years! The surprised investigators then searched for and found a subset of patients who appeared to benefit: those receiving 2 or more arterial grafts, including the radial artery. Although one can challenge a post hoc analysis of a negative trial, is it not worthwhile for any treatment to ask the questions, Who benefits? Who doesn’t? Who is harmed? At some level, we believe in “the right treatment for the right patient at the right time.” The right treatment involves discovering an individual patient treatment effect, the essence of precision medicine, not an average treatment effect as from a randomized trial, the gold standard for evidence-based medicine.

INDIVIDUAL TREATMENT EFFECT: MORE UBIQUITOUS THAN YOU THINK!

For many therapies, individual patient responses depart widely from the average treatment effect (Figure). This variable response was quantified by Framingham Heart Study investigators, using the first application of multivariable logistic regression followed by widespread door-to-door public distribution of a cardboard “slide rule” for individuals to calculate their personal risk of developing coronary artery disease. Multivariable logistic regression models are now widely used to generate risk-adjusted prediction of outcome at the individual patient level for results after cardiac interventions; the intention is in part to identify low- and high-performing institutions.

INDIVIDUAL TREATMENT EFFECT FOR CLINICAL DECISION MAKING

Although we think of American Heart Association/American College of Cardiology guidelines as being based at the highest level on randomized trials, authors of the first guidelines for coronary artery bypass grafting recognized wide variability of mortality among patients whose ischemic heart disease was managed medically or by percutaneous or surgical procedures. The writers therefore included a section entitled, “Patient-Specific Guidelines and Indications for Coronary Artery Bypass Operation.” Equations were provided in appendices and on a floppy disk prepared...
to allow physicians to generate survival curves according to individual patient characteristics for medical management, percutaneous transluminal coronary angiography, and coronary artery bypass grafting. They anticipated that these would be useful for making therapeutic recommendations and for informed patient decisions. Only 60 requests were made for these disks, indicating that clinicians were not ready to adopt quantitative tools like this, particularly in an era (which includes the present) before it was possible to extract values for model variables from the electronic medical record, perform the calculations, and display results automatically. Simpler graphical nomograms to accomplish this in cancer were introduced by Nam’s group, and these individual patient decision tools have gained considerable traction.

**FORMALIZING ELEMENTS FOR PATIENT-SPECIFIC COMPARISONS**

A variable-rich dataset is essential for accurate individual patient outcome predictions after alternative therapies. Furthermore, not all patients are eligible for all alternatives. For example, in considering alternative treatments for ischemic cardiomyopathy, mitral valve repair or replacement would not be indicated if mitral regurgitation were not present. Propensity methods or machine learning can aid in identifying which treatments are applicable for a given patient. Ultimately, formal trials are needed to determine whether outcomes are better using individual treatment effect decision making versus following average treatment effect guidelines. These include N-of-1, basket, umbrella, and adaptive designs.

**AVERAGE TREATMENT EFFECT: FOUNDATION OF EVIDENCE-BASED MEDICINE**

Results from randomized trials represent the classic example of average treatment effect. The value of such trials and their centrality to evidence-based medicine is unassailable. However, of the many explicit or implicit decisions made in the everyday practice of medicine, few are based on randomized trial evidence. This includes not only what seem like small therapeutic decisions, but even national models of healthcare delivery and financing. Indeed, reluctance of institutional review boards to lift requirements for informed consent and permit randomized examination of commonly used medicines, devices, and procedures that are inconsistently or diversely used in practice is a major impediment to identifying effective and safe medical practices while discarding ineffective or unsafe ones.

**LIMITATIONS OF RANDOMIZED TRIALS FOR INDIVIDUAL PATIENT TREATMENT DECISIONS**

Randomized trials focusing on average treatment effect hide heterogeneity in individual patient response. This is what drove ART investigators to dig into their data to identify a subgroup that appeared to benefit from multiple arterial grafting. Attempts to ferret out subsets who may benefit (or be harmed) are hypothesis generating. The high quality of data collected in randomized multisite trials renders them good sources for exploring individual treatment effects. However, randomized trials often have restrictive inclusion and exclusion criteria in the name of homogeneity that may artificially narrow the scope of patients potentially eligible for a particular treatment. Thus, real-world data are needed as well, with breadth of eligibility empirically discovered.

**PRECISION MEDICINE VERSUS EVIDENCE-BASED MEDICINE**

In the words of Tonelli and Shirts, precision medicine explicitly prioritizes the individualization of care and focuses attention on unique characteristics of a particular patient. In this fashion, it differs greatly from evidence-based medicine, which seeks to determine the best course of action for a patient with an appeal to generalizable knowledge gained from population-
based studies…. To realize the goals of [precision medicine], the hierarchy of evidence pyramid must yield to a more horizontal conception of medical knowledge.”

I have attempted to illustrate that precision medicine based on individual treatment effect and understood in its broadest sense has been embedded in cardiovascular medicine since at least the Framingham Study. Today, results of our therapies are being scrutinized and programs judged using individual treatment effect predictions. What remains unproven is whether real-world experience coupled with advanced analytic methods to generate individual treatment effect predictions will result in better decisions and outcomes than following guidelines developed from randomized trials focusing on average treatment effect. Meanwhile, the ART investigators have opted to mount a new randomized trial (ROMA [Randomization of Single vs Multiple Arterial Grafts] to test the benefit of multiple arterial grafts.

ARTICLE INFORMATION

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REFERENCES