The Meaning of Life Expectancy:

What Is a Clinically Significant Gain?

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IMAGINE THAT A 40-YEAR-OLD MAN presents for an annual health examination. His history and physical examination are unrevealing; however, laboratory evaluation reveals a total serum cholesterol concentration higher than the 90th percentile for his age and gender. Recall that the Framingham Study[1] revealed a strong correlation between cholesterol concentration and the later development of ischemic heart disease. In addition, several intervention trials have indicated that reducing serum cholesterol levels can decrease the incidence of cardiovascular death. For example, the Lipid Research Clinics Coronary Primary Prevention Trial[2] demonstrated a 24% reduction in the incidence of cardiac deaths in asymptomatic middle-aged men who were treated with cholestyramine for an average of seven years. On the other hand, a recent decision analytic model predicts that a 40-year-old man who is above the 90th percentile for cholesterol concentration and who manages to achieve a lifelong cholesterol reduction of 10% would gain only 8 months of life expectancy, even when the potential adverse effects of cholesterol reduction on total mortality are ignored.[3, 4]

What specific recommendation should be made to this patient regarding the treatment for his hypercholesterolemia? A 24% reduction in the incidence of ischemic heart disease–related death observed in the short term seems worthwhile. However, the fact that this treatment benefit translates into a long-term gain of only 8 months seems disappointing, especially when treatment would require that the patient make a significant dietary change and/or take costly and potentially toxic drugs for the rest of his life.

In fact, the benefits of many therapies for chronic disease, when expressed in terms of gains in life expectancy, seem modest. For example, coronary artery bypass surgery for a 55-year-old man who has severe angina, normal left-ventricular function, and triple-vessel coronary artery disease would yield an additional 10.8 months of life-expectancy, compared with conservative management.[5] Another decision analysis predicted that

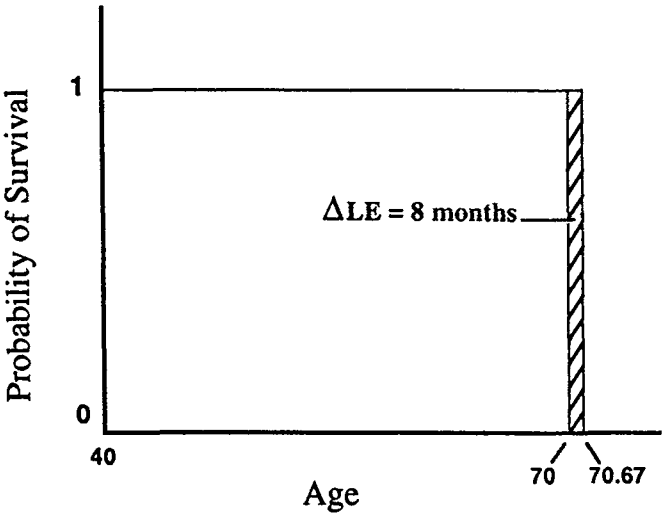

FIGURE 1. Usual understanding of a gain in life expectancy. A 40-year-old man perceives his life expectancy to be roughly 30 years. He sees a gain of 8 months as if it would be "tacked" onto the end of his life. This gain has almost no value because of the "discounting" of future life years. ΔLE = gain in life expectancy.

postmenopausal women who are treated with estrogen replacement would gain 10.3 months of life expectancy.[6] A 30-year-old asymptomatic diabetic patient who has gallstones would gain 6.1 months of life expectancy with cholecystectomy instead of expectant management.[7] Finally, warfarin would extend the life of a 75-year-old who has dilated cardiomyopathy by 2.5 months, even though it reduces the yearly incidence of systemic emboli by 83%.[8]

