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REVIEW

Hazardous to Your Health: Kinetic Foundations of Risk Stratification and Therapeutic Triage

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ABSTRACT

BACKGROUND: Risk stratification is widely used in the prognostic assessment of patients with a variety of clinical disorders on the unquestioned assumption that the intensity of treatment should be proportionate to the threat of an adverse event over some finite period of time (risk). However, just as the physical trajectory of an object depends on its current magnitude of displacement (velocity) and the concurrent rate of change of that displacement (acceleration), the prognostic trajectory of a patient depends on the current magnitude of risk and the concurrent rate of change of that risk (hazard). Clinical risk stratification nevertheless relies only on the former.

METHODS: We therefore integrated the quantitative assessment of risk and hazard by way of a kinetic model that characterizes the development of an adverse event as a series of exponential state-to-state transitions—from stable to unstable to event. This model serves to shift the clinical emphasis from prognosis (the assessment of risk) to treatment (the improvement in outcome). In this context, treatment is well advised (even in low-risk individuals) when the hazard is large (risk is rising), and is less well advised (even in high-risk individuals) when the hazard is small (risk is stable).

RESULTS: The kinetic model outlined here thereby promises to supersede the superficial practice of risk stratification with a more sophisticated strategy of therapeutic triage that allows one to predict the incremental clinical benefit of alternative treatment strategies.

KEYWORDS: Risk; Hazard; Kinetics; Prognosis; Risk stratification; Mathematical modeling; Prediction models

Diseases desperate grown
By desperate appliance are relieved . . .
Hamlet (Act IV, Scene iii)

Like Hamlet's uncle, the thoughtful clinician takes it to be self-evident that the intensity of therapy should be proportionate to the risk of disease.[1,2] Ever since Bigger coined the term "risk stratification" to characterize this intuitive process,[3] more than 3000 articles have been published on the subject—at a rate that is doubling every 5 years. Approximately 40% of these articles focus on cardiovascular medicine, where "risk stratification" has become something of a mantra for rational, evidence-based clinical management.

Although numerous semiquantitative algorithms are in wide use—the neonatal Apgar score,[4] the Tumor-Node-Metastasis (TNM) Classification,[5] and the Glasgow Coma Scale,[6] to name a few examples—the most sophisticated risk stratification algorithms use multivariate statistical regression models derived from empirical databases.[7]

Consider a simplistic application: 2 patients (Dick and Jane) undergo exercise-redistribution myocardial perfusion scintigraphy because of symptoms suspicious of ischemic heart disease. In each case, the test reveals reversible regional hypoperfusion of similar magnitude. What, they ask, is their risk for a morbid event, and what should be done to reduce that risk? Risk stratification provides a seemingly straightforward answer to these questions. A quantitative statistical regression algorithm estimates the 1-year risk of a clinical event to be 12% for Dick and 6% for Jane (the difference resulting from factors other than hypoperfusion).

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Thus, because Dick has a higher risk than Jane, he is thereby considered deserving of more aggressive therapeutic intervention.[7]

Suppose, however, that both had undergone similar testing a year ago. At that time, Dick's risk was slightly lower (11% vs 12%) and Jane's risk was much lower (1% vs 6%). In this context, Jane's risk, although lower than Dick's, has been increasing more rapidly, and if we were to extrapolate to some future time, Jane's risk would eventually exceed Dick's risk (Figure 1, *top*). This simple hypothetical example illustrates the conceptual independence of *risk* (the probability of loss over some putative interval of time) and *hazard* (the rate of change in risk). The terms are sometimes used differently; in environmental risk management, a hazard is a potential risk. The formal distinction between risk and hazard is precisely the same as that between *velocity* (distance per unit of time) and *acceleration* (the rate of change in velocity). Thus, just as velocity alone is an insufficient specification of motional dynamics, risk stratification is an insufficient specification of clinical dynamics and, therefore, an incomplete basis for therapeutic decisions.

CLINICAL SIGNIFICANCE

- *Risk* and *hazard* (the rate of change in risk) are often confused.
- Treatment can be directed against risk or hazard.
- Treatment might be well-advised (even in low-risk individuals) when hazard is large, and less well-advised (even in high-risk individuals) when hazard is small.
- A kinetic model provides the formal basis to explore the therapeutic implications of these distinctions.

