ACE Inhibitors in Acute Myocardial Infarction
Patient Selection and Timing

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A
ngiotensin-converting enzyme inhibitors have earned their place along with aspirin, β-blockers, and thrombolytic agents as medical therapies proven to reduce mortality rates in acute myocardial infarction.1 The results of well-conducted, randomized, controlled clinical trials have been so consistent and so conclusive that the emphasis now shifts from research to implementation. Because the trials demonstrated that the oral use of an ACE inhibitor can save lives, the pragmatic questions of who and when to treat are left to the frontline physicians. Unlike the clinical trial experience with its protocol-directed inclusion and exclusion criteria, time window for initiation, and the informed consent process, the practicing physician must make decisions on the basis of his or her current assessment of the relative merits as well as the potential for harm by an ACE inhibitor for individual patients. Because any further major placebo-controlled trials of ACE inhibitors in acute myocardial infarction are not likely, physicians must use the sum of the currently available information to make the best choices for their patients.2

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The leaders of major trials of antiplatelet3 and thrombolytic4 therapies in acute myocardial infarction have formed collaborative groups that pool their collective data in an attempt to better understand the safety and efficacy information of their combined experience. This collaborative approach goes beyond routine meta-analysis because the group not only attempts to develop more uniform definitions but, importantly, pools their individual data to derive more reliable life-table experiences and projections. An ACE Inhibitor Collaborative Group was convened with these same objectives in the hope of developing a consensus for recommending ACE inhibitors in patients with acute myocardial infarction. One of the group’s initial decisions was to categorize the ACE inhibitor trials of myocardial infarction into those that were early-onset, broad-inclusion and short-term trials or selective-inclusion, long-term studies for separate analysis. The first report of the ACE Inhibitor Collaborative Group in this issue of Circulation summarizes the survival and safety data from the four major early-onset, broad-inclusion, short-term studies.5

When therapy started within 36 hours of the onset of chest pain, the survival benefit attributed to the use of ACE inhibitors in the broad-inclusion, short-term studies was modest and consistent. The 7% reduction in 30-day mortality translated into 5 lives saved per 1000 patients assigned to the ACE inhibitor. This overall effect was inclusive of a neutral study that raised an important caution against the intravenous administration of the first dose of the ACE inhibitor. Although this modest early survival benefit has been well known, the power of the present report stems from the ability to describe the timing of these lives saved and to quantitate efficacy and risk in specific well-characterized patient populations.

The extension of the previous report from the ISIS and GISSI groups of the early survival benefits with this use of an ACE inhibitor6 is an important feature of the current systematic overview. In the overview, of the 239 lives saved that are attributed to the use of an ACE inhibitor, 200 occurred within the first week, most of them in the first 2 days from randomization. These survival benefits are supported by mechanistic studies that demonstrated either less enlargement/expansion or a prompter recovery of left ventricular function with the early initiation of an ACE inhibitor.7-10 The 30-day mortality data from the combined trials should provide an impetus for the early initiation of an ACE inhibitor. In this context, it is equally important to note that an analysis of survival relative to the time from onset of symptoms to randomization to either control or ACE inhibitor did not show a time-related trend within the first 36 hours. Therefore, unlike aspirin and reperfusion strategies, it is not critical to introduce the ACE inhibitor in the hyperacute myocardial salvage phase. There is no therapeutic window in which an ACE inhibitor must be administered, but the overview suggests that opportunities can be lost by unnecessary delays of days or weeks. Therefore, the time-dependent priority decisions are the use of aspirin, reperfusion, and β-blockade, followed by reevaluation for ACE inhibitor therapy. An important aspect of the latter therapy not emphasized in the overview is that the survival benefit of an ACE inhibitor is independent of and additive to the use of these other proven therapies.

The overview recommendations were clearly for early (day 1 to 2) initiation, but there was less unanimity within the Collaborative Group concerning patient selection. In general, the proportional reduction in mortality rates across the major subgroups appeared to be uniform. Therefore, the overall data set from all 98,496 patients demonstrating that this early, broad use of an ACE inhibitor probably will result in a 7%
(95% confidence interval, 2% to 11%) reduction in mortality rates within the first 30 days of the acute myocardial infarction affords the most valid projection. This leads to the defensible recommendation for the early treatment of a broad population of acute myocardial infarction patients who were eligible for the trials (systolic blood pressure $>100$ mm Hg and no contraindications to the use of an ACE inhibitor). The Collaborative Group appropriately cautioned that with the nonstatistically significant tests for heterogeneity of the proportional effect (percent reduction in mortality rate) with the ACE inhibitor, in most of the subgroup analyses the overall proportional effect should be considered as the most reliable estimate.

