Numerous registries have shown that evidence-based therapies are often not prescribed despite strong evidence that they reduce mortality and morbidity.\textsuperscript{1} In this edition of the journal, Mukherjee et al\textsuperscript{2} describe the use of a composite appropriateness score to assess the potential effect of evidence-based therapies on 6-month mortality in 1358 consecutive patients presenting with an acute coronary syndrome (ACS). Fifteen percent of these patients had ST-elevation myocardial infarction (MI), 55% had non–ST-elevation MI, and 30% had unstable angina. Most were in Killip class I or II, and 48% underwent either percutaneous coronary intervention or coronary artery bypass grafting while in the hospital. The study found that the use of antiplatelet therapy, statins, angiotensin-converting enzyme (ACE) inhibitors, and β-blockers had apparently additive effects in reducing 6-month mortality. There was also a strong trend (\(P=0.08\)) toward increased survival in patients who underwent revascularization procedures—a finding consistent with the results of the Fragment and Fast Revascularization During Instability in Coronary Artery Disease (FRISC-II) study in patients with non–ST-elevation ACS treated for 5 to 7 days with the low molecular weight heparin, dalteparin.\textsuperscript{3}

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Mukherjee et al\textsuperscript{1} report that the odds ratio for 6-month mortality was reduced to 0.10 (95% CI, 0.03 to 0.42; \(P<0.0001\)) by the use of all indicated therapies versus none, 0.17 (95% CI, 0.04 to 0.75; \(P=0.0013\)) by the use of 3 indicated therapies, 0.18 (95% CI, 0.04 to 0.77; \(P=0.01\)) by the use of 2 indicated therapies, and 0.36 (95% CI, 0.08 to 1.75; \(P=0.20\)) by the use of 1 indicated therapy. Because of the overlapping CIs, it could be argued that the use of additional therapies apparently produced no incremental benefit. However, it should be noted that the odds ratios decreased substantially with the use of 1 therapy, decreased again when a second or third therapy was added, and decreased further still with the addition of a fourth therapy.

No interactions in the treatment effects of these 4 therapies have been noted in trials of patients with ACS; thus, the risk reduction associated with each therapy would be expected to remain consistent in the presence or absence of the other therapies. If each of the 4 therapies reduced mortality by 25%, the cumulative risk reduction might be estimated at 68% (ie, \(1-(0.75\times0.75\times0.75\times0.75)\)).\textsuperscript{4} However, the actual risk reduction observed with 4 therapies was 90%.

This study has a number of limitations. First, it has all of the limitations of a retrospective registry. Second, the usage of therapies was not randomized, and it is possible that some patients were not prescribed various therapies for good clinical reasons, although the authors did exclude documented contraindications and adjusted the multivariate analysis for other variables known to affect survival, such as left ventricular function and revascularization. Third, the study focused only on therapies that have been shown to significantly reduce mortality rather than the composite end point of death, myocardial infarction, or stroke. The study predates recent findings on the benefits of clopidogrel in patients with non–ST-elevation ACS,\textsuperscript{5} ACE inhibitors in patients with coronary disease,\textsuperscript{6} and ramipril in patients with vascular disease or diabetes.\textsuperscript{7}

The Global Use of STrategies in patients with Occluded coronary arteries (GUSTO)-IIB investigators\textsuperscript{8} previously calculated that greater usage of aspirin in a population of “ideal” non–ST-elevation ACS patients would save 9 lives per 1000 patients treated, whereas greater usage of β-blockers would save 11 lives per 1000, and greater usage of ACE inhibitors would save 23 lives per 1000. They also calculated that 13 lives per 1000 would be saved by not using calcium-channel blockers. Mukherjee et al\textsuperscript{1} do not discuss the usage of calcium-channel blockers.

It is possible that some combinations of agents with different biological modes of action produce additive effects. However, there is little information available about the additive effects of commonly co-prescribed cardiovascular therapies, and there have been few randomized trials of these therapies based on a 2×2 factorial design. There have also been no studies in which patients were stratified on the basis of therapy usage at baseline. There have been several studies in which the majority of patients were prescribed evidence-based therapies as background treatment and were then randomized to receive another therapy. Examples include recent lipid-lowering trials such as the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study\textsuperscript{9} and the Cholesterol And Recurrent Events (CARE) trial,\textsuperscript{10} in which >80% of patients were on aspirin.

In the Anglo-Scandinavian Cardiac Outcome Trial (ASCOT),\textsuperscript{11} 10 305 patients with a mean blood pressure of
138/80 mm Hg and a baseline cholesterol level of <250 mg/dL (<6.4 mmol/L) were randomized to receive either 10 mg of atorvastatin or a placebo while receiving background treatment with different randomized antihypertensive regimens (a β-blocker with or without a diuretic versus a calcium-channel blocker with or without an ACE inhibitor). The patients had an average of 3.7 risk factors (in addition to hypertension) at 3.3-year follow-up. The combined incidence of coronary mortality and MI was reduced by 36% (from 3.0% to 1.0%, \( P=0.0005 \)), and the risk of stroke was reduced by 27% (from 2.4% to 1.7%, \( P=0.02 \)), showing that statin therapy adds significantly to the benefit of antihypertensive therapy in this population.13 In the recent European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease (EUROPA),6 patients with coronary disease and no heart failure were randomized to receive either the ACE inhibitor, perindopril, or a placebo. Background therapy consisted of platelet inhibitors in 92%, β-blockers in 62%, and lipid-lowering therapy in 58%. Perindopril was found to reduce the combined incidence of cardiovascular death, MI, and cardiac arrest by 20% (\( P=0.0003 \)), and it can be concluded that the benefit of perindopril was additive to the benefits of these background therapies at these usage rates.

It has recently been suggested that a “polypill” should be formulated for use in patients over the age of 55 years and patients with vascular disease. Such a polypill would probably contain aspirin and would treat 3 cardiovascular risk factors (hypertension, dyslipidemia, and increased homocysteine levels). Hypothetical modeling has suggested that this could reduce the risk of ischemic events by 88% and stroke by 80%.12 One could also argue that a polypill should be prescribed for patients who have had an ACS, containing a fixed dose of aspirin and a statin together with various doses of a β-blocker and an ACE inhibitor. The major rationale for such a polypill would be to improve patient compliance while simultaneously reducing multiple risk factors. Clearly, the availability of such a polypill may compel physicians to prescribe 4 evidence-based therapies rather than 1 or 2 as at present. However, one of the major concerns with a polypill would be the difficulty in identifying the culprit component in the event of adverse effects. The proposers of the polypill for primary prevention have estimated that adverse effects would occur in 15% of patients, necessitating cessation of treatment in 2%.12

In the study by Mukherjee et al.,2 ACE inhibitors were used in only 60% of the 1104 patients deemed eligible for their use (81.3% of the total population; ie, patients with hypertension, heart failure, diabetes, or an ejection fraction of <40%). Given the results of the Heart Outcome Prevention Evaluation study (HOPE),7 which showed that the ACE inhibitor ramipril benefited patients at high risk of cardiovascular events, and the EUROPA trial,6 which showed that perindopril was beneficial, it is recommended that all patients with coronary disease, such as those in the study by Mukherjee et al.,7 should be prescribed ACE inhibitors regardless of their ejection fractions.13

Audit is an important component of quality improvement, but little is known about the effectiveness of quality improve-
smoking cessation, achievement of ideal weight, and graded exercise programs. There should also be insistence on long-term patient and physician commitment to these programs, with periodic testing of biomarkers and reassessment of the target variables for which the various therapies have been prescribed, in association with regular clinical examinations, stress testing, and selected imaging assessments.

References


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