Acute coronary syndrome: the illusion of treatment!

Mario Marzilli, MD, PhD
Cardiovascular Medicine Division, Pisa University Medical School, Pisa, Italy

Correspondence: Professor Mario Marzilli, Professor and Chairman, Cardiovascular Medicine Division, Pisa University Medical School, Via Paradisa, 2, 56100 Pisa, Italy
E-mail: mario.marzilli@med.unipi.it

Abstract
Acute coronary syndrome is a critical area for the “illusion of treatment,” which is a phenomenon where there is an unjustified enthusiasm for a treatment by both patients and doctors. Therapeutic illusion is not the only factor driving overtreatment, as treatment decisions are also influenced by reimbursement pressures, quality measures, fear of litigation, and patients’ expectations. Despite the other factors involved in overtreatment, therapeutic illusion is the one contributor that all cardiologists can begin to address immediately by evaluating their own practice, verifying adherence to the guidelines, and applying simple conscious heuristics to more rational evidence-based care.

Keywords: acute coronary syndrome; percutaneous coronary intervention; therapeutic illusion

Introduction
In recent years, increasing efforts are recommended to reduce inappropriate tests and treatments in medicine, the most visible one being the Choosing Wisely Campaign in the United States. To be successful, these efforts must overcome the tendency of human beings to overestimate the effects of their actions, a phenomenon well known to psychologists who call it the “illusion of control.” In medicine, it can be called the “illusion of treatment,” which is an unjustified enthusiasm for treatment on the part of both patients and doctors.1,2 Acute coronary syndrome is a critical area for the “illusion of treatment,” both for the pathophysiologic approach, which may be too simplistic, and for the therapeutic approach, which may be too optimistic.

The “simplistic” approach to the pathogenesis of acute coronary syndrome
Acute coronary syndrome is commonly attributed to acute coronary thrombosis superimposed to atherosclerotic plaques. Several features have been identified as predictive of plaque instability. These features of vulnerability vary according to the diagnostic tool. At intravascular ultrasound, plaques presenting with a large lipid core and a thin superficial layer (thin-cap fibroatheroma) are supposed to be the most prone to sudden rupture, erosion, or fissuring. However, these features are not consistently found in patients with acute coronary syndrome. Actually, up to 30% of patients with acute coronary syndrome do not have any visible plaque at invasive angiography.3,4 Moreover, in patients with acute coronary syndrome, only 37.5%
had plaque rupture at the presumed culprit lesions, while 79% presented with ruptured plaques in non-culprit lesions.5

When searching for ruptured plaques in patients with an acute myocardial infarction and in patients with stable angina, it was observed that up to 30% of patients with an acute myocardial infarction had no ruptured plaque and that 30% of patients with stable angina did have ruptured plaques.6 Finally, it is interesting to note that longitudinal intravascular ultrasound studies have shown that plaques undergo dynamic changes with most of the lesions that initially present with the features of a “vulnerable” profile, progressing to a stable profile at follow-up and vice versa and that these dynamic changes had no clinical counterpart.7 Therefore, the common assumption of a close link between “vulnerable” plaques and acute coronary syndromes is not supported by conclusive evidence, and acute ischemic syndromes in patients with no visible atherosclerotic obstruction are increasingly recognized and diagnosed, such as acute myocardial infarction with normal angiogram (eg, takotsubo syndrome, etc).

It is interesting to note that, in patients with known coronary and/or systemic atherosclerosis that do suffer an incident myocardial infarction, 79% of these infarctions were not classified as a type 1 myocardial infarction (the classic thrombosis-on-plaque infarction), but as a type 2 myocardial infarction, that, according to the universal definition of myocardial infarction, identifies the infarctions due to conditions other than coronary atherosclerosis.8

**The “optimistic” approach to treatment**

Two recent trials in acute coronary syndrome—PROSPECT and Compare-Acute—clearly show how biased the reading of clinical reports may be today.

