Actual and Actuarial Probabilities of Competing Risks: Apples and Lemons

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The probability of a type of failure that is not inevitable, but can be precluded by other events such as death, is given by the cumulative incidence function. In cardiac research articles, it has become known as the actual probability, in contrast to the actuarial methods of estimation, usually implemented by the Kaplan-Meier (KM) estimate. Unlike cumulative incidence, KM attempts to predict what the latent failure probability would be if death were eliminated. To do this, the KM method assumes that the risk of dying and the risk of failure are independent. But this assumption is not true for many cardiac applications in which the risks of failure and death are negatively correlated (ie, patients with a higher risk of dying have a lower risk of failure, and patients with a lower risk of death have a higher risk of failure, which is a condition called informative censoring).

Recent editorials in two cardiac journals have promoted the use of the KM method (actuarial estimate) for competing risk events (specifically for heart valve performance) and criticized the use of the cumulative incidence (actual) estimates. This report has two aims: to explain the difference between these two estimates and to show why the KM is generally not appropriate. In the process we will rely on alternative representations of the KM estimator (using redistribution to the right and inverse probability weighting) to explain the difference between the two estimates and to show how it may be possible to adjust KM to overcome the informative censoring.

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"Tissue valves suffer from structural failure, with an average lifetime of 10 to 12 years before replacement is needed [1]."

This quote seems like a reasonable answer to the question, "What is the average lifetime of a tissue valve" . . . or is it? The average lifetime of a group of patients can always be determined exactly by someone who outlives the last patient. But a fundamental difference exists between the lifetime of a patient and the lifetime of a tissue valve. The probability that a patient will die is 100%, but the probability that her tissue valve will fail is far less than 100%, because in most cases it will still be functioning when she dies, say from an accident or cancer. In a recent simulation study of aortic tissue valves, estimates of the percentage of valves that fail ranged from 40% to 50% in the youngest age group of patients to less than 10% in the oldest age group [2]. This complicates the estimation or even the meaning of the average lifetime of a tissue valve. How does one estimate the average lifetime of the valves in a series if more than half never reach their end of life and are thus not available to even contribute to this average?

To do this, one would have to eliminate deaths that occur before valve failure, since they censor (hide) the valve's latent failure time (see Appendix 1). One cannot do this in reality, so attempts are made to virtually eliminate the intervening deaths by statistical means, using the valves that do fail to predict the latent valve failure times for the patients who die with functioning valves, and thus complete the censored lifetimes statistically. This is what the Kaplan-Meier (KM) estimate for death does. The KM method completes the survival experience of the censored valves by assuming that they ultimately die at a future time, and at the same rate as those who have already died. However, this last assumption, of noninformative or ignorable censoring cannot be proven to be true [3, 4], and it is in fact false in many cases including the valve failure example. Patients who die before valve failure are generally older than those who do not, whereas the rate of tissue valve failure is lower in older patients. Thus the (counterfactual) future failure rate in deceased (censored) patients would be lower than that of the (generally younger) patients who did live to experience valve failure.

The probability of valve failure in a particular patient population is given by a function called the cumulative incidence, also known as the actual probability in the cardiac literature, because it estimates the percentage that will actually fail from each of the competing risks. The most common use of actual analysis in the cardiac literature is for structural valve deterioration (SVD) of tissue valves [5–10], but it has also been used for other events, including heart transplantation listing [11], coronary artery reintervention [12], reoperation in patients

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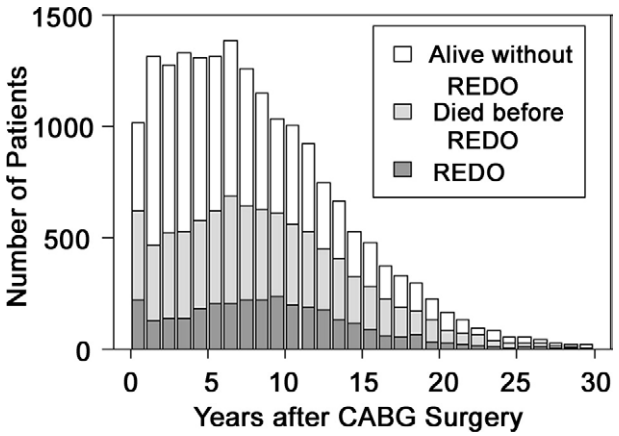

Fig 1. The current status of patients after coronary artery bypass grafting (CABG) surgery by years after operation. (REDO = reintervention.)

with aortic dissection [13], and complications of combined carotid and coronary artery surgery [14].

