Optimal Therapy for Acute Coronary Syndromes: The More the Better?
To the Editor:

In their comments on the report by Mukherjee et al., White and Willerson emphasized that as many as 4 drugs should be routinely started in patients with acute coronary syndromes (on a lifelong basis) so as to reduce mortality. By contrast, not so long ago, Bogaty and Brophy asked whether the increasing burden of treatment in acute coronary syndromes was really justified. Where does the right approach lie?

The core of Bogaty and Brophy’s criticism was that the blanket prescription of evidence-based interventions resulted in an overwhelming proportion of treated patients deriving no benefit because of the tiny difference in absolute risk reduction when the event rate is low, no matter how great the relative reduction. They recommended a research effort to identify those patients most likely to benefit from treatment. This effort is unlikely to come from most promoters.

The Mukherjee et al. study makes no use of absolute benefits; indeed, no data on actual outcomes are given to the reader. Also, its scoring system for appropriateness is arbitrary; can it really be assumed that to give 2 medications when 3 are indicated (appropriateness level II) is less appropriate than to give 3 when 4 are indicated (level III)? Furthermore, why did the authors use the few patients who received no drug as the reference group for their regression analysis? One cannot help but wonder what the features were of these 21 unhappy patients who served as a benchmark for the rest. Did some of them die while still in the emergency room? With such a reference group, the interpretation of the mortality odds ratio becomes problematic.

As an observational study, this report may suggest an incremental benefit of drugs but in no way prove it. Still less does it help to identify the majority who will not benefit from them. It is no sound basis for the stark prescriptive statements of White and Willerson. The blanket prescription approach may be felt by some to be the only one left to us if we wish to obtain small net benefits at any price. However, to take such a view is a matter of personal values (not unlike those in negative utopia) rather than the inescapable consequence of the evidence we have. The shotgun add-on strategy should be viewed as simply makeshift until research develops better-targeted approaches.

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Response

We read with interest the letter by Permanyer-Miralda et al regarding our recent article on the impact of combination evidence-based medical therapies in patients presenting with acute coronary syndrome. The authors quote Bogaty and Brophy, who stated that blanket prescription of therapies for acute coronary syndrome typically benefits only a small fraction of the treated patient cohort. The obvious pitfall lies in the imposition of an increasing burden on many patients who will not derive benefit. The point is a valid one, as most drugs are only effective in a fraction of the treated patient population.

As our understanding of pharmacogenomics improves, we may envision a time of tailored medical therapy, which would be of considerable economic benefit to both society and patient. This would target only those medications most likely to benefit the individual patient and thus significantly decrease the number of adverse effects. The anticipated benefits of pharmacogenomics or tailored therapy include safer, effective medications that can be administered in the optimum dose in an individual patient. However, we do not yet have the tools to identify individual drug responsiveness and have to provide therapies that are considered globally beneficial on the basis of current evidence. Single-nucleotide polymorphism (SNP) analysis is likely to be incorporated in future clinical trials, and results of such studies may then be used to design subsequent trials incorporating genetic prescreening. Practicing clinicians can then avoid the usual trial-and-error approach with drugs and use predictive genetic testing for optimal therapy.

Despite the limitations mentioned above, the absolute incremental benefit with combination therapy noted in our study across appropriateness levels 0 through IV was highly significant (33.3% versus 17.5% versus 11.5% versus 9.8% versus 7.9%). The 21 patients who did not receive any of the medications were actually discharged home after their initial presentation on the basis of our study definition but had a high mortality rate at 6 months. Our scoring system was based on American College of Cardiology/American Heart Association guidelines, which are based on large clinical trials and which by and large have shown the agents to be both effective and cost-effective. If anything, the observational evidence is that combination treatment using these classes of medications suggests synergy, not just added benefit. Also, because we now have generic agents for each of the classes, the societal cost is much lower than might appear at first.

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