Suppose 3 treatment options are available to Jane. Given "no treatment" her risk is presumed to increase almost linearly with respect to time (being 11% in 1 year and 16% in 2 years). Given "surgical treatment," her risk is presumed to decrease immediately to some lower baseline (say 1%), but will nevertheless continue to increase at the same rate as before (because we presume surgery would not affect the underlying causal factors). As a result, Jane's risk will be back to pretreatment levels after a relatively short period of time. Given "medical treatment" (which we presume would affect the causal factors) the slope of the risk line (the hazard) falls immediately, even though the risk itself is not yet affected. At some future time, then, the risk associated with surgical treatment eventually becomes greater than that for medical treatment because of the differential slopes (hazards) associated with the two treatments (Figure 1, *bottom*). We see, therefore, that treatment can affect risk and hazard independently, with very different prognostic consequences.

A KINETIC MODEL OF RISK

A kinetic model makes the qualitative and quantitative distinctions between risk and hazard explicit.[8] Such a model is mathematically more complex than those typically encountered in the medical literature, but, as we shall see, this complexity is justified by the model's fidelity to the underlying pathophysiologic principles, its empirical foundation, and its applicability to a broad range of clinically important questions.

Kinetic models have been used for centuries in the physical sciences[9] and have been successfully applied to the study of a variety of biologic processes including plasma membrane electrodynamics,[10] digitalis pharmacokinetics,[11] contractile periodicity,[12] myocardial imaging,[13] cancer chemotherapy,[14] and clinical epidemiology.[15] Briefly, a kinetic model quantifies the time-dependent transition from state A to state B (denoted $A \rightarrow B$), the states being expressed in terms of absolute or relative prevalence (denoted $[A]$ and $[B]$), and the time dependence being expressed in terms of an empirically determined rate constant (k) or half-life ($t_{1/2} = \ln 2/k$). The canonical transition of this kind is that of a monotonic exponential decay ($[A] = e^{-kt}$), where $[A] = 1$ at $t = 0$, the rate of change for $[A]$ is inversely proportional to its prevalence, and the rate constant, k, is the hazard:

$$\frac{d[A]}{dt} = -k[A]$$

The simplest such model capturing the essence of the transition from a stable clinical state to a manifest clinical event is shown below:

$$S \underset{k_1}{\overset{k_2}{\leftrightarrows}} U \overset{k_3}{\rightarrow} E$$

According to this model, a stable clinical state (S) transitions to an intermediate unstable state (U), which then transitions back to the stable state or to an irreversible event state (E). This general pattern is characteristic of many clinical syndromes—the underlying disease remaining stable and quiescent for long periods of time, interrupted briefly by acute exacerbations that either regress to quiescence or progress to an irreversible morbid event. From this perspective, the frequency of events can increase in only 3 ways: by an increase in the rate of transition from stability to instability ($S \rightarrow U$), by a decrease in the rate of transition from instability to stability ($U \rightarrow S$), or by an increase in the rate of transition from instability to the event ($U \rightarrow E$).

The rate of each transition is quantified by its associated rate constant (k_1 through k_3). Assuming the transitions obey a simple exponential law, we can construct a kinetic model for the process in terms of a set of linear differential equations (hazard functions):

