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EDITORIAL COMMENT

A Long-Term Perspective on Short-Term Outcomes*

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Outcomes matter in cardiology. We need reliable data about long-term outcomes to evaluate which treatments work, whether they do more good than harm, and which patients benefit the most. The outcomes that matter most are the ones that patients and their families care about: death and major complications such as myocardial infarction (MI) and stroke. (Other patient-centered outcomes, such as symptoms, functional capacity, and quality of life, are also important, even though they are more difficult to ascertain reliably.) The tremendous progress we have made in treating cardiovascular disease is the direct result of clinical research studies that have evaluated treatments rigorously and followed up patients to document their clinical outcomes.

Even though there is consensus that documenting outcomes is important, there is great variation among clinical research studies in the length of follow-up. Long-term follow-up seems like a good idea, but how long? Some conditions may have a clear natural time scale during which all the key outcomes should develop and the full effects of treatment ought to become evident. Acute illnesses have a shorter natural time scale than chronic diseases, but an acute illness may have long-lasting effects. An acute MI develops suddenly, with a narrow time window of a few hours during which coronary reperfusion is effective and a subsequent healing period of a few weeks, but it leaves permanent damage that may have long-term sequelae (e.g., susceptibility to late arrhythmia or heart failure). Also, the underlying coronary atherosclerosis remains and provides the substrate for a future cycle of acute occlusion and recurrent MI. So what is the "natural time scale" for assessing outcomes of an acute MI? Large-scale clinical trials generally measure primary outcomes at 4 to 6 weeks, which is long enough to identify short-term treatment effects yet short enough to be reasonably practical: a short-term time frame to assess an acute disease treated with a 1-time therapy.

But is a few weeks long enough to assess the results of therapy for acute MI? Timely reperfusion might provide long-term benefits by limiting myocardial damage, but implantation of a coronary stent may have long-term consequences, such as stent thrombosis. We can't document late effects of treatment, either good or bad, unless we follow up patients over the long term. Unfortunately, we usually do not.

Why is long-term follow-up important? Many treatments have effects that will not be immediately evident, so short-term follow-up would not capture the full lifecycle of these therapies. For instance, implanted devices may fail after a few years, and drug therapy might take time to alter the natural history of disease; the survival curves for niacin and placebo in the Coronary Drug Project began to separate only after 8 years of follow-up (1). In contrast, 10-year follow-up studies of patients treated with thrombolysis for acute MI showed parallel survival curves after 1 year, with no evidence of either late benefit or late harm from treatment (2,3).

There are many barriers to obtaining long-term follow-up. Research sponsors want results quickly; commercial sponsors want to have their products approved without delay; and even the National Institutes of Health wants its investments in research to have tangible results soon. Consequently, length of follow-up may be a few weeks at most, and 1 year of follow-up is often considered "long-term." It is

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expensive to follow up patients long-term, especially if research staff must locate and contact each individual over many years. It would be much simpler and much less expensive to document outcomes using routinely collected data, such as hospital discharge and vital statistics records. My colleagues and I recently showed that linking clinical trial data with Medicare claims could provide a reliable method to identify late cardiac events (4), which suggests that long-term surveillance of clinical research subjects using routine administrative data could be an extremely useful way to obtain extended follow-up in clinical trials. Although it is conceptually simple to follow up patients by linking research databases with national administrative records, this is hugely difficult to accomplish in the United States. Our healthcare system is fragmented, with multiple payers; many patients are uninsured; Americans are obsessed with privacy and distrust the government and large corporations; and regulations designed to protect participants in high-risk clinical interventions have been applied indiscriminately to low-risk research studies.

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Other countries, such as Denmark, have universal healthcare systems and different attitudes about privacy and use of personal data for research purposes. In this issue of the *Journal*, Danish researchers highlight the value of their country's willingness to allow linkage of multiple healthcare and administrative data resources and assess the long-term outcomes of patients treated for an acute MI (5).

Pederson and associates nicely document the late outcomes of primary percutaneous coronary intervention (PCI) for acute MI (5). The survival curve clearly shows 2 distinct phases, indicated by a clear break in the slope of the curve at about 6 months of follow-up. The early high-risk period is almost entirely attributable to cardiac mortality, which is not surprising in a cohort of patients who have had an acute MI. Successful primary PCI reduces but does not eliminate the mortality of an acute MI. More subtly, there is a treatment selection bias for primary PCI, since patients with a serious noncardiac disease are unlikely to be chosen, which reduces the risk of an early noncardiac death.

After about 6 months, the survival curve flattens out as the early risk phase of the acute MI passes, and the later-phase steady-state risk becomes evident. In this later phase, cardiac mortality appears to be only half of total mortality: patients with an acute MI remain vulnerable to noncardiac disease, and some of the same factors that put them at risk for an MI also increase their risk for noncardiac death. Diabetes, for instance, is a strong predictor of late mortality, only some of which is cardiac. Lung disease and cancer due to smoking also pose long-term risks to survivors of an acute MI. The reduction in mortality from primary PCI can only be a short-term success, and in the long term, other forces of mortality will come to the fore.

One implication of these observations is that we cannot rest on our laurels after successful treatment of an acute MI. We need to recognize the factors, both cardiac and noncardiac, that pose the greatest risk to patients who survive an MI and initiate the therapies and behavior changes that will reduce the risk of late mortality. Long-term results matter, even for acute illnesses and short-term therapies. We need to develop methods to obtain long-term follow-up efficiently so we can document outcomes and identify optimal strategies to reduce long-term risk.

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