HHS Public Access

Author manuscript

J Clin Epidemiol. Author manuscript; available in PMC 2019 October 15.

Published in final edited form as:

J Clin Epidemiol. 2012 August ; 65(8): 877–886. doi:10.1016/j.jclinepi.2012.02.011.

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

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

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

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 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 in-variably 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

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

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 for equations. The difference between the curves reflecting on vs. off treatment is shown as "QOL gained" (Fig. 1E) and "QALYs gained" (Fig. 1F). These curves illustrate an important feature regarding the distinct time courses of benefit in the primary and secondary prevention settings. In primary prevention, the QOL curve decays more slowly on treatment than off treatment (reflecting the treatment's benefit), and the net benefit on treatment persists for many years (Fig. 1E). In contrast, patients in secondary prevention die more rapidly overall,

Supplementary material
Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jclinepi.2012.02.011.

such that their treatment-related benefit peaks earlier but declines more quickly because of the higher death rate. A similar pattern is seen in the cumulative QALYs curve.

Two important observations follow from this simple model. First, the magnitude of QOL benefit in the short run will always be greater in the secondary prevention setting. This corresponds to the general clinical intuition that patients at higher baseline risk will have greater immediate benefit from preventative medications. Secondly, despite the greater absolute risk reduction conferred by treatment in secondary prevention, the long-term QALYs benefit is always greater in primary prevention. Simple calculations demonstrating these two important dynamics are shown in the Appendix A.

It is useful to summarize whether a particular model can (for any set of parameters) exhibit greater treatment benefit in primary vs. secondary prevention. In this first model, there is only one possible "benefit profile" of long-term QALYs for the treatment (Table 1): treatment always confers net benefit in both primary and secondary prevention, with the greatest benefit (largest QALY's gain) in primary prevention. This pattern in this (over)simplified model follows directly from the reasonable assumption that $b > a$.

It is also worth emphasizing again that the net QALYs gained initially favor secondary prevention because the same relative protection is being applied to a larger transition rate to the death state (Fig. 1F). However, over time the lines crossover as more patients in primary prevention survive relative to secondary prevention. Thus, the time frame of the observation will influence the net QALYs gained. More realistic clinical circumstances allow for different benefit profiles, which we consider next.

2.2. Model 2

We next introduce a treatment harm factor (h) into the transition rates from primary prevention and secondary prevention states to death. The treatment benefit is still modeled as a decreased transition rate to death. However, this benefit is offset by the harm factor, which is represented by an independent path to the death state applied equally to primary and secondary prevention states (Fig. 2A, B). The QALY's curves on treatment decay faster in this case (compared with Fig. 1), owing to the harm factor, shown for two harm levels (Fig. 2C, D). Panel C shows the effect of an amount of harm small enough (relative to the treatment benefit) that the treatment is still beneficial in both primary and secondary prevention. The presence of an overall benefit indicates the death rate decreases with treatment; for primary prevention, this implies that benefit ($a\alpha$) and harm (h) are favorably balanced such that $a\alpha + h < a$. This inequality specifies that the treatment benefit outweighs the treatment harm. For secondary prevention, benefit ($b\alpha$) and harm (h) are favorably balanced such that $b\alpha + h < b$. Overall benefit is preserved, despite the harm factor, because we choose the harm h to be less than the absolute risk reductions, $a(1 - \alpha)$ and $b(1 - \alpha)$.

Fig. 2D shows the effect of a larger amount of harm, chosen so that treatment yields net harm in primary prevention, while providing net benefit in secondary prevention. This pattern holds for this inequality: $h > a(1 - \alpha)$, and $h < b(1 - \alpha)$. The clinical intuition is that one would be more tolerant of treatment-related harm in the secondary prevention setting but less tolerant of that harm in primary prevention. When the harm factor outweighs the benefit

factor in primary prevention, but does not yet outweigh the secondary prevention benefit, then treatment will always have net benefit for secondary prevention and net harm in primary prevention.

The spectrum of possible benefit profiles (long-term QALYs) for Model 2 can be summarized as follows (Table 1). As in Model 1, it remains possible (when the harm factor is relatively small) for treatment to be most beneficial in primary prevention, while still providing benefit in secondary prevention (Fig. 1). However, for larger harm factors, it is possible to obtain positive benefit in secondary prevention, while the benefit in primary prevention is smaller (Fig. 2B) or even negative (Fig. 2C). It is also possible to do net harm in both primary and secondary prevention (not shown), but such treatments clearly would never be used (and if they were used, the amount of harm would always be greater in primary than in secondary prevention). By contrast, it is not possible to set Model 2 parameters such that a treatment does more harm in secondary compared with primary prevention, nor is it possible to confer harm in secondary prevention while remaining beneficial in primary prevention. These clinical possibilities require an additional modification, which we consider next.

