VIEWPOINT
Should Evidence Come with an Expiration Date?

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It is not unusual for accepted therapies to be abandoned in the face of new evidence. Usually, this occurs as a medical reversal, when a therapy adopted without strong evidence is later shown to be ineffective in a well-designed randomized trial. Sometimes, however, therapies once supported by robust evidence are proven to no longer work. The basis of this declining efficacy is diverse but includes changing population risk, newly adopted adjunctive medical therapy, and, for screening interventions, more effective treatments, which obviate the gains from early detection. Recently published trials showing aspirin's lack of efficacy in the primary prevention of cardiovascular disease (CVD) offer an example of this phenomenon. The lesson of aspirin for primary prevention is a broad one. What was once well-supported by data may prove ineffective in the future. Conversely, some interventions found to be ineffective may have worked if tested a decade earlier. We propose an "evidentiary statute of limitations" as a core principle of evidence-based medicine, wherein consideration is given to factors that may require the efficacy of accepted therapies to be reevaluated.

Multiple trials have evaluated the efficacy of aspirin in the primary prevention of CVD, and recent studies find that the benefits are outweighed by the harms.[1] A representative study by Gaziano and colleagues randomized participants at moderate risk for cardiovascular events to aspirin or placebo.[1] The primary endpoint was a composite of cardiovascular events, and adverse effects included hemorrhagic events. In the intention-to-treat analysis, there was no benefit to aspirin therapy (hazard ratio [HR] 0.96; 95% CI 0.81–1.13; $p = 0.6038$). Gastrointestinal bleeding events were more common in the aspirin group (HR 2.11; 95% CI 1.36–3.28; $p = 0.0007$).

This contrasts recent studies with those from decades ago when aspirin was shown to be effective. The Physicians' Health Study, one of the early successes in the era of evidence-based medicine, and subsequent meta-analysis demonstrated efficacy.[2, 3]

WHY DOES A THERAPY PROVEN EFFECTIVE STOP WORKING?

The physiologic effects of aspirin are no different today than they were 20 years ago. Nor is this an example of regression to the mean as multiple older studies showed similar levels of efficacy for aspirin. The decreasing efficacy of aspirin is likely due to a change in the characteristics of the population (or population studied). Compared with the 1980s, participants in the current studies have healthier lifestyles and improved risk factor management. Additionally, the participants enrolled in recent studies include a mix of men and women while older studies were overwhelmingly male. Although difficult to compare studies of different population done decades apart, the population differences are reflected in the rate of the composite endpoint that was 4.48% in the placebo group of the Gaziano study: a rate lower than all but one of the studies included in the meta-analysis referenced above (and markedly lower than that predicted by the American College of Cardiology/American Heart Association risk calculator).[1] The rate of myocardial infarction (MI) in this trial was about 373 per 100,000 person-years compared with 439.7 in the Physicians' Health Study.[1, 2]

Aspirin's waning efficacy is not an isolated example. Other therapies whose benefit was proven have been found to be ineffective in later studies. Trials initially showed a benefit of angiotensin-converting enzyme inhibitor (ACE-I) therapy in patients with vascular disease.[4] A later trial, conducted in patients on more up-to-date preventative therapy (higher rates of lipid-lowering therapy and aspirin use) no longer revealed a benefit.[5]

It is also possible to identify negative trials that might have been positive had they been performed at an earlier date. A 2009 trial that examined the benefit of adenosine-stress radionuclide myocardial perfusion imaging to screen for coronary artery disease (CAD) in patients with type 2 diabetes found no improvement in cardiac death or non-fatal MI.[6] The negative results of this trial were, to a great extent, based on the lower-than-expected event rates in the participants. Had this trial been conducted 10 years earlier when cardiac event rates would have been higher (and closer to those on which the power calculations were based), it is possible that CAD screening would have been written into guidelines and still be in use today.

There are interventions accepted today that one might anticipate will not be effective in the future. Screening for lung

cancer has already been shown to result in rates of overdiagnosis that may be unacceptable given the relatively small benefit.[7] As the intensity of smoking decreases and the success of therapies for lung cancer increases, it is possible that, even among patients who qualify, screening will no longer be beneficial. Screening for abdominal aortic aneurysms may follow a similar trajectory.

Should the evidence on which we base our practice come with an expiration date? An "evidentiary statute of limitations" would require the occasional reassessment of accepted therapies to consider which might no longer be of use—possibly because of changes in the population as a whole, a changing understanding of whom the treatment is appropriate for, or evolving therapies for the prevention or treatment of the disease in question. Not only should we consider if older data still applies, we should also strive to anticipate the factors to which the results of a newly published positive study might be sensitive. For instance, is there an event rate in the control group below which the harms of the therapy might outweigh the benefit? Is there a treatment success rate that, when achieved, would make screening inefficient?

A cyclic re-assessment of clinical data is a necessary next step for evidence-based medicine. Only by periodically checking whether our interventions are still working may we confidently treat our patients in a manner built on a solid foundation of reliable and up-to-date evidence.

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