The risk–treatment paradox describes a treatment selection bias in which low-risk individuals are more likely to receive therapy than those patients at higher risk for poor outcomes from the underlying condition. The implications of the risk–treatment paradox are 2-fold. For clinicians, it is important to consciously work to avoid the paradox because the relative benefits of most therapies are similar across patient subgroups defined by baseline risk, and thus the absolute benefits of therapy are greatest in those patients at highest baseline risk. For individuals conducting (or reading) comparative effectiveness research, the risk–treatment paradox is an important source of confounding to be cognizant of when drawing conclusions about treatment effects on the basis of associations between treatment exposure and outcomes. Observational studies can provide spuriously high estimates of treatment benefit if the risk–treatment paradox is manifest because low-risk patients are both more likely to be exposed to the therapy of interest and also less likely to experience the outcome regardless of therapy.

In this issue of the Journal, Motivala et al. (1) report data from the Get With The Guidelines–Coronary Artery Disease (GWTG-CAD) program demonstrating that although adherence with guideline-recommended care in U.S. patients with myocardial infarction has improved over the past decade, a risk–treatment paradox remains in that those patients with the poorest prognosis are also those least likely to receive guideline-recommended care. However, the magnitude of the risk–treatment paradox declined over the years studied, and it is worth noting that patients in the high-risk tertile in 2008, who received the “poorest” quality of care in that year, still received excellent care: 91% received all guideline-recommended interventions for which they were eligible, and discharge prescription rates were 97% for aspirin, 96% for beta-blockers, 92% for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in those with systolic dysfunction, and 89% for lipid-lowering drugs in those with elevated levels of low-density lipoprotein cholesterol. In fact, the care provided to the high-risk tertile in 2008 was substantially better than the care received by patients in lower risk tertiles in earlier years of the study. The rising tide in quality of care in the GWTG-CAD over the past decade lifted all boats—the adjusted composite performance measure improved each year by 30% to 33% in the low-, intermediate-, and high-risk tertiles. Importantly, the observed improvements in quality of care over time were due to numerator enhancement (i.e., increased treatment of eligible patients) rather than denominator minimization (i.e., increased exclusion of patients due to more rigorous recording of contraindications).

The risk–treatment paradox has been attributed to gaps in the evidence base (i.e., uncertainty about the risk:benefit ratio in patients at higher risk who are generally underrepresented in randomized trials) and/or information gaps inherent in administrative databases (i.e., lack of data on confounding clinical and functional variables that the clinician must weigh in making clinical decisions but which are not captured in administrative databases). Echoing a recent report from the GWTG–Heart Failure program (2), Motivala et al. (1) found that higher risk patients did have a greater prevalence of contraindications to many guideline-recommended therapies but that the risk–treatment paradox was still present even when the analyses were restricted to only eligible patients and even when adjustment was made for multiple clinical covariates not typically captured in administrative datasets (e.g., body mass index, smoking status, heart rate, blood pressure, laboratory values).

Thus, other factors must be driving the persistence of the risk–treatment paradox in myocardial infarction. As clinicians, we tend to be risk-averse, and errors of omission (e.g., not prescribing a preventive therapy) are easier to accept than errors of commission (e.g., prescribing a medication that then causes an adverse effect in a patient), especially in patients whom we perceive to have a poor prognosis. Thus, it is not surprising that an analysis of Medicare data revealed that utilization of cardiac catheterization in elderly patients with acute myocardial infarction was more closely correlated with markers of potential harm (i.e., patients’ bleeding risk and number of comorbidities) than with potential to benefit (i.e., patients’ baseline risk) (3). This problem is compounded by the fact that as clinicians we underestimate the potential benefits and overestimate the risks of preventive therapies for cardiovascular conditions (4,5), especially in older or sicker patients. Indeed, an analysis from the Canadian ACS (Acute Coronary Syndromes) II Registry did confirm that physicians’ subjective risk assessments for
patients with acute coronary syndromes correlated poorly with their Thrombolysis In Myocardial Infarction, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin, and Global Registry of Acute Coronary Events validated risk scores (6). In fact, the risk–treatment paradox in that dataset was entirely due to this imperfect risk stratification because treatment intensity was directly related to the patient at baseline as perceived by the treating physician. Wider availability of risk prediction models that permit physicians to accurately calibrate the potential long-term benefits and risks from preventive therapies will be a key step in ultimately eliminating the risk–treatment paradox for CAD and other cardiovascular conditions.

Although the risk–treatment paradox as it is currently defined is likely to continue to shrink over time as quality of care improves for patients across the spectrum of risk, I have one reservation with the current definition. Namely, all studies of the risk–treatment paradox thus far have focused on the underutilization of evidence-based therapies in at-risk individuals. However, the other side of the quality coin is the overutilization of nonevidence-based therapies. Additional studies should examine to what extent overutilization differs across patient risk strata. It has been estimated that nearly one-quarter of outpatient prescriptions in the United States were for “off-label” indications (i.e., not supported by randomized trial evidence or guideline recommendations) (7). Similar off-label utilization rates have also been reported for cardiac devices such as implantable cardioverter-defibrillator, cardiac resynchronization therapy, drug-eluting stents, and percutaneous coronary interventions (8–11). Of course, off-label use is not necessarily inappropriate; skilled clinicians often use clinical judgment in extrapolating beyond the limits of the randomized trial data for individual patients, and what is considered off-label in 2011 may become an on-label indication in subsequent years as the evidence base evolves.

In conclusion, although the rising tide of quality appears to be attenuating the risk–treatment paradox in acute myocardial infarction, there are multiple other areas in cardiology (and other fields of medicine) in which gaps in care are still sufficiently large (12) that the risk–treatment paradox remains an important issue for clinicians and purveyors/consumers of comparative effectiveness research. It is premature to declare the end of the risk–treatment paradox.

Reprint requests and correspondence: Dr. Finlay A. McAlister, 2F1.21 WMC, University of Alberta Hospital, 8440 112 Street, Edmonton, Alberta T6G 2R7, Canada. E-mail: Finlay.McAlister@ualberta.ca.

REFERENCES


Key Words: guideline adherence • myocardial infarction • paradox • risk • trends.