2.3. Model 3

We next incorporated a transition (c) from primary to secondary prevention states (Fig. 3A, B). This nonlethal event pathway leads to higher risk of death by virtue of this transition to the high risk secondary prevention state. Although we conceptualize the transition to secondary prevention as a discrete event (e.g., a nonlethal myocardial infarction), the same construct could be used for subclinical progression of disease. The essential element is the acquisition of higher risk for future events/death. For some diseases, it is appropriate to include in the model a decrement in QOL at the time of transition, as when the nonlethal event may leave the patient disabled [11]. For simplicity, we assume no loss of life quality (similar results follow if a quality adjustment factor is included).

This primary-to-secondary transition in Model 3 allows primary prevention to progress to death in one of two ways: directly, as before, or indirectly, via the secondary prevention state. This additional transition pathway introduces new dynamics to the QALYs analysis and, consequently, a richer set of possible risk–benefit profiles (Table 1 and Fig. 3). In addition, we introduce a “protection factor,” β, to reflect the benefit of a treatment in reducing the transition from the primary to secondary prevention state. This aspect of treatment-related benefit can be different than the risk reduction parameter (α). For example, HMG coenzyme A reductase inhibitors (statins) are found to confer different levels of relative risk reduction for lethal vs. nonlethal outcomes of ischemic stroke and myocardial infarction [11].

Parameters can be chosen in this model to achieve net benefit that is greater in primary prevention (as in Models 1 and 2) or in secondary prevention (as in Model 2). It is also possible to chose parameters to simultaneously achieve net harm in primary prevention but net benefit in secondary prevention, or net harm in both but with the greater harm done in primary prevention (as in Model 2). More interestingly, it is also now possible to choose parameters to achieve the following challenging clinical outcome (not possible in Model 1 or

2): a benefit solely in primary prevention while net harm occurs in secondary prevention (Fig. 3, C-F). This model demonstrates the difficulty with assuming that treatment-related harm is always more tolerable in higher risk (i.e., secondary prevention) settings.

In contrast to Models 1 and 2, the dynamics governing the loss of life in primary prevention using Model 3 now consist of a mixture of two different exponentially decaying curves, corresponding to the direct and indirect (via secondary prevention state) transition from primary prevention to death. Graphically, this dynamic is reflected in the observation that the on-treatment and off-treatment curves can crossover one another. For example, in Fig. 3C, the off-treatment curve initially decays more slowly than the on-treatment curve. However, after a sufficient proportion of the population has transitioned to secondary prevention, the curves cross, and beyond this point the decay is slower in the on-treatment condition.

We next consider the “maximum tolerable harm,” defined as the value of the treatment-related harm factor that exactly offsets treatment benefit (Fig. 4A). In the case of secondary prevention, which has only one transition to consider (to the death state), the maximum tolerable harm is simply the value of the harm factor h that exactly offsets the risk reduction conferred by the treatment, that is, $h = b(1 - \alpha)$. For primary prevention, the maximum tolerable harm depends on five variables, a, b, c, β, and α, taking into account the direct and indirect pathways to death. The maximum tolerable harm is a threshold concept that can be visualized by holding constant the transition parameters a, b, and c, and the benefit parameter (α), and plotting the long-term QALYs gained across a range of harm factors. In Fig. 4A, the zero crossing of this curve is the maximum tolerable harm for primary prevention for one set of parameters.

Fig. 4B illustrates the dependence of the cumulative (long-term) QALYs gained in primary prevention (encoded by the grayscale) on two variables: the harm factor (h) and the protection factor (β). The thick contour curve indicates the point of net zero benefit. Combinations of h and β to the left of this line result in net benefit, whereas combinations to the right produce net harm. The dashed vertical line marks the value of the harm parameter at which there is zero net benefit in the *secondary* prevention setting. Note that for any given value of h, moving from high β (indicating low protection against transition from primary to secondary prevention) to low β (indicating good protection), one crosses into contour zones of increasing level of benefit. The magnitude of protection (β) required to achieve a net QALYs benefit depends on the harm factor: greater protection is required to counterbalance greater harm. More importantly, the plot illustrates areas of the parameter space in which net benefit occurs in primary prevention (left of the zero contour). A small range of parameters allows net benefit in the primary prevention setting and net harm in the secondary prevention setting (right of the vertical dashed line). If we consider circumstances in which the treatment α value were lower (more protective) in the secondary than in the primary prevention settings, the possibility of a treatment having benefit in primary prevention but harm in secondary prevention would be very small, whereas a smaller (more protective) value of β in primary prevention would increase the chances of this situation.

