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Editorial Comment

Beta-Adrenergic Blocking Agents or Angiotensin-Converting Enzyme Inhibitors, or Both, for Postinfarction Patients With Left Ventricular Dysfunction*

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The use of pharmacologic agents for the secondary prevention of sudden and non-sudden death and recurrent myocardial infarction (MI) in patients who survive an acute MI has proved to be effective in a large number of multicenter, randomized clinical trials and is now commonplace. Drugs frequently used for this purpose include aspirin, beta-adrenergic blocking agents, angiotensin-converting enzyme (ACE) inhibitors and, more recently, lipid-lowering agents (1–10).

Whether the beneficial effects of multiple-drug therapy for secondary prevention are additive in various groups of postinfarction patients is an important question. This is particularly true concerning the combined use of beta-blocking drugs and ACE inhibitors in high risk patients, particularly in those with depressed left ventricular (LV) systolic function.

Beta-adrenergic receptor blockers. The long-term benefit of beta-adrenergic receptor blockade in the secondary prevention of death after MI has been demonstrated in several randomized clinical trials (3–5). Although most of the salutary effects of beta-blockers occur within the first week of infarction, continuing reduction in mortality has been documented for up to 6 years (11).

Mechanisms by which beta-blockers may be efficacious include, among others, a reduction in the arrhythmogenic and myocardial ischemic effects of catecholamines. The salutary effects of long-term beta-blocker therapy are most marked in high risk patients, such as those with depressed LV systolic function (12). Unfortunately, beta-blockers are underutilized in patients with impaired LV performance after acute MI, even though these patients have the most to gain from such treatment (13). Furthermore, it has been uncertain whether these agents confer additional benefit to patients with asymptomatic LV dysfunction who are also being treated with an ACE inhibitor.

Beneficial effects of ACE inhibitors. Angiotensin-converting enzyme inhibitors are beneficial in selected patients who have recovered from an acute infarction because of their ability to interfere with ventricular remodeling and thus attenuate ventricular dilation over time. The clinical result is a lesser incidence of the development of congestive heart failure, recurrent myocardial infarction and death (14).

Nine trials with a cumulative enrollment of >100,000 patients have documented the beneficial effect of ACE inhibition on mortality in a prospective, randomized manner (15). Five of these trials studied the selective use of ACE inhibitors in higher risk patients after acute myocardial infarction. In SAVE (6) and TRACE (16), patients were selected by laboratory evidence of an LV ejection fraction ≤40% or wall motion abnormalities. In AIRE (7), heart failure was the entry criterion. In SMILE (8) and CATS (17), the selection criterion was anterior infarct location on the electrocardiogram. A statistically significant mortality reduction of 40 to 70 lives saved per 1,000 patients treated was documented in four of these five trials (15). Thus, it would seem appropriate to initiate therapy with ACE inhibitors, either limited to patients at high risk or in a nonselective manner as long as no contraindications exist, and then consider withdrawing the drug later in patients who demonstrate a lack of high risk characteristics (15). Some rationale exists for the long-term use of these drugs in all patients after MI, and the results of this approach are currently being studied in adequately designed prospective clinical trials (18).

Neurohumoral activation in patients with acute MI. In asymptomatic patients with LV systolic dysfunction, neuroendocrine activation often occurs before overt heart failure ensues and is evident even in untreated patients (19,20). Activation of neurohumoral systems occurs during the first few days of an acute MI but generally subsides by hospital discharge, except in certain patients taking diuretic drugs and in many with LV dysfunction (21). In the neurohumoral substudy of the SAVE trial (22), significantly higher levels of plasma renin activity, aldosterone, norepinephrine, dopamine, arginine vasopressin and atrial natriuretic peptide were found in 534 patients than in age-matched control subjects.

When various neurohumoral systems were considered as activated or not, along with other variables known to modify survival in a multivariate analysis, only activation of atrial natriuretic peptide remained significantly related to 1-year cardiovascular mortality (22). Both atrial natriuretic peptide and plasma renin activity remained associated with total cardiovascular mortality in the neurohumoral subgroup of patients who were followed up for an average of 38 months. Activation of arginine vasopressin continued to be related to recurrent MI, whereas plasma renin activity, atrial natriuretic peptide, arginine vasopressin and aldosterone were independently related to the combined end point of recurrent MI, severe heart failure or cardiovascular death. Thus, neurohu-

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
LV = left ventricular
MI = myocardial infarction

moral activation at the time of hospital discharge in post-MI patients appears to be an independent sign of poor prognosis (21), particularly with plasma regard to renin activity and atrial natriuretic peptide.