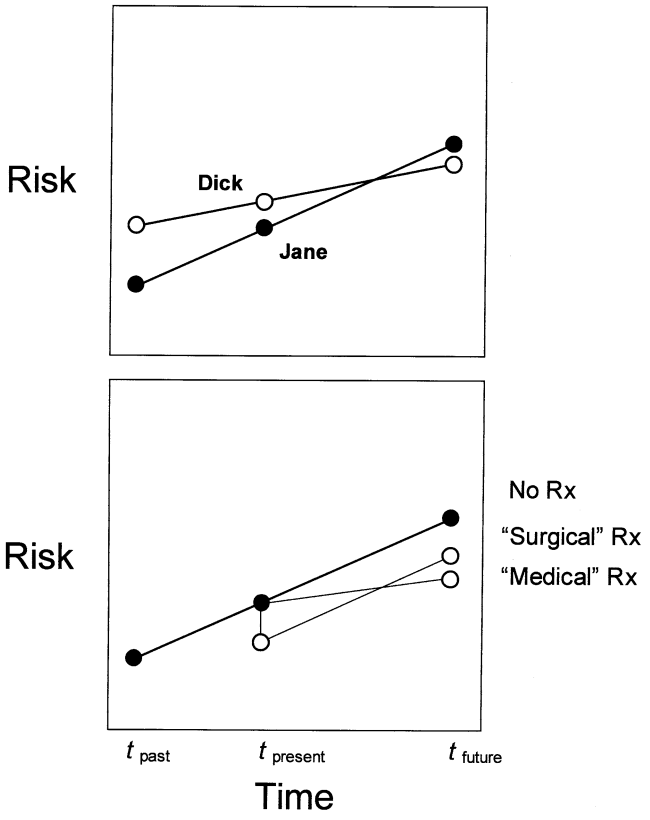

Figure 1 The conceptual independence of risk and hazard. The slope of the line representing the rate of change in risk (hazard) is greater for Jane (*solid circles*) than for Dick (*open circles*) (*upper panel*). As a result, although Jane's risk is less than Dick's at the present time (t), it will eventually become greater, at some future time. Risk stratification is therefore an incomplete basis for therapeutic triage as shown by the differential effects of treatment on risk and hazard (*lower panel*). See text for further discussion.

$$\frac{d[S]}{dt} = -k_1[S] + k_2[U]$$

$$\frac{d[U]}{dt} = -k_1[S] - (k_2 + k_3)[U]$$

$$\frac{d[E]}{dt} = k_3[U]$$

where $[S]$, $[U]$, $[E]$ are the population prevalences of states S, U, E; k_1, k_2, k_3 are the rate constants for the individual state-to-state transitions; and $[S]+[U]+[E] = 1$ in any finite population. The prevalence of each state over time is given as the solution to these differential equations.[8]

$$[S] = \frac{k_2[U]_0 - (k_1 + m_2)[S]_0}{m_1 - m_2} e^{m_1 t} - \frac{k_2[U]_0 - (k_1 + m_1)[S]_0}{m_1 - m_2} e^{m_2 t}$$

$$[U] = \frac{(k_1 + m_1)(k_2[U]_0 - (k_1 + m_2)[S]_0)}{k_2(m_1 - m_2)} e^{m_1 t} - \frac{(k_1 + m_2)(k_2[U]_0 - (k_1 + m_1)[S]_0)}{k_2(m_1 - m_2)} e^{m_2 t}$$

$$[E] = 1 - \frac{(k_1 + k_2 + m_1)(k_2[U]_0 - (k_1 + m_2)[S]_0)}{k_2(m_1 - m_2)} e^{m_1 t} + \frac{(k_1 + k_2 + m_2)(k_2[U]_0 - (k_1 + m_1)[S]_0)}{k_2(m_1 - m_2)} e^{m_2 t}$$

where

$$m_1 = -\frac{1}{2}\left[(k_1 + k_2 + k_3) + [(k_1 + k_2 + k_3)^2 - 4k_1k_3]^{1/2}\right]$$

$$m_2 = -\frac{1}{2}\left[(k_1 + k_2 + k_3) - [(k_1 + k_2 + k_3)^2 - 4k_1k_3]^{1/2}\right]$$

and $[S]_0$ and $[U]_0$ are the initial prevalences of states S and U, respectively.

Casual inspection of these complex algebraic expressions reveals a simple underlying exponential pattern (ae^{bt}) where a and b are combinations of the initial prevalences and the rate constants. Because the event