Fig. 4C illustrates how net QALYs in primary prevention (encoded by the grayscale) depend on two distinct factors: 1) the off-treatment death rate in primary prevention (a, expressed

here as a percentage of b, the off-treatment death rate in secondary prevention), and 2) the protection factor (β) that decreases the transition from the primary to secondary prevention state. The contour line indicating zero net benefit is again marked with a bolded black line. Combinations of a and β to its left confer net benefit, whereas combinations to its right produce net harm. Note that the contours on either side of the zero-benefit contour bend in opposite directions, further away from each other as the baseline death rate in primary prevention increases. To the right of the zero net gain contour line, for any given value of β, the net benefit varies with the difference between the pre- and posttreatment death rates, $a - (\alpha a + h) = a(1 - \alpha) + h$, which increases with a (i.e., the higher the baseline risk, the larger the absolute difference made by the intervention). Thus, moving up along any vertical line to the right of the zero contour, one crosses into contours of larger benefit or, more precisely, decreasing levels of harm. However, to the left of the line, β is sufficiently small to produce some net (positive) benefit, via sufficiently preventing the transition to the high-risk secondary prevention state. Under these conditions, the advantage of the treatment hinges on the relatively lower risk of death in primary prevention (a) when compared with secondary prevention (b). So, for any given value of β small enough to produce a net benefit (by keeping enough patients in the primary prevention state) the treatment benefit is greater for smaller values of a; hence, one encounters contours with larger net benefits by moving *down* the plot, toward $a = 0$.

Fig. 4D shows a two-factor contour plot of the maximum tolerable harm in primary prevention as a function of the “direct” (α) and “indirect” (β) benefits of treatment, with values for the other parameters held constant. Larger harms are tolerated when the treatment confers greater risk reduction via either of the two available paths: decreasing the rate of death (small α) or decreasing transition into the higher-risk secondary prevention state (small β). At the upper right corner, the treatment confers no benefit and, accordingly, the maximum tolerable harm is zero. By contrast, at the lower left corner, the treatment is perfectly protective against the direct pathway to death ($\alpha = 0$) and the transition to secondary prevention ($\beta = 0$), effectively rendering the patient “immortal” except for harmful treatment effects, hence the maximum tolerable harm is large. Most interestingly, the results emphasize the importance of protecting against the transition from primary to secondary prevention states. For essentially any value of α, setting β small enough still places one within the black contour, implying a large degree of tolerable harm. In other words, a certain amount of treatment risk may be theoretically justified even if the sole effect of the treatment is to prevent transition to the secondary prevention state, even without altering the baseline risk. We recognize that, in practice, for diseases such as heart attack and stroke, complete decoupling and hence differential targeting of these model pathways may not presently be possible. For example, antiplatelet or lipid-lowering medications decrease the risk of both lethal and nonlethal cardiovascular and cerebrovascular events. Nevertheless, the possibility of such treatments in principle is not widely appreciated and should not be overlooked.

3. Discussion

We provide a framework to approach several important considerations that frequently arise in the risk–benefit balance of medical treatment decisions. First, it is crucial to distinguish

relative vs. absolute differences in quantifying degree of benefit. This is true in the general sense that impressive relative benefits may not actually be clinically meaningful when considered in terms of actual magnitude. In our models, the same relative protection afforded by a treatment confers different absolute net benefit (in long-term QALYs gained) depending on other parameters, including time frame of observation. Secondly, the time frame of observation can markedly alter the interpretation of benefit. An early smaller net benefit in primary prevention may at a later time show the reverse pattern—smaller in secondary prevention. This benefit dynamic was evident even in our simple Model 1, and certainly occurs in the more realistic Model 3. More importantly, a relative risk reduction applied to a low-risk level over a lifetime (as in primary prevention) can ultimately produce a larger cumulative benefit than when applied to a higher level of baseline risk with shorter life expectancy (as in secondary prevention). Thirdly, the clinical intuition that adverse treatment effects should only be tolerated in high-risk (secondary prevention) settings is not absolute, as our models demonstrate the possibility of circumstances in which treatment-related harm can be tolerated even for the sole purpose of primary prevention. When we model treatment benefit to include preventing the transition to a higher-risk (secondary prevention) state, the possibility emerges of substantial benefit in treating the low-risk primary prevention population even when the treatment produces frank net harm in the higher-risk secondary prevention population. One could discontinue such a treatment once an event occurred, such as coumadin for primary stroke prevention, if the eventual stroke were considered to place the patient at high risk for anticoagulation (such as a cerebellar stroke that increased the fall risk).