The general setting in all of these examples is that of competing risks [15]. In the case of valve replacement, two processes are "competing" to terminate the function of the heart valve (ie, the wearing out of the valve [SVD] and the wearing out of the patient [death]). Similarly, in assessing the durability of coronary artery bypass grafting surgery (CABG), reintervention (REDO) ends the success of the original intervention, or the patient may die of other causes before having to undergo REDO. The setting of tissue valve SVD has been used before to compare the actual and actuarial methods [16–18]. Thus in this report we will use instead our CABG surgery data to demonstrate: (1) the cumulative incidence (actual probability) of REDO; (2) the KM estimate of REDO, based on the incorrect assumption; and (3) a method of correcting the KM estimate.

Clinical Material

From 1968 through 2003, 20,835 patients underwent at least one isolated CABG procedure on our service. For this exposition, we excluded patients who died in hospital or within 30 days (2.7%) and patients who survived the operation but were followed for fewer than 30 days (8%). The remaining 18,596 patients have been followed for 171,959 patient-years, during which 16% have had REDO, 35% have died without REDO, either surgical or percutaneous, and 49% were last known to be alive and REDO-free at the time of analysis (Fig 1). The maximum follow-up is 35 years, but we truncated the figures at 30 years, beyond which only 50 patients had follow-up.

Survival or Mortality?

For characterizing time-related events in mathematics, the most fundamental function is the distribution function or curve, which plots the cumulative percentage of events occurring with time. In survival analysis, the complement of this curve is used (ie, the percentage event-free at each point in time). Herein we will keep the death (event), rather than the survival (event-free) perspective, because it is more fundamental (and is consistent with the ubiquitous use of operative mortality rather than operative survival). Thus the KM estimate we use is the complement of the usual KM estimate. (One could always invert these curves, physically or in one's mind's eye, if the event-free perspective is desired.)

1. Cumulative Incidence (Actual Probability) of REDO

The probability of REDO is given by the cumulative incidence function or curve (actual failure), which can be derived from the data in Figure 1. If the series were completed (ie, if no patients were still alive), then the probability of REDO is obtained by simply adding up the number of REDOs in time and dividing by the total

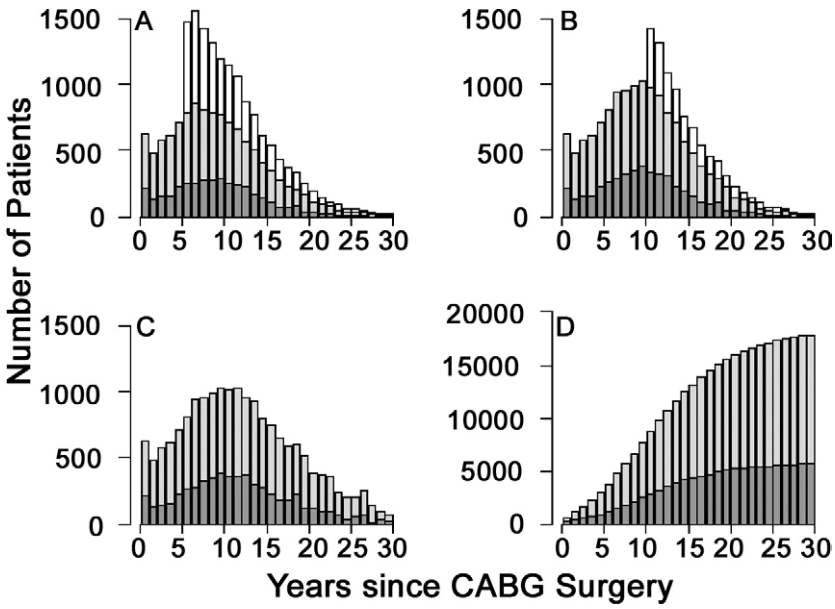

Fig 2. How the current status data in Figure 1 is transformed into the cumulative incidence function in Figure 3. The legend in Figure 1 defines the shaded areas. The alive patients (white bars) are redistributed to the right into the darker panels (panels A and B) becoming future deaths or reinterventions (REDOs) according to the risk patterns of these events already established. Panel A shows redistributions after 5 years, panel B after 10 years, and panel C after the process is completed. Panel D is the cumulative sum of the bars in Panel C, which can be converted to percentage to produce the cumulative incidence curves (shown by the solid lines in Figure 3). (CABG = coronary artery bypass grafting.)