When considered together with other important variables, the independent predictive value of plasma norepinephrine remained significant only for the development of severe heart failure and combined cardiovascular end points. This differs from patients with chronic heart failure, where plasma norepinephrine is a major predictor of subsequent mortality after adjusting for other contributing factors (23).

Effects of ACE inhibitors on neurohumoral activation. The salutary effects of ACE inhibitors in patients with chronic heart failure has been greatest in those with the most neurohumoral activation, particularly of the renin-angiotensin system (20,24). However, in the neurohumoral substudy of the SAVE trial, captopril had little effect on the prognostic value of neurohormone levels on any of the measured end points, except for slightly modifying the prognostic value of plasma renin activity and arginine vasopressin on 1-year cardiovascular mortality (22). Low statistical power due to an inadequate sample size in the SAVE neurohumoral substudy is a possible explanation. Alternatively, activation of the renin system may be particularly deleterious in the first year after MI, or early post-MI high levels may not accurately reflect long-term activation of this system. Finally, the benefits may be due to ACE inhibitor-related effects that are not necessarily reflected by levels of circulating plasma renin activity (22).

Relation of neurohumoral activation and beta-blocker efficacy. In this issue of the Journal, Vantrimpont et al. (25) present a retrospective analysis of the relation between beta-blocker use at the time of randomization, neurohumoral activation and the subsequent development of cardiovascular events in the neurohumoral substudy group from the SAVE study. Beta-blockers had no greater beneficial effect in patients with neurohumoral activation, with the exception of atrial natriuretic peptide. Interestingly, neurohumoral activation of norepinephrine and aldosterone actually appeared to reduce the efficacy of beta-blockers in postinfarction patients.

In the SAVE population, neurohumoral activation did not identify patients who would benefit most from long-term treatment with a beta-blocker. Possibly, neurohumoral activation may be an indicator of disease severity, whereas the beneficial effects of beta-blockers may be due to other mechanisms. Perhaps, the unspecified doses of beta-blockers used were insufficient to prevent the harmful effects of norepinephrine in patients with activation of the sympathetic nervous system (25). Also, plasma norepinephrine concentrations may underestimate cardiac sympathetic activation, which is known to be elevated in patients with severe LV dysfunction. Furthermore, a single determination of neurohumoral activity performed at rest early after MI may not reflect long-term neurohumoral activation after MI. Again, the possibility of low statistical power due to inadequate sample size and small number of events must be considered (25).

Additive effects of beta-blockers and ACE inhibitors in postinfarction patients with LV dysfunction. In the entire SAVE population of 2,231 patients, the use of beta-blockers in 789 was significantly associated with lower 1-year cardiovascular mortality, total cardiovascular mortality, incidence of severe heart failure and occurrence of the combined end point. Use of beta-blockers was associated with a lower risk of a recurrent MI that did not reach statistical significance. Although a quantitatively similar decrease in risk was associated with beta-blocker use in the neurohumoral group, only the reductions of 1-year cardiovascular mortality, total cardiovascular mortality and development of severe heart failure were statistically significant, most likely because of the small number of patients and, thus, wider confidence intervals (25).

More important, in the total SAVE population, when the use of beta-blockers was considered with other variables influencing prognosis (including randomization to captopril), the favorable influence of beta-blockers remained significant, albeit somewhat smaller. In the neurohumoral subpopulation, the reductions in risk due to the use of beta-blockers were not statistically significant, perhaps because of the small number of events in proportion to the number of independent variables used in the multivariate analyses. In the SAVE study, the use of beta-blockers in post-MI patients with LV systolic dysfunction was associated with an independent decrease in cardiovascular mortality and reduction in the incidence of severe heart failure. Beta-blocker treatment was associated with a 26% reduction in 1-year cardiovascular mortality and a 30% reduction in cardiovascular mortality over the length of the study. These results are consistent with the findings of previous randomized trials.

Thus, the current report by Vantrimpont et al. (25) suggests that the beneficial effects of beta-blockers and ACE inhibitors on hard cardiovascular end points are additive during an average follow-up period of 42 months in patients with a LV ejection fraction ≤40% after an acute MI. The previously reported salutary effects of beta-blocker therapy in post-MI patients with impaired LV systolic function are confirmed and strengthened by the current study; improved survival occurs in patients whose short- and long-term prognosis due to LV dysfunction is also enhanced by the use of ACE inhibitors.

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