Relating the framework outlined here to clinical trial data can be considered best in the context of Model 3. The transition values can be extracted from the literature as follows. Primary prevention trials contain rates of death from the event in question (transition *a*), and contain rates of nonfatal events (transition *c*). Secondary prevention trials contain rates of fatal events (transition *b*). Adverse effect rates (harm) can be extracted from both kinds of trials, as can the benefit provided by the treatment. For reasons of power in low probability event settings (such as heart attack or stroke), gathering all of these transitions and values from a single trial is usually impractical, and thus data from primary and secondary prevention trials would be combined to populate models such as these. Therefore, decision analysis serves an important purpose of rationally approaching what cannot easily be achieved by means of a single clinical trial.

The simple models studied here suggest that clinical circumstances may theoretically support any possible combination of favoring or avoiding a treatment in either primary or secondary prevention. In turn, this means that physicians should consider the potential downside of the heuristic of reserving treatments only for those deemed to be at high risk by reflexively withholding treatments until the secondary prevention setting (or alternatively, not treating at-risk patients in primary prevention as often occurs with statins [22]). The added complexity of the primary vs. secondary risk– benefit calculations discussed here also suggest a greater need for careful decision-theoretic models, especially for treatment policies that affect large patient populations. Using randomized prospective trial data (when available) to estimate parameters in such models is critical for translating the theoretical points raised by this analysis into practical decision support for clinicians. Understanding the

potential complexities involving primary and secondary prevention strategies illustrated by our results may inform future trial design and meta-analyses in the arena of preventative medicine.

Acknowledgments

We thank Drs Steven M. Greenberg and Mark H. Eckman for valuable discussions.

The authors are supported by the Department of Neurology, Massachusetts General Hospital (M.T.B. and M.B.W.), and the Clinical Investigator Training Program: Harvard/MIT Health Sciences and Technology—Beth Israel Deaconess Medical Center, in collaboration with Pfizer, Inc. and Merck & Co. (M.T.B.). The funding sources had no role in the design, interpretation, or publication of this work.

Appendix A

The time at which the benefit is maximal is earlier in secondary prevention. This can be verified by setting the derivative of the benefit curves (Fig. 1E) equal to zero and solving for the peak time, t^*; the results are $t_P^* = \log(\alpha)/(a(\alpha - 1))$ and $t_S^* = \log(\alpha)/(b(\alpha - 1))$ for primary and secondary prevention, respectively. The ratio $t_S^*/t_P^* = a/b$ is smaller than one (because $b > a$, by assumption), indicating that the benefit peaks earlier in secondary prevention. The magnitude of the peak benefit is the same for the primary and secondary prevention settings. This is easily verified by plugging in the peak time values above, and noting that the off-treatment transition rates to death (a and b) cancel out.

The absolute risk reduction (ARR) in secondary prevention is $ARR_S = b(1 - \alpha)$ vs. $ARR_P = a(1 - \alpha)$ in primary prevention, hence the ratio is $ARR_S/ARR_P = b/a$, which is greater than one because $b > a$. This ratio is inverted when comparing cumulative benefits: The net benefit (NB) of treatment (i.e., the asymptotic cumulative difference between QALYs on treatment and off treatment) in primary prevention is $NB_P = (1 - \alpha)/(\alpha a)$ $(1 - \alpha)/(\alpha a)$ vs. $NB_S = (1 - \alpha)/(\alpha b)$ in secondary prevention, yielding a ratio of $NB_S/NB_P = a/b$, which is smaller than one.

Appendix B

References

[1]. Kakafika AI, Athyros VG, Tziomalos K, Karagiannis A, Mikhailidis DP. Primary and secondary coronary heart disease prevention using statins: is targeting Adam or Eve equally effective? Expert Opin Pharmacother 2008;9:1437–40. [PubMed: 18518775]

[2]. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, et al. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline. Stroke 2006;37:1583–633. [PubMed: 16675728]

[3]. Ong HT. Evidence-based prescribing of statins: a developing world perspective. PLoS Med 2006;3:e50. [PubMed: 16478294]

[4]. Ong HT. The statin studies: from targeting hypercholesterolaemia to targeting the high-risk patient. QJM 2005;98:599–614. [PubMed: 16006501]

[5]. Goldman L, Weinstein MC, Goldman PA, Williams LW. Cost-effectiveness of HMG-CoA reductase inhibition for primary and secondary prevention of coronary heart disease. JAMA 1991;265:1145–51. [PubMed: 1899896]

[6]. Pletcher MJ, Lazar L, Bibbins-Domingo K, Moran A, Rodondi N, Coxson P, et al. Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering. Ann Intern Med 2009;150:243–54. [PubMed: 19221376]

[7]. Annemans L, Wittrup-Jensen K, Bueno H. A review of international pharmacoeconomic models assessing the use of aspirin in primary prevention. J Med Econ 2010;13(3):418–27. [PubMed: 20632895]

[8]. Cadmus RR. Prevention: good medicine, but not good economics. Hosp Health Netw 1994;68:8.

