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Should risky treatments be reserved for secondary prevention? Theoretical considerations regarding risk−benefit tradeoffs

M. Brandon Westover, Nathaniel A. Eiseman, Matt T. Bianchi*

Department of Neurology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA

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Abstract

Objective: Clinical intuition suggests that risk-reducing treatments are more beneficial for patients with greater risk of disease. This intuition contributes to our rationale for tolerating greater adverse event risk in the setting of secondary prevention of certain diseases such as myocardial infarction or stroke. However, under certain conditions treatment benefits may be greater in primary prevention, even when the treatment carries harmful adverse effect potential.

Study Design and Setting: We present simple decision-theoretic models that illustrate conditions of risk and benefit under which a treatment is predicted to be more beneficial in primary than in secondary prevention.

Results: The models cover a spectrum of possible clinical circumstances, and demonstrate that net benefit in primary prevention can occur despite no benefit (or even net harm) in secondary prevention.

Conclusion: This framework provides a rationale for extending the familiar concept of balancing risks and benefits to account for disease-specific considerations of primary vs. secondary prevention.

Keywords: Clinical trials; Human; Trial design; Public health; Prevention; Risk

1. Introduction

In the absence of cost or risk, effective preventative medicine would always be appropriate. However, cost and adverse event risk mandate balance between the risks and benefits of therapy in relation to disease severity. Preventative strategies are commonly dichotomized as primary vs. secondary, depending on whether the disease event (such as heart attack or stroke) has occurred. Some treatments that carry high adverse event risk may be reserved for patients deemed to be at higher disease event risk, as is commonly the case for event survivors, that is, the secondary prevention setting. In contrast, primary prevention strategies, which may be undertaken in more broad populations for longer time frames, are often reserved for treatments with safer profiles. Many approaches to risk−benefit balance in primary vs. secondary prevention have been reported [1−14], which variably consider factors such as disease severity, capacity to risk stratify, medication efficacy, and adverse event risk.

Here, we use simple Markov decision models [15−19] to compare outcomes in primary and secondary prevention across a range of treatment risks and benefits. We define primary prevention as treating asymptomatic patients to reduce the chances of a disease event, and secondary prevention as treating patients who have already suffered at least one disease event (and thus are in a higher risk category) to reduce the chances of additional events. We recognize that the public health literature sometimes specifies secondary prevention as referring to affected but asymptomatic patients and tertiary prevention as referring to affected symptomatic patients. The cardiovascular and cerebrovascular literature generally uses primary and secondary prevention as we have defined it here.[a] Our analysis generalizes therefore to primary prevention when compared with either secondary or tertiary prevention—so long as the risk associated with the disease is increased in the secondary or tertiary states. We compare the primary vs. secondary prevention settings to illustrate the different risk−benefit balance issues; we recognize that in some settings the same treatment may be used in primary and secondary prevention, and that some treatment decisions do not require a comparison of risk benefit

* Corresponding author. Tel.: 617-724-7426; fax: 617-724-6513.
E-mail address: mtbianchi@partners.org (M.T. Bianchi).

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[a] www.uptodate.com, topic "Benefits and risks of aspirin in secondary and primary prevention of cardiovascular disease," by Dr Hennekens (accessed July 2011).

What is new?

1. It is commonly held that treatments carrying risk of harm should be restricted to secondary/tertiary prevention—that is, to patients at high risk of morbidity and/or mortality. Our results suggest that primary prevention strategies need not be limited to low-risk interventions.
2. Our results complement traditional wisdom (such as "an ounce of prevention is worth a pound of cure," or "high-risk patients have greater benefit from risk-reducing medications") by providing a quantitative framework for approaching these opposing risk–benefit strategies.
3. A spectrum of factors should be considered when making determinations of risk–benefit balance in primary vs. secondary prevention. In particular, it is a useful heuristic to consider the transition from primary to secondary prevention risk states as an important theoretical and practical target for risk–benefit analysis. If the risk status change associated with such a transition is large, primary prevention treatments associated with more than minimal risk may still be an option.

between primary and secondary prevention circumstances. We show the critical importance of the transition from the primary prevention state (i.e., no prior event) to the secondary prevention state (i.e., survived a prior event)—and that delaying this transition can carry substantial weight in terms of overall benefit. Interventions that reduce this transition rate prevent progression to the high-risk secondary prevention state. In certain circumstances, preventing this risk upgrade can be so dominant that primary prevention may be favored over secondary prevention even for a risky intervention. The results challenge the notion that interventions with nontrivial side effect profiles should invariably be restricted to patient populations at high disease risk such as those in the secondary prevention state.

2. Methods and results

We begin with two simplified models in which primary and secondary prevention are risk states. These basic models aid our understanding of more complex/realistic models. Moreover, clinical trials typically consider either primary or secondary prevention populations, but not both. In the former, clinical endpoints such as death or a nonfatal event are often low probability. Thus, to evaluate an intervention for secondary prevention, clinical trials enroll patients who already meet these criteria, as opposed to enrolling nonfatal event subjects from a primary prevention trial. Here, we model both clinical settings in parallel. Extending the simple models, as we do later, by allowing transitions from primary to secondary prevention allows more realistic comparisons of primary and secondary prevention settings.

We implemented model simulations using custom code in MATLAB (Natick, MA). The parameter values are intentionally discussed in abstract terms for illustrative purposes only: these are values that *might* possibly arise in particular situations, but are not based on actual clinical examples. Thus, the magnitudes of the harms and benefits shown in the figures may be very different for particular applications, even when the qualitative risk–benefit relationships are similar to those shown in the figures.

2.1. Model 1

We first consider the simplest possible case (Fig. 1A): transition from a state of health to death from an event such as myocardial infarction or stroke. Patients in the primary prevention state are by definition at lower risk for the event than those in the secondary prevention state. The a and b terms denote the (untreated) event risk in primary and secondary prevention, respectively. Secondary prevention is a higher risk state, such that $b > a$.

We represent the impact of treatment as a fractional reduction of the transition rate to death, applied equally to primary and to secondary prevention. This relative risk is denoted by α (Fig. 1B). Treatment benefit is therefore represented by decreasing the baseline event risks in primary and secondary prevention from a and b to αa and αb, respectively. Note that, while the *relative risk reduction* $(1-\alpha)$ is the same in primary and secondary prevention, the *absolute risk reduction* is greater in the higher risk state of secondary prevention (because $b(1-\alpha) > a(1-\alpha)$). We assume here that all events are lethal; primary prevention cases never transition to secondary prevention cases. Comparisons of these two models will therefore be analogous to comparisons between different clinical trials that contrast treatment effects within primary vs. secondary prevention categories. In typical trials, patients are followed until reaching a clinical endpoint without the possibility of primary prevention patients "crossing over" into the secondary prevention state for continued observation.

We display outcomes of simulated patients in terms of quality of life (QOL) and a related term that captures the cumulative QOL, quality-adjusted life years (QALYs) [20,21]. These measures may be interpreted at a population level (fraction of surviving individuals) or in terms of the individual (probability of remaining alive). QOL values vary between 1 ("full health," the default initial state) and 0 (death). Death is an absorbing state, so that QOL ultimately decays to zero, whereas the cumulative value, QALYs, approaches a final asymptotic value.

The mean QOL (Fig. 1C) and the cumulative QALYs over time (Fig. 1D) are shown on and off treatment; see Appendix B on the journal's Web site at www.jclinepi.com