Why should effective treatments for chronic diseases produce relatively modest gains in life expectancy? Of course, calling a gain large or small involves assigning an arbitrary value judgment to a number. The real question is not "why are the gains in life expectancy for effective therapy small?" but rather "why do we perceive the gains for effective therapies to be small?" This perception has two sources: first, clinicians do not understand what a gain in life expectancy really means (in particular, clinicians confuse it with an increase in life span, which occurs at the end of a patients life); and second, clinicians have an overinflated sense of what constitutes a large gain. The purpose of this article is to address these issues: that is, to explain what life expectancy and gains in life expectancy mean and to suggest why physicians' perception of a significantly large gain is inflated. We hope to establish a conceptual frame-

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work within which clinicians can decide whether a gain is clinically significant. It should be noted, however, that the purpose of this article is not to advocate life expectancy gain as the best way of expressing the benefit of a therapy. Rather, decision analysts use life expectancy gain as a measure of treatment benefit when they explore the long-term consequences of health policies.[9,10] Since it is increasingly common for such decision analytic models to appear in journals read by general internists and other primary care physicians,[11–18] it is important for clinicians to have the necessary tools to properly interpret them.

THE MEANING OF LIFE EXPECTANCY

When clinicians and patients think of a gain in life expectancy, they usually visualize the benefit incorrectly as an increase in life span (Fig. 1). A 40-year-old man who has a 30-year life expectancy perceives a gain of 8 months as if it will be "tacked" onto the end of his life. He thinks the gain is insignificant because he "discounts" the value of future life years.[19] Discounting refers to the relative loss of value of a commodity as the time at which it will be obtained moves further and further into the future. For example, most people would rather receive $1,000 today as opposed to obtaining the same amount ten years from now. Money obtained today can be invested and can earn interest over the next ten years, whereas the same amount obtained ten years from now cannot. Thus, the value of $1,000 obtained ten years from now is discounted relative to $1,000 today by an amount equivalent to the interest that could have been earned over the ten years. Most people view healthy life years as a discountable commodity; that is, a year of healthy life in the present has much more value than the same amount of healthy life 30 years from now. As a result, the adverse aspects of a therapy assume much more importance because they may occur immediately. A modest gain in life expectancy that occurs at the end of a patient's life has almost no value because it is so heavily discounted.

In fact, a gain in life expectancy is not the same as an increase in life span, which occurs only in the future. Rather, a gain in life expectancy implies a potential immediate benefit. To see how this can be true, it is necessary to understand the relationship between gains in life expectancy and the more familiar ways of expressing a treatment benefit. Usually, clinicians think of a therapeutic effect in terms of the decrease in the proportion of adverse events that occur in a given period of time in a group of patients who receive a therapy, compared with a control group. There are several ways of summarizing the magnitude of the treatment effect.[20] For example, the absolute risk reduction is the difference in the proportions of adverse events in the two groups. If 50% of the patients in a control group suffer myocardial infarctions (MIs) while 40% of the patients taking a new drug have MIs, then the absolute risk reduction is (0.5 − 0.4) = 0.1, or 10%.

Another common way of expressing treatment benefit familiar to clinicians is the shift of a "survival" curve in response to a treatment. Figure 2 shows a hypothetical survival curve, which is a plot of the cumulative probability of avoiding an adverse event vs time. The survival curve for patients receiving a new drug, denoted by open circles, is shifted rightward and upward with respect to the curve for a control group of patients, denoted by closed circles. At the end of the trial, if only the proportions of adverse events in the two groups were compared, it would appear that the new drug had a very small treatment effect (i.e., a small absolute risk reduction). The calculation of treatment effect in this way is