[9]. Schwappach DL, Boluarte TA, Suhrcke M. The economics of primary prevention of cardiovascular disease—a systematic review of economic evaluations. Cost Eff Resour Alloc 2007;5:5. [PubMed: 17501999]

[10]. Harvey K Effects of the Heartbeat Wales programme. Health promotion is a waste of time and money. BMJ 1998;317:887.

[11]. Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, et al. A systematic review and economic evaluation of statins for the prevention of coronary events. Health Technol Assess 2007;11:1–160. iii–iv.

[12]. Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, Peto R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet 2009;373:1849–60. [PubMed: 19482214]

[13]. Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, et al. AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update: consensus panel guide to comprehensive risk reduction for adult patients without coronary or other atherosclerotic vascular diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106:388–91. [PubMed: 12119259]

[14]. Manuel DG, Kwong K, Tanuseputro P, Lim J, Mustard CA, Anderson GM, et al. Effectiveness and efficiency of different guidelines on statin treatment for preventing deaths from coronary heart disease: modelling study. BMJ 2006;332:1419. [PubMed: 16737980]

[15]. Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: Part 1—Getting started. Med Decis Making 1997;17:123–5. [PubMed: 9107606]

[16]. Detsky AS, Naglie G, Krahn MD, Redelmeier DA, Naimark D. Primer on medical decision analysis: Part 2—Building a tree. Med Decis Making 1997;17:126–35. [PubMed: 9107607]

[17]. Krahn MD, Naglie G, Naimark D, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 4—Analyzing the model and interpreting the results. Med Decis Making 1997;17:142–51. [PubMed: 9107609]

[18]. Naglie G, Krahn MD, Naimark D, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 3—Estimating probabilities and utilities. Med Decis Making 1997;17:136–41. [PubMed: 9107608]

[19]. Naimark D, Krahn MD, Naglie G, Redelmeier DA, Detsky AS. Primer on medical decision analysis: Part 5—Working with Markov processes. Med Decis Making 1997;17:152–9. [PubMed: 9107610]

[20]. Torrance GW, Feeny D. Utilities and quality-adjusted life years. Int J Technol Assess Health Care 1989;5:559–75. [PubMed: 2634630]

[21]. Raisch DW, Nawarskas JJ. Quality-adjusted life-years as decision-maker tools to address limitations inherent in number-needed-to-treat/harm values. Expert Rev Pharmacoecon Outcomes Res 2009;9:99–102. [PubMed: 19402794]

[22]. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA 2004;291:1864–70. [PubMed: 15100205]

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.

