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EDITORIAL COMMENT

Bleeding and Mortality With Dual Antiplatelet Therapy

The *Rashomon* Effect*

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In his cinematic masterpiece *Rashomon*, the great Japanese director Akira Kurosawa tells the story of a potentially heinous crime from the different perspectives of the characters involved. Each has a unique interpretation of the event with varying contradicting accounts of what happened. The film has led to the notion of the "*Rashomon* effect," or mutually contradicting interpretations of the same event, which can be exacerbated when there is a dearth of evidence to prove or disprove any specific version of the truth (1). In cardiovascular medicine, the sheer number of randomized clinical trials suggests that clinicians actually know the "truth" when it comes to assessing risks and benefits of treatment strategies. However, some areas of controversy that exemplify the *Rashomon* effect include the debate over whether periprocedural elevations of markers of cardiac ischemia (e.g., creatine kinase-muscle-brain) are clinically important or if coronary artery bypass grafting and percutaneous coronary intervention (PCI) yield similar outcomes in patients with multivessel coronary artery disease. While the datasets underlying the evidence for these issues are relatively robust, a large proportion of guidelines recommendations are not supported by the high-quality evidence provided by definitive clinical trials (2), and this can complicate clinical decision making when there are competing risks. The perspective from which one views the available evidence can influence making the "right" decision.

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In this issue of the *Journal*, Palmerini et al. (3) present a meta-analysis of 12 trials comprising >34,000 patients randomized to different duration strategies of dual-antiplatelet therapy (DAPT) to assess the association between bleeding and increased mortality. The background rationale for this analysis is rooted in the classic competing risks of ischemia and bleeding: prolonged DAPT after PCI reduces ischemic events such as myocardial infarction (MI) and stent thrombosis but increases bleeding and potentially increases mortality (i.e., DAPT). In the study by Palmerini et al., 6 trials (11,473 randomized patients) provided individual patient data, and all 12 trials provided aggregate data. In all of the analyses, bleeding was an independent predictor of 1-year mortality. Moreover, longer duration of DAPT was associated with more bleeding-related deaths compared with shorter duration of DAPT. Strengths of this study include the sample size, which provides significant power; the use of individual patient data for one-half of the trials; and the inclusion of bleeding and MI as time-adjusted covariates, which allows for an examination of the order of exposure and the outcome.

This is 1 of several recent studies that have examined outcomes with shorter versus longer duration of DAPT. The large Dual Antiplatelet Therapy Trial showed that 30 months of DAPT resulted in lower rates of major adverse cardiovascular and cerebrovascular events including stent thrombosis but higher rates of

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bleeding (4). There was also an increase in mortality with longer duration of DAPT that met nominal statistical significance (2.0% vs. 1.5%; p = 0.05). A meta-analysis of 69,644 patients in trials comparing shorter with longer DAPT across the spectrum of ischemic heart disease (including drug-eluting stent [DES] placement, secondary prevention, and atrial fibrillation) demonstrated no significant difference between the 2 strategies with respect to either cardiovascular or noncardiovascular mortality (5). By contrast, 2 other meta-analyses of trials of DAPT duration specifically after DES placement showed either a numerical (6) or a statistically significant (7) higher mortality with longer duration of therapy.

In a prior pooled analysis by Palmerini et al. (3), DAPT beyond 1 year post-DES placement was associated with an increase in mortality attributable primarily to noncardiac causes (7). As multiple studies have demonstrated the relationship between bleeding complications and an increased risk for short- and long-term mortality (8), the current study by Palmerini et al. (3) appears to confirm the hypothesis that noncardiac causes of mortality with prolonged DAPT are primarily related to bleeding. However, studies examining longer versus shorter duration of DAPT in a broad population of patients with acute coronary syndrome and those needing secondary prevention have not shown increased mortality with prolonged DAPT. Are patients undergoing PCI with DES really so different from those other groups? Is this an example of the *Rashomon* effect? Where does the truth lie?

One perspective is to invoke the qualitative interaction—treatment effects going in opposite directions in subgroups—that is infrequently seen in randomized trials (9). Therapies that are beneficial tend to be beneficial across patient subgroups. In other words, prolonged DAPT reduces ischemic events and does not increase mortality in a broad population of patients, so it should have the same effect in those undergoing PCI with DES. On the other hand, in the context of DAPT the issue is not subgroups, but rather different populations altogether. Thus, a different perspective is that patients undergoing DES placement are indeed different; their levels of platelet activation, their comorbidities and demographics, and the fact that they are undergoing PCI all may lead to a completely different balance of risk and benefit.