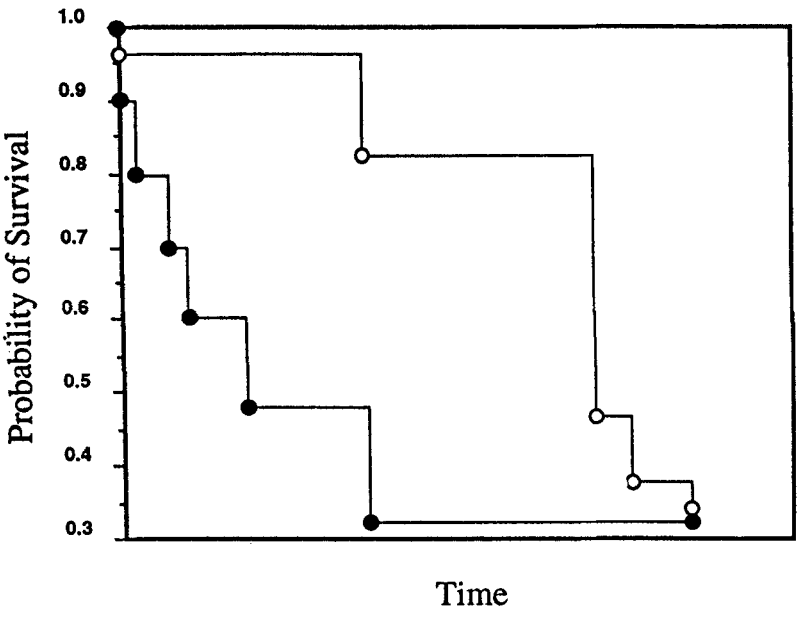

FIGURE 2. Two survival curves. Survival curves are a plot of the probability of survival vs time. The two curves in the figure represent the results of a hypothetical randomized clinical trial. The upper curve (open circles) represents the survival of patients treated with a drug, while the bottom curve (closed circles) represents the survival of control patients. Even though roughly the same proportions of patients eventually suffer an adverse event, the curve for the treated patients is shifted rightward and upward with respect to the curve for the control patients, which implies that treatment delays the adverse event. This benefit of therapy would not have been appreciated if only the absolute of relative risk reduction had been calculated at the end of the trial.

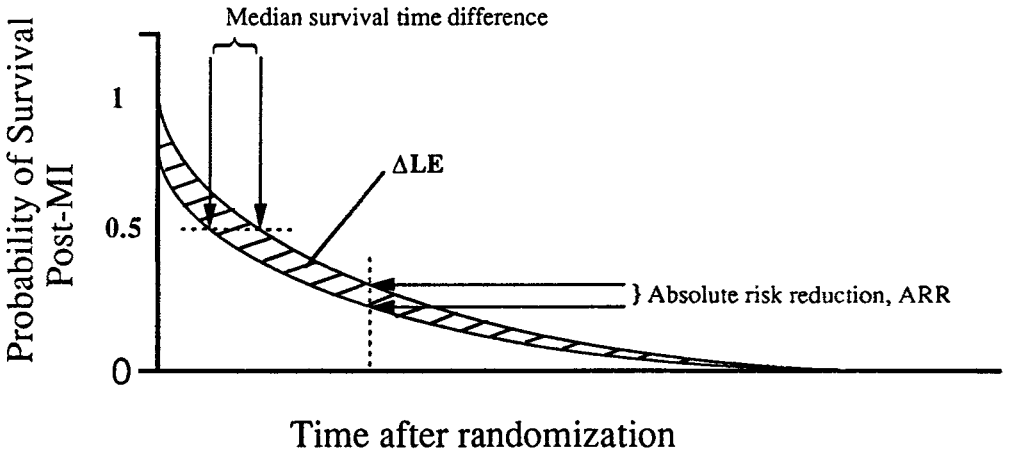

FIGURE 3. Relationship among expressions of treatment benefit. Two survival curves are shown with the curve for patients who receive beta-blockers post–myocardial infarction (MI) shifted rightward and upward with respect to the curve for patients who receive a placebo. The absolute risk reduction (ARR) at a given time is represented by the vertical separation between the curves at that time. The difference in median survival times is the horizontal separation between the two curves when the probability of survival is 50%. The gain in life expectancy (ΔLE) is the area between the two survival curves.

misleading: even though roughly the same proportion of events occurred in the group receiving the drug, the delay of adverse events is certainly worthwhile in its own right. In fact, since we all die, the benefit of any medical therapy, expressed as the difference in the proportion of deaths between two groups, must eventually be zero. However, even though death is certain, most people would prefer to die 60 years from now rather than tomorrow. Thus, treatment effect can be expressed as the extent to which a given therapy shifts the survival curve for patients with a certain disease. The magnitude of this shift is frequently summarized by the difference in median survival times or "half-times" (i.e., the time at which half of the cohort have suffered the adverse event).