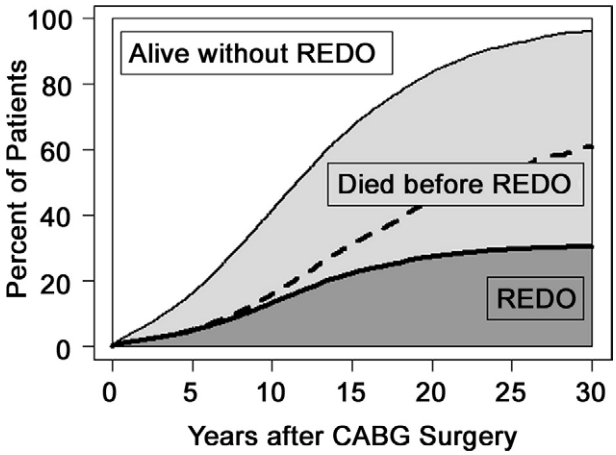

Fig 3. Status probabilities (shaded areas, solid lines) by time after surgery derived from the data in Figure 1 through the progression of steps in Figure 2, including the probability (cumulative incidence) of reintervention (REDO). The dashed line is the Kaplan-Meier REDO curve derived from the data in Figure 1 through the progression of steps in Figure 4. (CABG = coronary artery bypass grafting.)

number of patients. How can we estimate this curve when approximately half of these patients (Fig 1) have not yet reached their endpoint (death or REDO)? In this case, the calculation can be accomplished by distributing patients who are still alive without REDO proportionally into the other two groups. The proportions are based on the assumption of noninformative censoring (ie, patients alive without REDO will experience either future REDO or death before REDO at the same rate as those who have already done so). This assumption is usually reasonable because the majority of these patients are censored, simply because they have not been in the study long enough to reach one of the endpoints (ie, death or REDO). However, if there has been a change in patients recruited during the study timeframe, or if a large percentage of the censored patients are lost to follow-up, then this assumption may be violated.

This process can be demonstrated graphically by showing the modification to the current status data of Figure 1. We can gradually develop the cumulative incidence estimate by distributing the patients who are alive in each bar of Figure 1 out across time to "complete" their experience, ending in either the REDO or the dead status. Panels A and B in Figure 2 show this process of redistribution to the right [19] partially completed, and in panel C it is complete. To approximate the cumulative incidence curves, the bars in panel C are simply cumulated in time (Fig 2D).

Figure 3 shows the cumulative incidence curves, which are smooth versions of the curves in Figure 2D, divided by the total number of patients to normalize the maximum to 100%. Note that the probability of REDO levels off to a percentage (30%) that estimates the percentage of CABG surgeries that will actually undergo REDO. For this reason, the cumulative incidence is called a subdistribution function [4], which emphasizes that it is an "improper" distribution function that does not reach 100%, because (unlike death) not all patients will experience the event.

2. Kaplan-Meier Estimate of REDO

For the event death, the KM method works the same way as previously mentioned, and gives an estimate of the percent mortality at each time by distributing the patients who are still alive (censored) into future deaths at similar rates as those who have already died. But for events that are not necessarily fatal, such as REDO after CABG, KM estimates the probabilities by treating both the patients who are alive and those who have already died as censored. The KM method makes the assumption that both subgroups will eventually have REDOs and that their rates will be the same as that of those who have