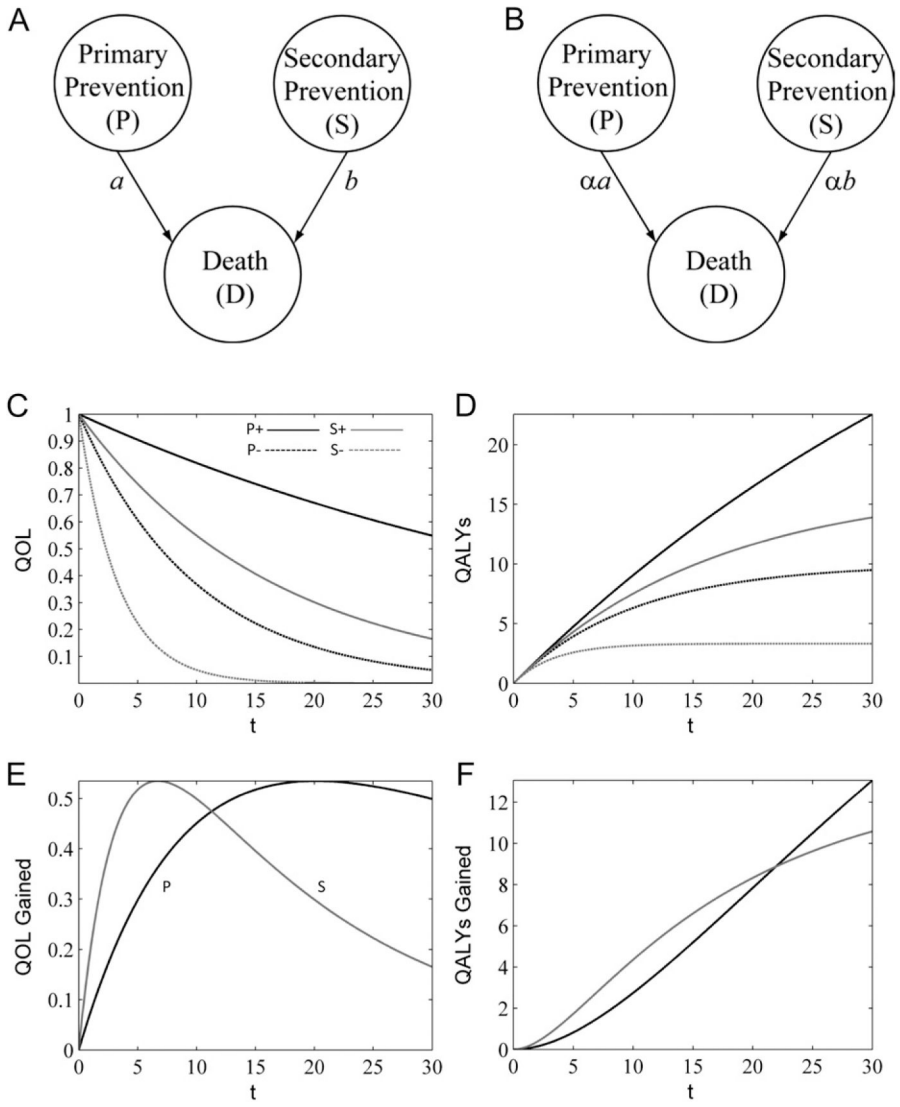

Fig. 1.

Simplified primary and secondary prevention model. A. Three-state model illustrating transitions between a state of health (primary prevention, P) and death (transition “a”), and a state of disease (secondary prevention, S) and death (transition “b”). B. Model in A adjusted for the beneficial effect of a treatment. Each transition is now multiplied by the fractional relative risk, a. C. Mean quality of life (QOL) is shown as a function of time for primary prevention (P, black lines) and secondary prevention (S, gray lines). The dashed lines indicate the off-treatment circumstance (−), whereas solid lines indicated treatment (+). The same black/grayscale and dashed/solid line conventions are used for the subfigures D, E, and F, and in subsequent figures. D. Cumulative quality-adjusted life years (QALYs) for primary (black) and secondary (gray) prevention, on- (solid) vs. off- (dashed) treatment. E. The gain in QOL is expressed by subtracting the dashed from solid curves for primary (black) and secondary (gray) prevention curves in panel C. F. The gain in QALYs is expressed by subtracting the dashed from solid curves for primary (black) and secondary (gray) prevention curves in panel D.

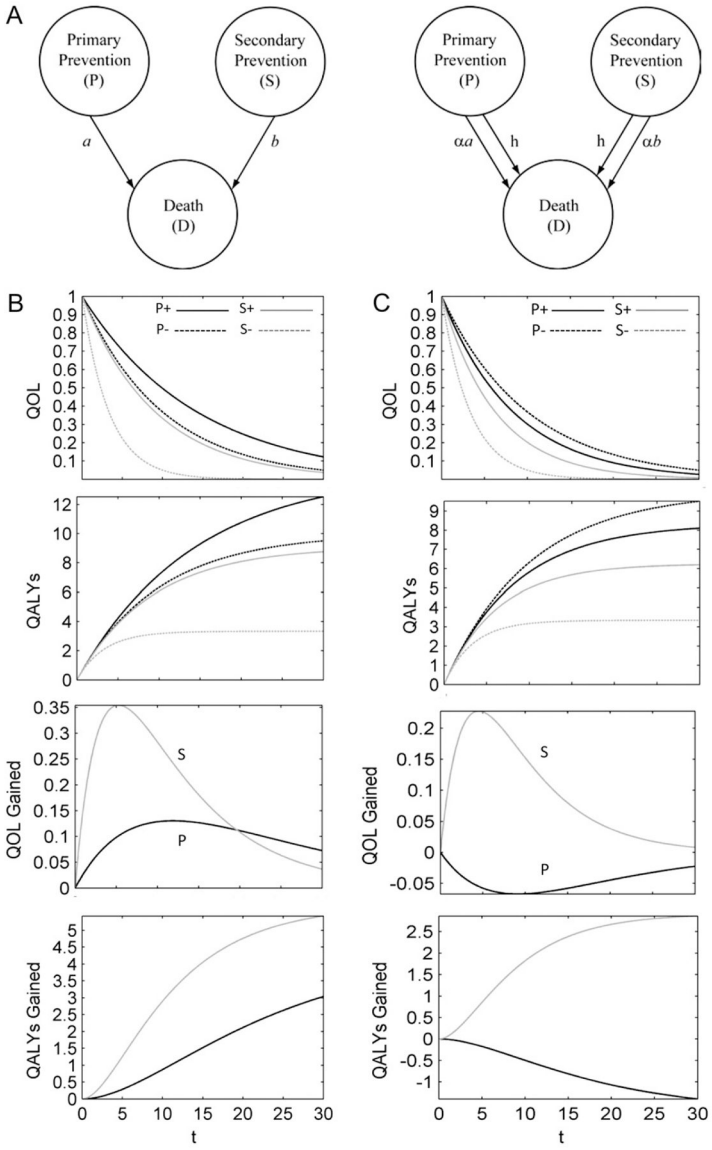

Fig. 2.