The concepts of life expectancy and life expectancy gain are no more than simple extensions of survival curves. To understand this point, some definitions are necessary. The life span of an individual at a particular time is defined as the number of years that person lives beyond that time. On the other hand, life expectancy at a particular time is defined as the average future life span of a group of like individuals at that time. For example, the life expectancy value for 40-year-olds in the general population is the average future life span of a cohort of healthy people who are all 40. In theory, life expectancy is easy to calculate: one sums the life spans of all the members of a group and then divides by the number of people at the start. It can be shown mathematically that this way of calculating life expectancy for a group of people is equivalent to finding the area under their survival curve. Thus, the gain in life expectancy due to the effect of a therapy is equivalent to the area between the survival curve for patients who receive the treatment and the curve for those who do not.

Figure 3 illustrates the interrelationships between these three ways of expressing a treatment effect. Two survival curves for patients post-MI are shown. The upper curve represents patients treated with a beta-blocker, while the lower curve represents patients treated with a placebo. The vertical separation between the two survival curves at a given time represents the difference in proportions of deaths at that time (i.e., the absolute risk reduction due to beta-blocker therapy); the horizontal separation of the two curves when the probability of survival is 0.5 or 50% represents the difference in median survival times for the two groups; and the area between the two curves represents the gain in life expectancy due to the beta-blockade.

Understanding life expectancy gain as the area between two survival curves has two key implications. First, as shown in Figure 3, a gain in life expectancy due to a therapy is related to a shift in the survival curve for the treated patients. This means that the treated patients enjoy an immediate increase in the probability of survival, compared with the control patients. In other words, some patients who would have died the day after the treatment is started may not die that day. A shift in the survival curve implies that the distribution of life spans for the treated patients is "shifted to the right" (i.e., toward longer life spans) with respect to the distribution for the control patients. Thus, life expectancy gain should be viewed in a "probabilistic" sense. A gain of 8 months for a 40-year-old man with a 30-year baseline life expectancy does not mean that he will live until age 70.67 years instead of 70 years. Rather, a gain of 8 months of life expectancy means that the probability of a longer life span has increased. The actual increase for a particular individual may be large, close to zero, or even negative. However, the most probable (i.e., the average) increase in life span is 8 months. Since the distribution of life spans is shifted, a gain in life expectancy implies that the probability of a longer life span is increased even for those patients who are destined to die soon

after the initiation of the therapy. This fundamental concept is worth reiterating: a gain in life expectancy implies an *immediate* benefit to patients.

Second, for equally effective treatments, the magnitude of a given gain in life expectancy depends on the slope of the survival curve for the control patients (i.e., the baseline risk of death). Two sets of survival curves are shown in Figure 4. Panel A illustrates the case of a particularly lethal illness (such as chronic myelogenous leukemia after blast transformation), while panel B illustrates the case of a disease that is less severe [such as chronic lymphocytic leukemia (CLL)]. As shown in Figure 4, the survival curves for patients who receive new chemotherapy regimens are shifted with respect to the standard treatments. At some point, the absolute risk reduction is 15% in both cases. However, the gain in life expectancy for the patients with blast crisis is substantially less than that for the patients with CLL, even though the absolute risk reduction is the same, since the slope of the "blast curve" is much steeper than the slope of the "CLL curve." In terms of the interpretation of gains in life expectancy, the converse of this argument is more important. A small gain in life expectancy may be associated with a risk reduction that most clinicians would consider to be important if the baseline risk of death in the control patients were high.