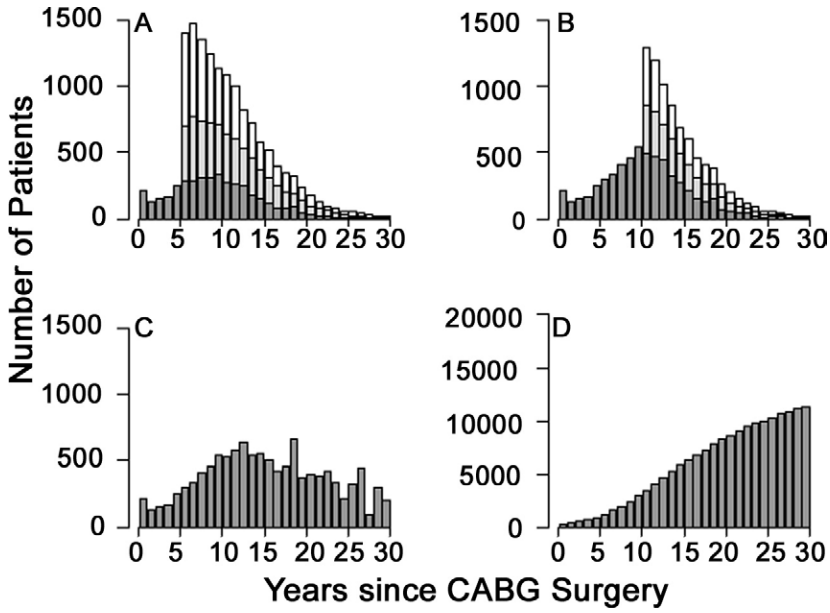

Fig 4. How the current status data in Figure 1 is transformed into the Kaplan-Meier estimate of reintervention (REDO). The legend in Figure 1 defines the shaded areas. Note that patients from both the white bars (alive) and the light gray bars (died) are distributed into the future REDO (dark gray) bars. Panel A shows redistributions after 5 years, panel B after 10 years, and panel C after the process is completed. Panel D is the cumulative sum of the bars in Panel C, which can be converted to percentage to produce the Kaplan-Meier curve (shown by the dashed line in Figure 3). (CABG = coronary artery bypass grafting.)

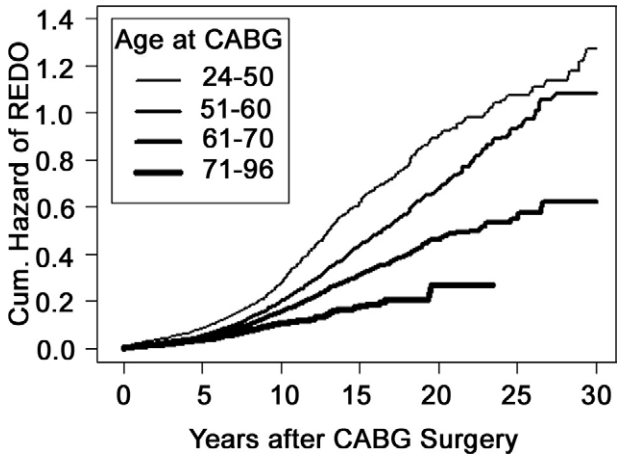

Fig 5. Cumulative hazard of death before reintervention (REDO) by age group. (CABG = coronary artery bypass grafting.)

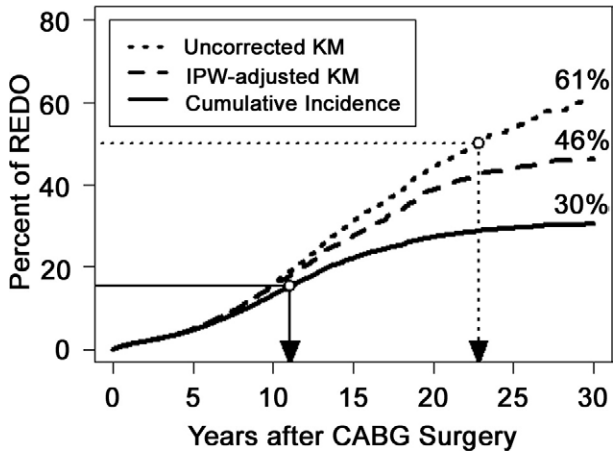

Fig 7. Three methods used to estimate the probability of reintervention (REDO) after coronary artery bypass grafting (CABG): Kaplan-Meier (KM) estimate (from Fig 3), cumulative incidence (from Fig 3) and KM with inverse probability weighting (IPW) correction. The grid lines and arrows locate the median times to REDO.

already had REDO. The way that KM redistributes both the dead and alive patients from Figure 1 is shown in Figure 4. The final KM estimate of REDO is about twice as high as the actual REDO curve, which is shown as a dashed line in Figure 3.

The KM method attempts to predict what the REDO rate would be if no patient ever died. Of course, this value would be higher than the actual value, but to do this, KM relies on the assumption of noninformative censoring for not only the patients who are alive, but also for the patients who have died, an assumption that is not true in this situation nor in many other medical applications. The cumulative hazard of death before REDO increases with patient age (Fig 5), whereas the cumulative hazard of REDO decreases with patient age (Fig 6). This informative censoring causes the KM REDO curve to be higher than it should be; if the patients who died before REDO were revived and allowed to continue on to REDO, they would lower the estimate given by the KM curve. We can estimate the amount of this lowering using a technique called inverse probability weighting.