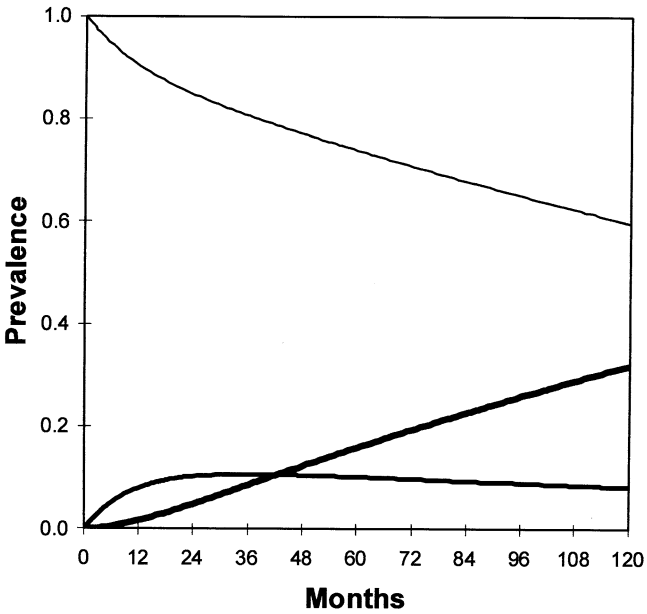

Figure 2 A hypothetic kinetic model based on a reversible transition between the stable (S) and unstable (U) states (k_1 = 0.012, k_2 = 0.058) and an irreversible transition between the unstable and event (E) state (k_3 = 0.029). Risk is quantified by the prevalence of events. The entire population begins from the stable state, $[S]_0$ = 1. Thereafter, the proportional prevalence for each state is plotted over 120 months of follow-up. The prevalence of the stable state (*light line*) falls as a simple exponential decay. The prevalence of the intermediate unstable state (*medium line*) rises to a maximum (at 36 months). As a result, the prevalence of events (*heavy line*) rises as a relatively flat curvilinear function over time.

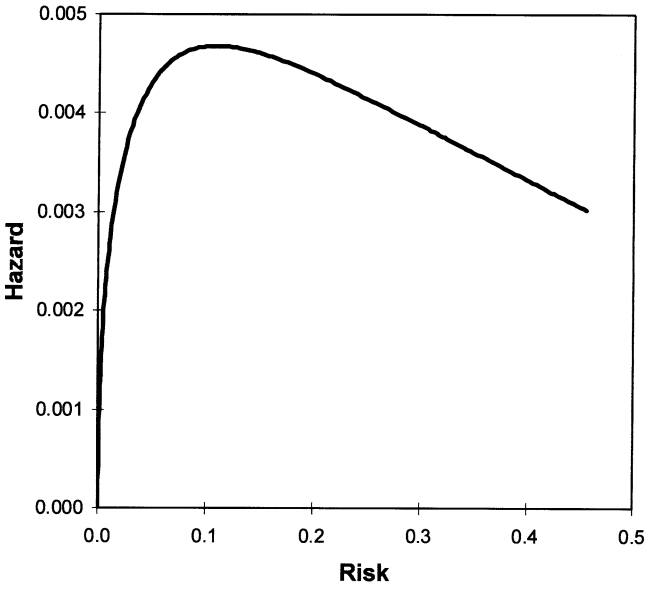

Figure 3 Risk versus hazard for Figure 2. Note that hazard and risk are positively correlated at low levels of risk and are inversely correlated at higher levels of risk. Among patients with these higher levels of risk—typically selected for more aggressive therapy under a risk stratification algorithm—the rate of change in risk is actually decreasing (the risk is increasing more slowly). Risk stratification alone is therefore an incomplete basis for therapeutic triage.

state E derives solely from the unstable state U, the hazard, $d[E]/dt$, is directly proportional to its prevalence, $[U]$, and the hazard function is therefore directly proportional (identical in shape) to the time course of instability. The maximum hazard occurs when the prevalence of the unstable state $[U]$ is at a maximum. This occurs at a time (t_{max}) when its derivative $d[U]/dt$ equals zero (the peak of the curve).

A representative kinetic model is illustrated in Figure 2. According to this model, the prevalence of the stable state $[S]$ decreases, whereas the prevalence of the unstable state $[U]$ increases to a peak at t_{max}. As a consequence, the prevalence of events $[E]$ increases as a complex curvilinear function. A recent study of cholesterol-induced atherogenesis is consistent with this pattern of responses. Just as predicted by our kinetic model (and in contrast with a conventional statistical model), the expression of inflammatory mediators in ApoE-deficient mice increased to a peak and decreased thereafter, even as the atherosclerotic plaque continued to enlarge.[16] Thus, as shown in Figure 3, the relation between risk and hazard is not necessarily linearly correlated even though they are often thought of as being interchangeable.