Treatment risk vs. benefit in the simplified primary vs. secondary prevention model. A. Three-state model of primary vs. secondary prevention, building on the model shown in Fig. 1B (left) by the addition of a harm factor, h, to each transition rate to death (right). B. Mean quality of life (QOL) and cumulative quality-adjusted life years (QALYs) are shown in the top row, for primary prevention (black lines) and secondary prevention (gray lines), comparing on treatment (solid lines) to off treatment (dashed lines), as in Fig. 1. The bottom row shows the net gain on treatment in each setting, by subtracting the off-treatment lines from the on-treatment lines of the QOL and QALYs curves. In this set of plots, the harm factor, h, was chosen to be small relative to the benefit factor (a) such that net benefit was achieved in both primary and secondary prevention. C. Plots are as in panel B, but in this case, the harm factor, h, was chosen to be large enough (relative to the benefit factor) that

secondary prevention is the only setting in which the treatment is predicted to provide benefit.

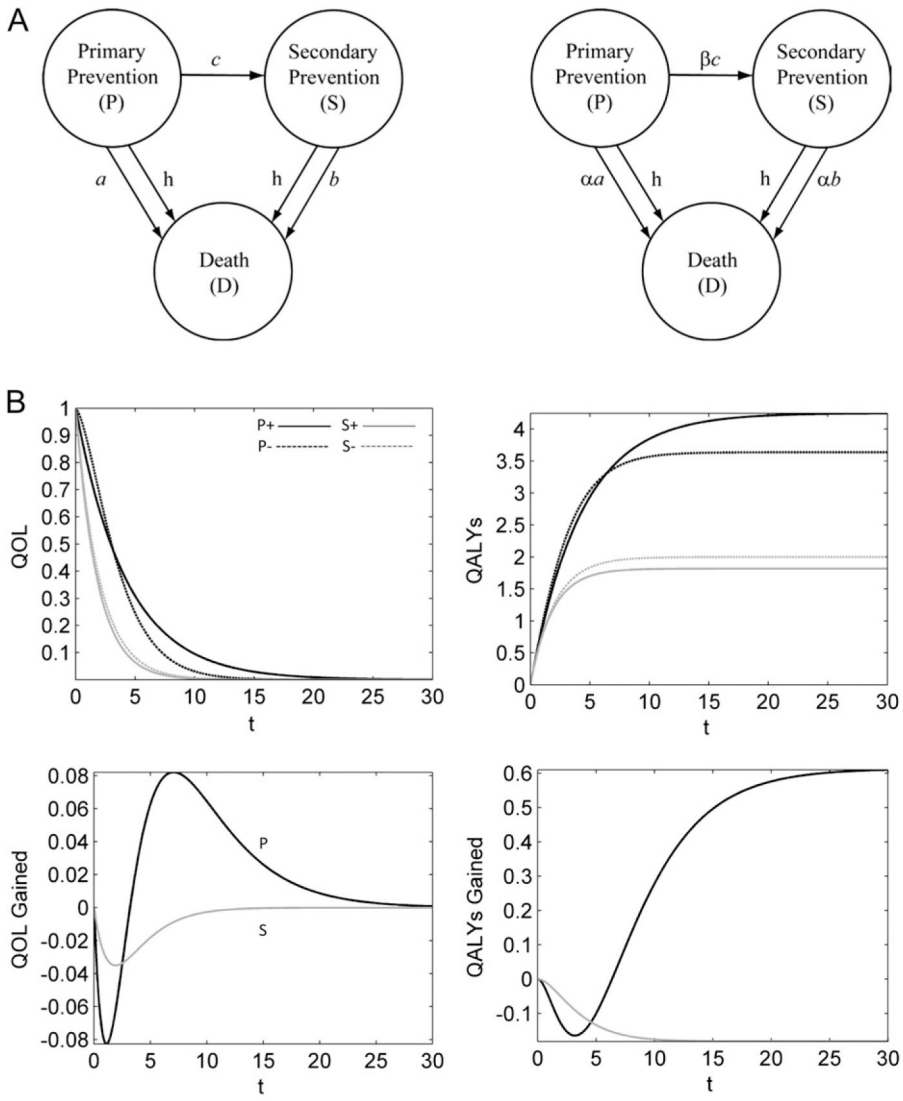

Fig. 3.