### Abbreviations

**Compare-Acute study:** Comparison between fractional flow reserve–guided revascularization versus conventional strategy in Acute STEMI patients with multivessel disease; **NSTEMI:** non–ST-segment elevation myocardial infarction; **PCI:** percutaneous coronary intervention; **PROSPECT trial:** Providing Regional Observations to Study Predictors of Events in the Coronary Tree; **STEMI:** ST-segment myocardial infarction

### PROSPECT trial

In the PROSPECT trial (Providing Regional Observations to Study Predictors of Events in the Coronary Tree), which was conducted in 37 sites in the United States and Europe, 697 patients presenting with an acute coronary syndrome (ie, unstable angina, non–ST-segment elevation myocardial infarction [NSTEMI], or ST-segment elevation myocardial infarction [STEMI]) were included and followed for 3.4 years.9 Each patient underwent a detailed investigation of all major coronary vessels by invasive angiography and intravascular ultrasound. Study inclusion required a successful and uncomplicated percutaneous coronary intervention (PCI) of all culprit lesions; 697 culprit lesions were identified and treated by PCI and stenting. Angiography post–PCI identified 1814 untreated lesions, whereas intravascular ultrasound post–PCI identified 3160 untreated lesions that were located in the proximal- to middle-third of the three major epicardial coronary arteries, including 596 lesions that presented with the ultrasonic markers of highly unstable plaques, ie, thin-cap fibroatheromas.

Despite the incredibly high number of plaques identified in patients deemed to be at an elevated cardiovascular risk, the number of hard events at follow-up (death and myocardial infarction) was as low as 1.4% per year. Moreover, the number of events occurring at the site of a stented lesion (n=118) was similar to the number of events occurring at the site of an untreated lesion (n=104). Taking into consideration that untreated lesions were in much greater number than the stented lesions, the hard event rate at the untreated sites was 3.3%, while the hard event rate at the stented sites was 16.9%.

An unbiased reading of these data can only conclude that PCI and stenting do not exert a preventive action against future ischemic events and that the ultrasonic markers of instability are much poorer predictors of hard clinical events at follow-up than commonly thought.

### Compare-Acute study

The Compare-Acute study (Comparison between fractional flow reserve–guided revascularization versus conventional strategy in Acute STEMI patients with multivessel disease) randomized 885 patients
with STEMI and multivessel disease who had undergone primary PCI on an infarct-related coronary artery in a 1:2 ratio to undergo complete revascularization of noninfarcted coronary arteries guided by fractional flow reserve (295 patients) or to no revascularization of noninfarct-related coronary arteries (590 patients).\textsuperscript{10} At the 12-month follow-up, the mortality rates were 1.4% in the “complete” vs 1.7% in the “noncomplete” revascularization group, the myocardial infarction rates were 2.4% vs 4.7%, respectively, and the cerebrovascular event rates were 0% vs 0.7%, respectively. None of these differences was statistically significant. Therefore, the additional procedures to achieve a “complete” revascularization did not result in a significant reduction in the risk of death, reinfarction, or stroke in patients with an acute myocardial infarction. Despite this evidence, the authors concluded by recommending the strategy of complete revascularization.

Actually, in both trials, the only difference at follow-up was the number of revascularization procedures. Both trials compared two strategies that resulted in a similar number of hard adverse events (death, acute myocardial infarction, and stroke), but differed in the number of PCIs. In both cases, the authors recommended adopting the strategy that increased the number of procedures. To reach this surprising conclusion, the same event, namely coronary revascularization, is considered a treatment or a major adverse coronary event simply based on the timing of its performance and despite the observation that, admittedly, in most cases, there was no compelling clinical indication.

Conclusions

Clearly, the therapeutic illusion is not the only factor driving overtreatment. Decisions about performing PCI and stenting are influenced by reimbursement pressures, quality measures, fear of litigation, and patients’ expectations.\textsuperscript{11} Overuse of medical services that are more likely to cause harm than good is a per-