In this setting, 1 significant variable is the DES platform itself. It is clear that current-generation DES are much safer, from the standpoint of the risk of late stent thrombosis, than are prior DES and even bare-metal stents (10). The more rapid healing of contemporary DES ostensibly requires shorter duration of DAPT, as reflected in current professional society consensus statements (11). By contrast, acute coronary syndrome reflects a more systemic thromboinflammatory state, and areas of multiple plaque ruptures and vulnerable plaques likely require longer DAPT to prevent future ischemic events. It should be noted that in the large DAPT trial, 30 months of DAPT reduced both stent-related and non-stent-related MI events, demonstrating the progressive nature of coronary artery disease and the protective effect of antiplatelet therapy.

Another perspective that must be considered is how the endpoints and relationships between events are assessed in each of these analyses. Several studies have demonstrated an association among bleeding events and MI, stroke, stent thrombosis, recurrent bleeding, and mortality (12). The mechanisms underlying this association are unclear. Intracranial hemorrhage or severe bleeding that leads to hypovolemic shock can directly cause death, but lesser bleeding events, which are also associated with an increased risk of mortality, may ultimately lead to death through intervening processes. For example, there may be unmeasured confounders such as frailty that drive the outcome, thus making bleeding a marker, but not a mediator, of mortality. A more obvious mechanism is that bleeding leads to cessation of antithrombotic therapy, which can place patients at risk for recurrent ischemic events including stent thrombosis and subsequent death. In this context, is bleeding the cause of death? Could the *Rashomon* effect be at play? On one hand, if the bleeding event had not occurred, antithrombotic therapy would not have been discontinued and the ischemic event would have been avoided; on the other hand, the event proximal to the death was the ischemic event, and perhaps the death should not be ascribed to the bleed. This demonstrates the challenge that is inherent in determining causality.

In the DAPT trial, all deaths were initially classified as cardiac, vascular, or noncardiovascular based on standardized definitions. Once the signal for increased mortality was seen, the deaths were readjudicated to determine whether they were related to bleeding, cancer, or trauma (13). A bleeding-related death was categorized as any death that was possibly, probably, or definitely related to any prior clinically evident bleeding event. After readjudication, there was no significant difference in rates of fatal bleeding (0.2% vs. 0.1%; p = 0.81) or rates of deaths related to any prior bleeding (0.3% vs. 0.2%; p = 0.36) between shorter and longer DAPT.

In the current study by Palmerini et al. (3), the investigators defined any death occurring within 1 year of a bleeding event as “possibly bleeding

related." Under this construct, a patient who developed an in-hospital bleeding event, recovered, and survived to hospital discharge but then developed stent thrombosis 9 months later and died would be adjudicated as a possible bleeding-related death. The temporal separation between the bleeding event and the death as well as the intervening stent thrombosis underscore the challenge of relating 1 or more nonfatal endpoints to a fatal one. Palmerini et al. (3) did not readjudicate the events using source data and do not present granular data on these types of scenarios. As in the movie *Rashomon*, the "truth" of whether prolonged DAPT increases mortality through bleeding seems to depend on how the data are viewed.

The determination of DAPT duration in patients undergoing DES placement is one that leverages the concepts of "personalized" medicine. Based on the available evidence, 6 months is likely the minimum duration of therapy in many patients, but imposing a uniform recommendation for all patients is not feasible. When weighing the risks and benefits of DAPT, different patient and procedural characteristics should be considered, including variables associated with increased bleeding risk such as age, sex, frailty, renal function, and prior bleeding as well as variables associated with an increased risk for ischemia such as multiple stents or complex PCI. Other practical issues such as the likelihood of medication adherence should also be part of the decision-making process. Importantly, the patient should be involved in these discussions. The DAPT score (14) is a readily available electronic tool that may inform this conversation by quantifying the benefits and risks of longer therapy in each individual patient. Beyond informing the clinical conversation, the study by Palmerini et al. (3) serves as a reminder that as clinical trials evolve to more pragmatic constructs, such as registry- or electronic health record–based designs, it will be important to maintain the accuracy and reliability of the measured endpoints. After all, knowing the "truth" regarding clinical evidence should not be a matter of perspective.

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