If we begin from the intermediate unstable state U, instead of the stable state S, the prevalences evolve in a very different manner. As shown in Figure 4, the prevalence of the unstable state $[U]$ decreases progressively, whereas that for the stable state $[S]$ increases to a maximum and tails off exponentially thereafter. Consistent with our intuitive expectations, the prevalence of events $[E]$ increases more rapidly for an unstable population than for the stable population in Figure 2.

CLINICAL IMPLICATIONS

Just as the physical trajectory of an object depends on its temporal displacement (velocity) and on the rate of change of that displacement (acceleration), the prognostic trajectory of a patient depends on the temporal threat of an adverse event (risk) and on the rate of change of that threat (hazard).[17] Although *risk* and *hazard* are often used interchangeably, their formal distinction has direct clinical relevance. In the same way we reduce a car's velocity by applying a suitable mechanical force (the brakes), we reduce a patient's risk by applying a suitable biomedical force (a therapeutic intervention). In this context, some interventions (replacing a worn tire or relieving a vascular stenosis) target the risk itself, whereas others (adjusting the tire's pressure or the patient's lipid levels) target its rate of change.

Most prognostic assessments nevertheless rely only on point estimates of risk alone. Even when more sophisticated approaches are used, they are rarely founded on plausible biologic principles representative of the underlying pattern of state transitions, but more often on obscure statistical formalizations such as minimization of variance or maximization of likelihood.

A kinetic model bridges this divide in 2 ways. First, because it quantifies the dynamics of the state-to-state tran-

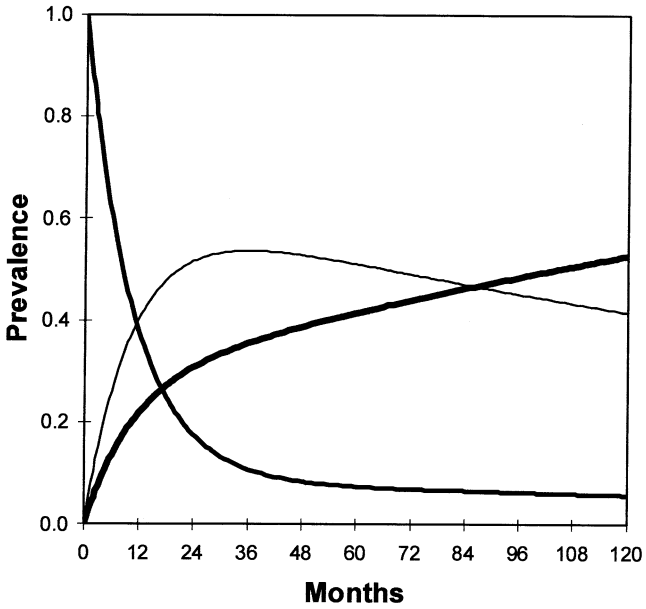

Figure 4 Evolution of the kinetic model in Figure 2 when the entire population begins from an initial unstable state, $[U]_0 = 1$, rather than a stable state. Now, the prevalence of the unstable state (*medium line*) falls, whereas the prevalence of the stable state (*light line*) rises to a maximum (again at 36 months). As a result, the prevalence of events (*heavy line*) rises steeply over the initial period of follow-up and more slowly thereafter.

sitions, instead of the static correlations among the states, it predicts changes in risk—hazard—in addition to the level of risk predicted by a statistical model. Second, instead of relying on clinically obscure standards such as minimization of variance, the kinetic model rests on a consistent and plausible biologic foundation (the particular pattern of these transitions). Consequently, its predictions will likely be better informed, richer in content, deeper in meaning, and more far-reaching in implication.

Consider the therapeutic implications. Figure 5 simulates an acute exacerbation of some disease (eg, an acute coronary syndrome or acute asthmatic attack) by a tenfold increase in the rate of transition from the stable state to the unstable state (k_1) that was used to construct Figure 4. As a result, the 1-year event rate has increased to 24% (*top panel*). A treatment that counteracts this process by an identical increase in the rate of transition from the unstable state back to the stable state (k_2) will reduce the event rate to 9% and leave the majority of patients in the stable state (*middle panel*). In contrast, an alternative treatment that slows the rate of transition from the unstable state to the event state (k_3) to the same degree will reduce event rate even further to 3%, but leave the majority of patients in the unstable state (*lower panel*). The clinical impact of this tradeoff would have to be determined empirically. An additional implication of the model is that treatment should be expected to be maximally effective if implemented at some time $t < t_{max}$ and to be less effective thereafter. Clinically relevant predictions such as these are directly verifiable through empirical observation.