THE LAW OF AVERAGES

As mentioned above, calculating the life expectancy of a group of people by finding the area under their survival curve is equivalent to summing all the individual life spans of the group and then dividing by the original number of people. Thus, calculating the life expectancy of a cohort of patients is analogous to finding their average hemoglobin value by summing all of the individual hemoglobin values and then dividing by the number of people in the group. It is important to realize that life expectancy values always represent averages. When decision analysts speak of the "life expectancy" of an individual with certain characteristics, they really mean the average life span of a group of people with those same characteristics. A person may have a life expectancy of 40 years, but his or her actual life span may be substantially different from the average span. Using the hemoglobin analogy, healthy men may have an average hemoglobin level (which corresponds to "life expectancy") of 140 mg/L, while individual hemoglobin values (which correspond to "life spans") may vary substantially around the average.

The gain in life expectancy is also an average value. The actual change in the life span for the individual members of a group may vary and may be distributed around the average change. A gain in life expectancy of a certain size can result from all of the members of the group's obtaining a small increase in life span or from a small proportion of a group's enjoying a large increase in life span. For example, cessation of smoking by all the members in a group of 1,000 smokers may improve the pulmonary function of all of these individuals, resulting in an increase in each of their life spans by one tenth of a year. On the other hand, use of preoperative antibiotics may prevent four of 1,000 patients from developing fatal wound infections, resulting in an increase in each of the life spans of these four by 25 years, while the other 996 patients have no gain in life span. The gain in life expectancy is 0.1 years for both groups, even though the distributions of the increases in life span are quite different.

The fact that the actual increase in life span for

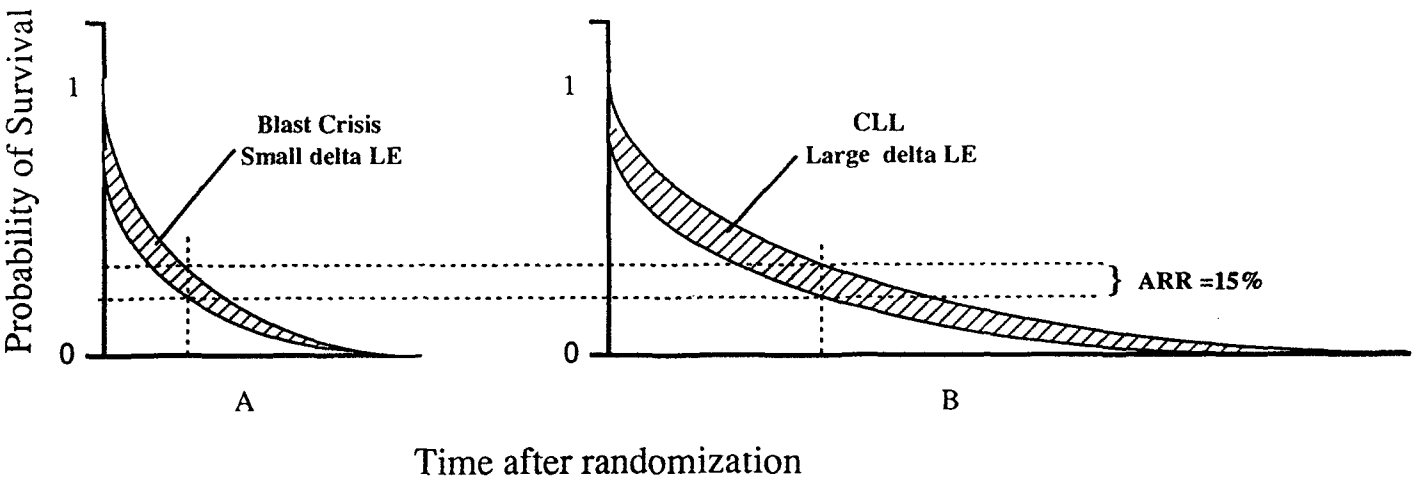

FIGURE 4. The magnitude of the gain in life expectancy (delta LE). The magnitude of a gain in life expectancy depends on the slope of the survival curve in the control group. In **A**, the upper curve represents the survival of patients with chronic myelogenous leukemia and blast transformation (i.e., "blast crisis") who receive a new chemotherapy regimen, while the lower curve represents similar patients who receive standard therapy. In **B**, the upper curve represents patients who receive a new therapy for chronic lymphocytic leukemia (CLL), while the lower curve represents patients who receive standard therapy. Both treatments are associated with an absolute risk reduction (ARR) of 15%. However, the gain in life expectancy associated with the treatment in A is much smaller than the gain for the treatment in B because the baseline risk of death in the control group in A is much higher than that in B.