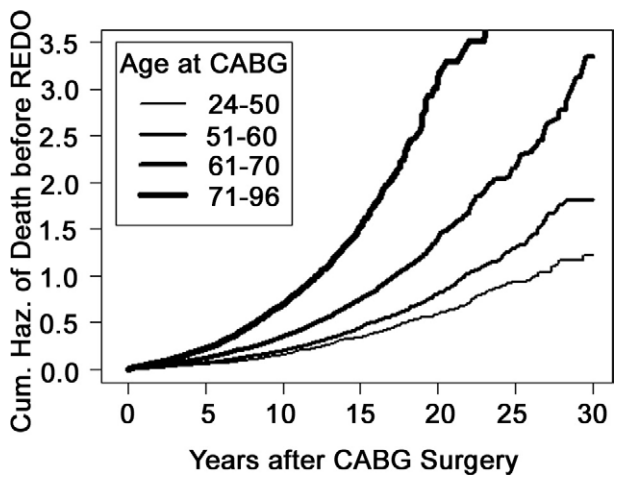

Fig 6. Cumulative hazard of reintervention (REDO) by age group. (CABG = coronary artery bypass grafting.)

3. Correcting the KM Estimate

Some methods to overcome the limitations of informative censoring have been suggested [20–22], but they are rarely used in the cardiac literature, and the incorrect KM method is used instead. One method of adjusting for informative censoring, called inverse probability weighting (IPW) [23, 24], can be used to illustrate and attempt to correct the KM estimate. The IPW method is based on an alternative but equivalent expression for the KM estimator. The KM estimator is usually expressed as a product of incremental survival probabilities computed at each event time (it is called the product limit estimator), but it can also be derived in other ways [25, 26], including the redistribution to the right technique demonstrated in Figures 2 and 4. A useful alternative representation is as a sum of weighted death probabilities, computed at each event time in which the weight is the inverse of the probability of that event being observed [23, 27]. Thus, the weight (IPW) assigned to each observed event increases as the probability that similar events were not (yet) observed increases (see Appendix 2).

The probability that each REDO event was observed (ie, not censored) was estimated by a Cox regression, based on age, diabetes and previous coronary intervention, and was used to (inversely) weight that REDO. (This Cox model was not intended as a clinically serious model, but just as an example to demonstrate the IPW technique. In practice, one would have to have the appropriate clinical information and to thoroughly evaluate the resulting Cox model to insure that it correctly estimated the probability of each REDO event being observed.) The resulting IPW-corrected curve is lower than the original KM curve (Fig 7). Note that if the correlation between REDO and censoring were positive instead of negative,

the IPW-corrected curve would be higher than the original KM curve.

Comment

The question posed at the beginning of this report was, "What is the average lifetime of a tissue valve?" We presented data on CABG REDO instead of heart valve failure, so we should translate the question to its analog: "What is the average durability (lifetime) of a CABG operation?" From the cumulative incidence curve in Figure 7, the actual answer has 2 parts (similar to the analogous answer for heart valve SVD): "Only about 30% of patients undergoing CABG surgery are expected to have a REDO (ie, the lifetime risk of REDO for a patient in this population is 30%), and for these patients, the median time to REDO is about 11 years." This method answers the durability question for a patient in a particular population: "Doctor, what is my risk of reoperation?" This answer can be extended to other patient populations as long as the death rates between the populations do not differ. An alternative to the "actual" computation method is offered by simulation techniques using Markov models [28, 29].

Using the uncorrected KM (Fig 7), the answer would be: "The median time to REDO is about 23 years." This is obviously a fictitious answer; why would anyone want to use it? The reason is that the percentage of REDO is affected by the death rate. There may be interest in determining what the REDO curve would look like if every patient lived long enough to undergo REDO. That is, if the area "died before REDO" were somehow eliminated from Figure 3, what would be the shape of the "REDO" area? Using KM, this would be the area below the dashed line in Figure 3. Although this may not seem clinically relevant in the case of CABG REDO, when this method is used for tissue valve failure the hope is to extract the latent failure probability to assess the intrinsic durability of the prosthesis itself in a death-free environment. An engineer designing a heart valve would not want the durability results to be contaminated by the death of a patient, nor would a cardiac surgeon who is trying to find the most durable tissue valve for his and her patients. Thus the KM estimate is an attempt to produce an indicator in a biological system of the true durability of the valve. This is an important clinical question for which the KM estimate, if it can be properly corrected for informative censoring, may be the preferred estimate.