Although the prototypical model presented here is potentially applicable to a number of realistic clinical situations, it will very likely require substantial refinement for more complex processes involving multiple interactive intermediate state transitions. Nevertheless, if we assume that particular treatments are capable of targeting particular state-to-state transitions (a decidedly nontrivial assumption), such treatment would be well advised (even in low-risk individuals) when the hazard is large (risk is rising) and less well advised (even in high-risk individuals) when the hazard is small (risk is stable). In contrast with risk stratification, a kinetic model formally discriminates between these alternatives and directly addresses the heartfelt questions posed earlier by Dick and Jane.

In summary, risk stratification alone is an insufficient basis for therapeutic decision-making. Instead, just as one slows the progress of a car by changing its acceleration, one slows the progression of a disease by changing its hazard. The kinetic model outlined here thereby promises to replace the superficial practice of risk stratification with a more sophisticated strategy of therapeutic triage and provides the formal basis by which we might explore the clinical relevance of this more enlightened perspective. We no more expect clinicians to begin solving differential equations in caring for their patients than we expect them to compute *P* values or tomographic image reconstructions. On the other hand, few doubt the practical benefits that attend the "desperate appliance" of such quantitative algorithms to clinical practice. It is time to make a more serious science of risk stratification.

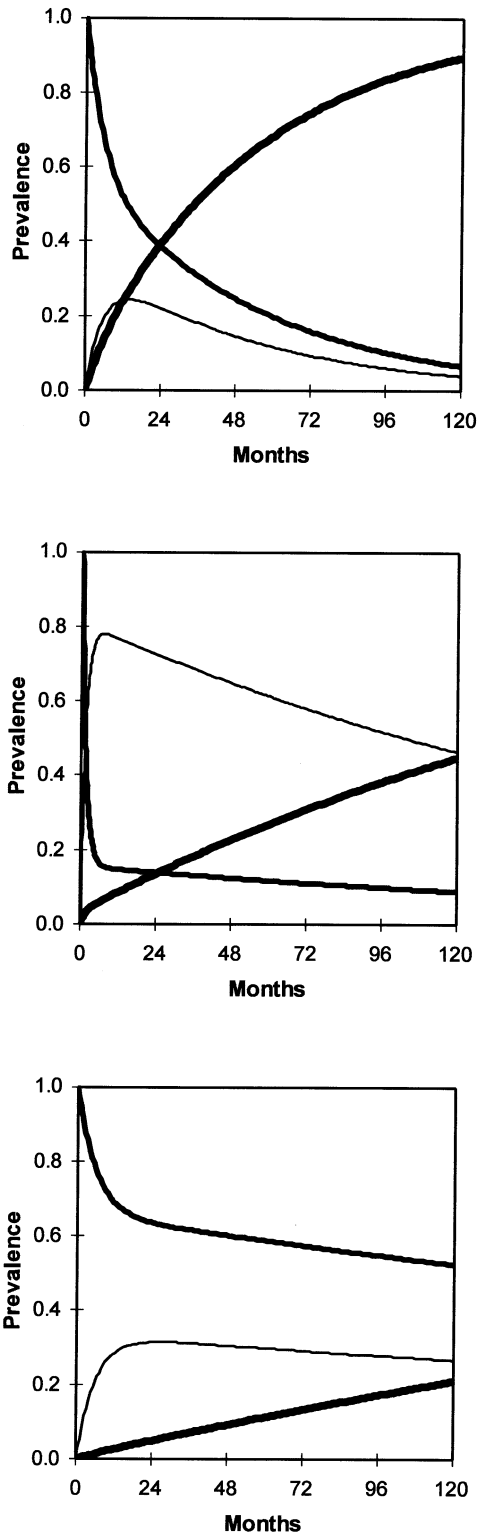

Figure 5 Therapeutic implications of kinetic modeling. ***The labeling is identical to that in Figure 4. See text for discussion.***

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