individuals is distributed around the gain in life expectancy (i.e., the average increase in life span) has implications for the interpretation of apparently small gains. A small gain in life expectancy can be interpreted as meaning that most patients will not benefit from therapy but a few patients will benefit substantially.[21] Does the fact that only a few patients obtain a substantial benefit from an intervention mean that the intervention is clinically unimportant? The answer is, of course, no. For example, chloramphenicol is rarely used as an antibiotic of first choice now because of concerns regarding idiosyncratic fatal bone marrow suppression, despite the fact that it is effective and inexpensive. In other words, only a few patients benefit from the intervention (avoiding chloramphenicol), but they benefit substantially. The gain in life expectancy for all potential recipients of chloramphenicol due to the avoidance of the drug is minuscule, but, nonetheless, it is important to clinicians (otherwise, chloramphenicol would be used). For the same reason, the gain in life expectancy for screening or immunization programs should be expected to be relatively small because few patients will benefit directly. Clinicians consider these gains to be clinically important because the few patients who are discovered by the screening process and are appropriately treated with benefit substantially.

INFLATED PERCEPTION

Another reason why gains in life expectancy of weeks to months seem modest is that our perception of what constitutes a big gain has been shaped by the population-wide gains achieved in this century. Since 1900 the life expectancy at birth has grown dramatically. For example, the life expectancy for a woman born in 1900 was 47 years, while the life expectancy for a woman born in 1988 was 75 years.[22] Most of this gain has been due to large decreases in neonatal and maternal mortality and deaths due to infectious disease, while relatively little has come from the modern therapies for the chronic degenerative diseases of middle-aged and elderly patients. In the future, gains in life expectancy are likely to be much more modest than those in the past because most interventions will be targeted at chronic diseases. For example, to increase the life expectancy at birth from 75 to 100 years would require the reduction of all causes of mortality across all ages for both men and women by 85%.[22] Set in this context, we should expect modest gains in life expectancy for management of chronic disease in older patients.

CONCLUSION

When confronted with a decision analytic model that predicts long-term gains in life expectancy of days, weeks, or months for a diagnostic or therapeutic intervention considered to be efficacious from short-term studies, clinicians are inclined to think that either the analysis is faulty or the interventions are worthless. In this article, we have attempted to show that neither of these conclusions is correct. Apparently small gains in life expectancy can be associated with clinically important therapeutic interventions. The gains themselves are neither large nor small; rather, clinicians place a value judgment on a given gain based on a misconception of what life expectancy gain means and based on an overinflated sense of what constitutes a "large" gain. We have shown that a gain in life-expectancy implies an immediate increase in the probability of survival for some treated patients rather than a heavily discounted benefit that occurs only in the distant future.

When confronted with a gain that seems small, clinicians should ask themselves two questions. First, what is the baseline mortality rate in the control group? If the underlying disease is especially lethal, an apparently small gain may be associated with a large and clinically important absolute risk reduction. Second, how many patients stand to benefit from the intervention out of the total population treated? If the number is small, then a small gain in life expectancy is to be expected. However, as for screening and immunization programs, clinicians may consider this small gain to be clinically important because the benefits are so dramatic for the relatively few patients who receive them.

Results of decision analyses are appearing commonly in the medical literature and the metric of health benefit frequently employed is life expectancy gain. We hope this article will provide clinicians with a conceptual framework within which the results of these analyses can be properly interpreted.

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