Baseline event rate, the Concorde fallacy, and the topography of cardiac risk

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**S U M M A R Y**

Cardiac risk stratification is the attempt to delineate who is at risk of cardiac event and who is not. Increasingly, the medical literature is filled with novel methods and markers of baseline risk assessment. This body of literature has been criticized broadly for making claims beyond what is statistically justified. In this hypothesis, we will explore an alternative explanation for the limitations of baseline risk assessment. I will contend that current risk models commit a logical error called the Concorde fallacy. The role of risk topography will be suggested as a novel method to rescue cardiac risk models.

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**Introduction**

Cardiac risk assessment—the likelihood a patient will undergo a nonfatal cardiovascular event, or death in the future—fulfills all the preconditions for being a useful clinical strategy [1]. Cardiovascular events are major source of morbidity and mortality, and there exist medicines, which can decrease one’s risk. Additionally, those medications are not equally effective: the greater one’s baseline cardiac risk, the greater one’s absolute risk reduction with treatment. Because of these facts, there has been widespread appeal in accurately describing a person’s baseline risk. Many authors have claimed to design models with better predictive value than the cardiology standard of the Framingham Risk Score. Unfortunately, most of these efforts have failed to provide additionally prognostic information. Ioannidis’ group systematically looked at claims of risk beyond the Framingham risk score and concluded that, “most had flaws in their design, analyses, and reporting that cast some doubt on the reliability of the claims for improved prediction.” [2] In this hypothesis, I will advance the case that these failures are secondary to a logical error—the Concorde Fallacy. Furthermore, I will advance a novel concept: cardiac risk topography, which may serve as a starting point for future investigations.

**Claims of risk beyond the Framingham risk score**

The Framingham Risk Score [3] (FRS) is one of the most validated risk models in medicine, and uses a collection of data points—age, gender, smoking status, cholesterol, blood pressure and use of antihypertensives—to provide a percentage likelihood a patient will undergo myocardial infarction or coronary death in ten years. This percentage is called baseline cardiac risk, and it may be lowered by blood pressure control, and lipid-lowering therapy, particularly the use of statin medications.

Since the FRS, there have been numerous attempts to better assess baseline cardiac risk. Parental history [4], lifetime event rates, novel biomarkers [5], improved imaging techniques [6]—all have been proposed as better methods to delineate who should be treated aggressively. However, as I have stated, many of these efforts have been criticized. Ioannidis, et al. systematically tracked articles that made claims of improved risk stratification, and found that most made common errors [2]. Specifically those were calculating the FRS incorrectly, applying it to a population it was unintended for, and finally, calculating the AUC (the best fit or area under the curve) in only one model [2].

Our obsession with better quantifying baseline risk has lead to a body of literature with little additional predictive power, and, unfortunately, is driven by a type of decision-making error called the Concorde Fallacy. In this fallacy, future action is erroneously justified by established fact, and not future expected gains. We propose a new model for treatment decisions involving cardiac risk—the idea of risk topography. Risk topography deters the Concorde fallacy, and suggests that there may be forgotten considerations when it comes to cardiac risk reduction. The case of Mr. Jones may be instructive.

Mr. Jones is a 53 yo gentleman who smokes a pack a day, and has for 30 years; his total cholesterol is 203, HDL 43, and systolic blood pressure is 120 on hydrochlorothiazide. Consequently, Mr. J has a Framingham risk score of 16%.

**What does this number mean?**

The number means that patients like Mr. Jones have a 16% chance of having a heart attack or dying of heart disease in ten years.

**Should Mr. J be started on a statin or other antilipidemic agent?**

Current US treatment guidelines consider the risks, benefits, and costs of lipid-lowering therapy. Statins are an option for those...
The benefits of treatment are large enough to justify its costs and risks. What makes the case of cardiac risk unique is that baseline risk seems directly proportionate to absolute risk reduction. Fig. 1 shows this linear relationship. Baseline risk is depicted along the x-axis, and the absolute risk reduction (ARR) expected from optimal medical management along the y-axis. All of the attempts to better risk stratify attempt to do what the black arrows depict. They seek to reclassify intermediate risk patients into either high or low risk categories. The precise values of ARR given baseline risk shown here are beside the point, and are subject to debate [10]. But, the concept is representative of our thinking; those with higher baseline risk are likely to reap greater ARRs, and thus warrant aggressive treatment. And, conversely, those with low baseline risk are likely only to receive minimal ARR. The cost effectiveness of treating this group may not be feasible.