Risk–benefit balance when primary prevention can transition to secondary prevention. A. Three-state model of primary vs. secondary prevention, building on the model shown in Fig. 2A by the addition of a transition from primary prevention to secondary prevention states (left). A protective factor, β, is added to this model to allow for treatment to decrease the transition from the primary prevention state to the secondary prevention state (right model). B. Mean quality of life (QOL) and cumulative quality-adjusted life years (QALYs) are shown in the top row, for primary prevention (black lines) and secondary prevention (gray lines), comparing on treatment (solid lines) to off treatment (dashed lines), as in prior figures.

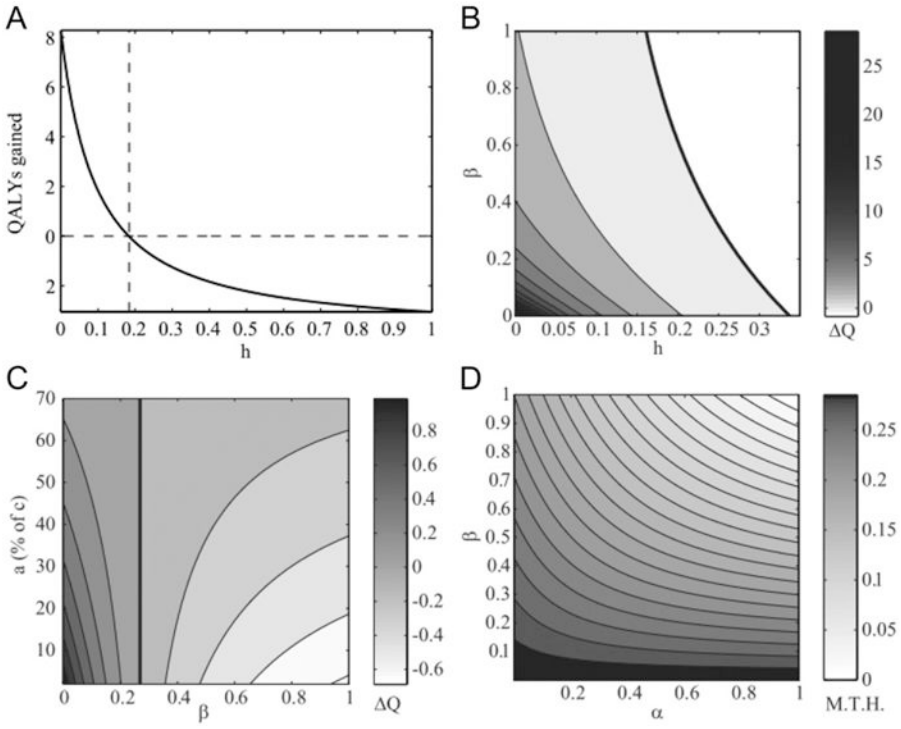

Fig. 4.

Summary plots of risk–benefit analysis. A. Long-term quality-adjusted life years (QALYs) gain in the primary prevention case of Model 3 are plotted against a range of harm factors, with the remaining parameters held constant. B. Using Model 3, net change in cumulative QALYs because of treatment (ΔQ) are shown for primary prevention as a grayscale dimension for combinations of treatment-related harm (h) and treatment-related protection against transition from primary to secondary prevention (β). The bolded contour line is the zero net benefit boundary between net benefit (to the left) and net harm (to the right). The dashed vertical line marks the value of h at where net benefit is zero in *secondary* prevention. C. Using Model 3, net QALYs (ΔQ) are shown for primary prevention as a grayscale dimension for combinations of off-treatment death rate in primary prevention (a) (expressed as a percentage of the off-treatment death rate in secondary prevention, b) and treatment-related protection against transition from primary to secondary prevention (β). As above, the bolded contour line is the zero net benefit boundary, with net benefit to the left and net harm to the right. D. Using Model 3, the maximum tolerable harm (MTH) is shown in grayscale as a function of the two benefit factors of treatment: decreased transition to death (α) and decreased transition to secondary prevention (β).

Table 1.

Exhaustive list of benefit profiles

Benefit profile		Model(s) in which this profile can occur
P	S	1,2,3
P	***S***	2,3
P	S	2,3
P	S	2,3
P	***S***	3
P	S	3

Exhaustive list of possible relative benefit profiles for primary vs. secondary prevention. Shading indicates sign of benefit: no shading denotes positive benefit, dark shading denotes negative benefit (harm). The pairs with the normal font denote relative magnitude of benefit or harm (e.g., darkly shaded italicized P denotes greater harm than for the darkly shaded S).