Recent editorials called for the banning of "actual" analysis and the preferential use of KM for reporting heart valve performance [30, 31]. However, as we have seen, the KM estimate has a fundamental though underappreciated problem: KM does not provide the desired latent probability when there is dependence between the competing risks of death (and hence censoring) and the event of interest. For tissue valve SVD, just as in the CABG REDO example, informative censoring would exist and need to be corrected. Heart valve patients censored by death would not have the same risk of eventual SVD if they lived as those who actually did live to experience SVD, because the risk of death is high in patients in which the risk of SVD is low (eg, the elderly), and vice versa. So the risks of SVD and censoring (by death before SVD) are negatively correlated, not independent. It is for this reason that the KM method has been repeatedly criticized as having in general no valid probability interpretation in the competing risks setting [26, 32–35].

These editorials also took exception with the use of the term actual (probability, failure, analysis) [30, 31]. We originally proposed this term [16] because it seemed appropriate, and because there was no consensus in the technical literature as to the best terminology to use. Potential terms, among others [18, 36, 37], included: cumulative incidence, crude probability, crude incidence, cause-specific failure probability, absolute cause-specific risk, and subdistribution function. Subsequently the actual terminology has been accepted by other investigators [5–14].

In conclusion, there are three methods for estimating the probabilities of time-related events, such as SVD or REDO, when death is a competing risk that can preclude their occurrence:

1. The actual (cumulative incidence) method estimates the probability that a patient will experience the event. This is the correct probability that should be used for clinical predictions, patient management decisions, cost-effectiveness studies, and so forth.
2. The usual KM estimate, which includes pre-event deaths as noninformative censoring, attempts to estimate the probability if no one died. This does not pertain to patient predictions, but could be useful in trying to elicit the latent or intrinsic risk of tissue valve failure. However, this use of KM is a bitter fruit: it is only valid if death is independent of the event of interest, which is usually not the case in cardiac applications, including SVD and REDO.
3. When there is dependence between the competing risks of death and the event of interest, the IPW technique could be used to correct KM for the resulting informative censoring, provided that a model for the censoring can be produced. This is the estimate that could be used by those interested in the hypothetical durability of a valve or surgical procedure, rather then its real durability in an actual patient.

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Appendix 1

What is Censoring?

If we know that a certain patient who was recruited into our interventional study 5 years ago is still alive, we have partial, but not complete, information on her post-intervention survival time (ie, we know that it is longer than 5 years). We say that her post-intervention survival time is (administratively) censored at 5 years. Censoring is an essential characteristic of event times. An artificial analogy could be constructed by using, say, a 5-foot ruler to measure height. For any patient whose height is less than 5 feet, we measure it exactly, but for patients taller than 5 feet, we can only say that their height is at least, or is censored at, 5 feet.

Appendix 2

Inverse Probability Weighting

The inverse probability weighting (IPW) provides another way of obtaining probability estimates from censored survival data, and in

the case of noninformative censoring it provides the same answer as the Kaplan-Meier (KM) method. It begins with the idea that if there were no censoring, then the mortality curve (the complement of the survival curve) would be given by the percentages of cumulative deaths with time, obtained by a simple summation.

However, suppose that an event has occurred at time (t), and that exactly half of the patients are currently censored before that time. That is, only half of the patients have passed that point so far in time, and have been exposed to the risk of an event at time t. Then, on average, one could expect that eventually one more event will happen at that time (ie, after the second half of the patients have experienced the risk associated with that point in time). Therefore, the total number of expected events is 2. In general, if P is the proportion of patients who have passed through that point in time, then the expected number of events (E) is $E = 1/P$. However, P is the proportion of patients who are not censored, so if PC is the proportion of people who are censored ($P + PC = 1$), then $E = 1/(1 - PC)$.

For example, if there is no censoring, then $PC = 0$ and $E = 1/(1 - 0) = 1$, that is, the expected number of events stays at 1 because there are no more patients left to increase the number of events at time t. If there is mild censoring, say $PC = 0.1$, then 1 observed event is expected to increase to $E = 1/0.9 = 1.1$, just a slight increase because there will be only a small percentage of patients in the future with the potential to increase the number of observed events at time t. On the other hand, if there is severe censoring, say $PC = 0.9$, then the observed event is expected to increase to $E = 1/0.1 = 10$ events. The previous examples assumed a homogeneous event risk. If there is informative censoring, then PC could vary from patient to patient, and it would have to be estimated individually according the risk factors of the patient experiencing the event. This is what was done in the coronary artery bypass grafting (CABG) data example, using a Cox regression to estimate the PC values at each event time, according to the characteristics of the patient who suffered that event.