Mr. Jones then is a patient who is of intermediate risk. Attempts to reclassify him might place him into a group of patients who have a 30% Framingham risk score, or alternatively <10% score.

The theoretical problem

There are two looming theoretical problems with baseline risk being used as a surrogate for absolute risk reduction. First, the linear relationship between baseline risk and absolute risk reduction was proven based on a Framingham risk score. Even if it is the case that novel methods improve baseline risk assessment, it does not necessarily follow that the ARR expected by optimal treatment will adhere to this linear model. One possibility is that we’d delineate a group of patients with a 20% FRS into two groups, one with a 10% risk and the other a 30% risk, and both groups may still expect only a 5–7% ARR with optimal medical management. Given our biological understanding of statins, this seems unlikely, however, it remains an open question.

Research that focuses on baseline risk must then do two things. First, it must show that the reclassification improves risk prediction, and then that treating according to the new scheme still

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maintains the linear relationship between ARR and baseline risk. The latter may be extremely difficult to do, and traditional models of baseline risk may prove limiting.

The second problem is that not all patients with the same baseline risk achieve the same absolute risk reduction with treatment. The linear relationship is increasingly being questioned. A statin intolerant patient with a high baseline risk (25%), may experience no absolute risk reduction with the alternative of fibrate therapy [14]. Alternatively, biological polymorphisms may make some patients ‘super’ responders to statins—a point I will return to.

Towards a new model

Perhaps however, there is a better way to think about risk and treatment decisions. Fig. 2 shows baseline risk along the x-axis, and the ARR (with simvastatin) along the y. The red line corresponds to the line in Fig. 1. Along the y-axis is a patient’s response profile. It represents factors that predict the magnitude of benefit independent of baseline risk.

Already there are ‘proof of principle’ examples that move us along this axis. Polymorphisms in KIS-6 gene may predict a greater benefit from intensive statin therapy [11]. This factor implies greater ARR for a given baseline risk, and has been shown independent of LDL and CRP.

To avoid the Concorde fallacy, we must make treatment decisions based on the expected ARR. The more we elucidate factors that predict response independent of baseline risk, the more prone we are to that error. Two patients, one with baseline risk of 12%, the other, 40%, each expecting a 10% ARR are equally worth treating. Conversely, a patient with significant baseline risk (35%) whose response profile suggests weak ARR (1%) may not warrant treatment. I call this model a topography of risk, and note it suggests treatment only at a certain altitude.

Likely the smooth, even landscape, Fig. 2 depicts will ultimately prove inaccurate. The topography of risk will be unique for each of the lipid lowering and anti hypotensive agents, across a spectrum of response profile factors. GRK5-L41 polymorphism found in African Americans confer inherent beta blockade, and may explain why beta-blockers offer little benefit in this population [12]. Patients with ADAMT51 matrix metalloproteinase gene variations may see huge ARR with pravastatin therapy, and thus may warrant treatment at lower baseline risk levels [13].

Some medicines (Ezetimibe, Atenolol) may affect absolute risk adversely among all patients. Fibrates likely have a 0% ARR based on meta-analysis [14]. The topography of these medicines is a flat plain, and their incorporation into treatment regimens, wholly unjustified.

Consequences of this hypothesis

The hypothesis I have advanced that dogged adherence baseline risk encouraged the Concorde fallacy, and that the idea of risk topography may free us from this error. This hypothesis is of profound importance. The implications for the rational use of antilipidemic treatment at a population level are broad. Specifically, when faced with the clinician’s dilemma of whom to offer treatment, conventional risk models, and my proposal reach diametric conclusions. Conventional models would have us treat a 42 yo male whose FRS is 33% and is already on simvastatin with fenofibrate before treating a 52 yo female non-smoker whose FRS is 13% with simvastatin. However, a topography of risk may reach the opposite conclusion, given her expected magnitude of response.

At its heart, the topography of risk is a hypothesis that forces us to make decisions based on the actual outcome of interest, and not a surrogate. It will allow management decisions to be consistent and no longer capricious. Returning to Mr. Jones, given his unique factors, the topography model may suggest treatment with simvastatin, possibly niacin, though it would likely opt against other classes of medicines.

As we move forward, we should remember it is only by considering both baseline risk and magnitude of response that treatment decisions can be reached systematically. The idea of cardiac risk topography provides us with a mental representation of this type of thinking. It may perhaps guide research along the forgotten axis of cardiac risk, and deter us from making a common error of reasoning.

Conflicts of interest

None

Acknowledgement

None

References


1 For interpretation of references to color in Fig. 2, the reader is referred to see the web version of this article.

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