Is CURE a Cure for Acute Coronary Syndromes?
Statistical Versus Clinical Significance

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Clopidogrel has been recently approved for treatment of non–ST-elevation acute coronary syndromes based on the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial. However, the trial’s findings are confounded by issues that lessen its clinical significance. Clopidogrel did not reduce mortality; its benefit was limited to preventing myocardial infarction, which was defined less stringently than in previous trials. Clopidogrel led to an increase in major and minor bleeding. Furthermore, clopidogrel increased bleeding risk in early cardiac surgery. Thus, widespread usage of clopidogrel, especially in centers with an early revascularization strategy, will have limited clinical benefit with considerable risk. (J Am Coll Cardiol 2002;40:218–9) © 2002 by the American College of Cardiology

The presentation of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial at the 2001 American College of Cardiology (ACC) meeting was met with overwhelming adulation. Labeled as a “blockbuster,” the trial was reported on Cable News Network (CNN) within 1 h of presentation and described as one of the “most significant advances for . . . acute coronary syndromes (ACS) since aspirin” (1). Yet, amidst all the exuberance, a simple question needs to be asked: is CURE, indeed, one of the “most significant advances” for patients with ACS?

Assessing the significance of a trial statistically is straightforward—review the primary end point and its associated p value. Clinical significance is, however, a far more complex concept requiring an analysis of the relative merits of all end points studied, a determination of the applicability of the study population to one’s own patients and, finally, a calculation of the incremental cost needed to achieve the reported benefits. Increasingly, clinical trials are reporting findings, which, although statistically significant, are not necessarily clinically significant. We believe CURE provides a telling illustration of this divergence.

CURE was, indeed, a positive trial; the combination of aspirin and clopidogrel compared with aspirin alone reduced the primary end point of cardiovascular death, myocardial infarction (MI) and stroke (2). However, although the individual end points of death, MI and stroke all show numerical improvement with clopidogrel, the differences are not statistically significant for death and stroke. Thus, clopidogrel does not reduce mortality (2). It is simply not a “life-saving” medication.

The reduction in the primary end point is driven by a 1.5% absolute reduction in the rate of subsequent nonfatal MI (2). Although certainly a worthy end point, it is not equivalent to a reduction in mortality. Furthermore, CURE used a definition of MI, which included patients with only elevated serum troponin levels. Therefore, an elevation of serum troponin even in the absence of an elevation in creatinine kinase levels would be considered sufficient to meet the MI end point. This is in direct contrast with nearly every other contemporary trial of ACS, which all use more restrictive definitions requiring elevations in creatinine kinase or its MB isoform (3–6). By using troponin, the extent of myocardial necrosis prevented by clopidogrel may not be as impressive as initially thought.

The most concerning complication noted with the addition of clopidogrel was an increased bleeding risk (1,2). The rate of major bleeding increased by an absolute rate of 1%, nearly half of which were defined as “life-threatening”. The risk of transfusion of ≥2 U of blood increased by an absolute rate of 0.6%, and the risk of minor bleeding increased by an absolute rate of 6.7%. Importantly, the definition of minor bleeding underwent considerable revision between the ACC presentation of the CURE trial data and its subsequent final publication. These changes resulted in a dramatic reduction in the reported rate of minor bleeding from 15.3% (when presented) to 5.1% (in final manuscript). This modification makes clopidogrel appear much safer than it really is. In fact, the morbidity associated with major bleeding and the need for blood transfusions may be as clinically significant as preventing nonfatal MI when assessing the relative risks and benefits of clopidogrel.

Yet, the most important concern of the CURE trial is whether it can be applied to the American approach to ACS. In contrast with Europe and Canada (origin of >95% of the CURE patients), the management of ACS in the U.S. centers around rapid access to cardiac catheterization and subsequent early percutaneous or surgical revascularization in appropriate patients (7). The need for surgical
revascularization in patients with ACS is considerable with approximately 20% of patients having “surgical disease” (7). Although CURE showed no significant excess of major bleeding after coronary artery bypass grafting (CABG), patients had clopidogrel withheld for a median of five days before surgery (2). In countries outside the U.S., where the median time to surgery after an ACS is more than 10 days, this waiting period is inconsequential (7). Yet, in the U.S., the median time is less than four days (7). Therefore, routine administration of clopidogrel to all patients with ACS will expose the surgical subset to either an excessive bleeding risk with surgery or significant delays in undergoing surgery. These concerns regarding excess bleeding and delays are not theoretical. Among patients in CURE who stopped clopidogrel less than five days before CABG, the incidence of major bleeding increased by an absolute rate of 3.3% (2). Furthermore, a number of reports have documented an increased transfusion requirement and a four- to 10-fold increased risk of surgical reexploration for postoperative bleeding in patients who underwent CABG within three days of clopidogrel administration (8–10).

These are not trivial risks. If clopidogrel is administered to 1,000 patients with ACS to prevent 15 nonfatal MIs, 10 additional patients develop major bleeding, 69 additional patients have minor bleeding, and 200 patients have surgical decisions complicated by its administration. In addition, 978 patients taking clopidogrel derive no significant benefit from this drug, and all of this occurs without saving one life.

Proponents argue that widespread use of clopidogrel could prevent “50,000 to 100,000 heart attacks, strokes, or deaths” in North America and “250,000 to 500,000 events” worldwide based on the CURE results (1). However, it is important to understand that attainment of these benefits would require administration of clopidogrel to approximately 2.3 million to 4.6 million patients in North America alone and approximately 11.5 million to 22.7 million patients worldwide. At $3 per tablet, the absolute costs involved are approximately $2 billion to $4 billion in North America and $10 billion to $20 billion worldwide.

Other examples of divergent statistical and clinical findings abound. In ACS, should all patients receive “upstream” IIb/IIIa inhibitors when the clinical benefit is limited to those who undergo percutaneous intervention (11,12)?

Abbreviations and Acronyms

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<tr>
<th>Abbreviation</th>
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<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
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<tr>
<td>ACS</td>
<td>acute coronary syndrome</td>
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<td>CABG</td>
<td>coronary artery bypass grafting</td>
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<td>CURE</td>
<td>Clopidogrel in Unstable Angina to Prevent Recurrent Events trial</td>
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<td>MI</td>
<td>myocardial infarction</td>
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Khot et al. 219

Is CURE a Cure for ACS?

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