Despite the potential hazards of overzealous subgroup analyses, when properly conducted and interpreted, these special patient population data can generate useful information for clinical decisions. Even accepting the premise of a similar proportional mortality reduction across subgroups with ACE inhibitors, the absolute benefit of therapy would be greater in the subgroups at a higher risk of death. A strikingly consistent feature from the systematic overview was that with the exception of advanced age, each of the clinical or infarct-related descriptors of predefined subgroups at higher risk for mortality, such as clinical history of prior infarction, diabetes or hypertension, anterior ECG location, elevated heart rate, or Killip class above I, identified a group with higher mortality rates and a greater absolute reduction in death with the use of an ACE inhibitor. Indeed, for the anterior ECG location and higher resting heart rate, the statistical test for heterogeneity was significant, indicating greater proportional as well as absolute survival benefits with the use of an ACE inhibitor in these clinically recognizable subgroups. As described for patients with anterior myocardial infarction, the 14% reduction in mortality rate corresponds to $\approx11$ lives saved per 1000 treated. Indeed, $>85\%$ of the lives saved attributed to ACE inhibitor therapy in the overview occurred in the anterior myocardial infarction subgroup that represented 37% of the overall population. It is likely that the converse analysis, indicating that the majority of patients can be classified at lower risk with less absolute potential benefit, has influenced practice patterns of many physicians.

Information outside of the trials analyzed in the Collaborative Group’s first systematic overview supports the position of less of a benefit with the use of an ACE inhibitor in lower-risk myocardial infarctions. The initial animal experiments and clinical mechanistic studies targeted myocardial infarctions with sufficient damage to produce left ventricular dysfunction and ventricular remodeling as the suitable subjects for ACE inhibitor therapy. The major clinical outcome trials that have selected for higher risk patients using either depressed left ventricular function or clinical signs of failure such as SAVE, AIRE, and TRACE, each demonstrated an $\approx20\%$ reduction in mortality rate with long-term administration of an ACE inhibitor. In addition to the select versus broad inclusions, the obvious differences in therapy duration between the short- and long-term studies make comparisons difficult. Although we cannot extrapolate beyond study duration in the broad inclusion, short-term studies, the 30-day survival data are available from the long-term, selective-use studies. The lives saved per 1000 patients treated during the first 30 days in each of these selected higher-risk populations was greater than that in the broad-inclusion studies of the overview. The TRACE study, which consecutively screened all patients with enzyme-confirmed myocardial infarctions, probably provides the best comparative data. The TRACE investigators estimate that their higher-risk patients who were selected by echocardiographically detected wall motion abnormalities represent $\approx25\%$ of the acute myocardial infarction population. Their finding of 24 lives saved per 1000 patients treated with the ACE inhibitor in the first 30 days is fourfold to fivefold greater than the 5 lives saved per 1000 treated in the broad inclusion population. These numbers become quite comparable if there is a negligible ACE inhibitor survival benefit in the remaining 75% of the lower risk patients, the so-called “dilutional effect.”

A quantitative assessment of the adverse experience that can be anticipated with this use of an ACE inhibitor is the other important ingredient in the decision regarding its use. Fortunately, this is a particularly strong feature of the overview. The incidence of persistent hypotension almost doubled from 9.3% in the control group to 17.6% in the ACE inhibitor group. Similarly, the incidence of reported renal dysfunction increased from 0.6% to 1.3% with this early use of an ACE inhibitor in acute myocardial infarction. A pertinent and relatively unique aspect of the overview was the fact that the absolute risk for experiencing these adverse events appeared to be uniformly distributed across both the high and lower risk groups. For example, a twofold increased risk of experiencing persistent hypotension with the use of an ACE inhibitor was observed in both anterior and other ECG locations. Because there was no difference in the rate of hypotension in their respective control groups, an absolute augmentation in this medication-induced complication of $\approx80$ per 1000 treated was produced in both the higher and lower mortality risk groups. Similarly, both the relative and absolute risks of persistent hypotension were similar between patients with Killip class I and those with class II.

Although there was general agreement on the factual aspects from the overview, the Collaborative Group concluded with two alternate treatment strategies as recommendations to the practicing physician. One strategy, supported by the majority, was that all patients with a systolic blood pressure $>100$ mm Hg who were without contraindications to the use of an ACE inhibitor should receive this therapy, commencing early (within 1 to 2 days of an acute myocardial infarction). This strategy implies that a reassessment is made at a later date to either discontinue the ACE inhibitor in lower-risk patients or continue therapy in those considered at higher risk. This strategy would maximize the number of lives saved; however, it would also expose the greatest number of patients to the adverse consequences of ACE inhibitor therapy in the early phase of the myocardial infarction. As previously advocated, a more selective approach for the use of ACE inhibitors was also adopted by the Collaborative Group. By selecting patients at higher risk of death, this approach uses subgroup analyses with all its limitations and other information to adopt the position that the vast majority of the lives that can be saved with the early use of an ACE inhibitor reside in clinically identifiable populations.
From my admittedly biased perspective as a member of the Steering Committee, this overview provides a concise compendium of the results of the broad inclusion, short-term trials of ACE inhibitors in acute myocardial infarction. The information concerning the importance of early initiation of therapy and the qualitative safety data that suggest that the low-risk, potentially low-benefit patients are as likely to experience an adverse event attributed to therapy with an ACE-inhibitor are unique, strong features of the overview. As concluded, both of two treatment strategies, broad or selective, can be justified by the data. I believe that the recent ACC/AHA Task Force guidelines for the management of patients with acute myocardial infarction have captured the essence of the issue.\textsuperscript{22} They designated ACE inhibitors for a class I recommendation, a condition in which there is evidence and/or general agreement that a treatment is beneficial, useful, and effective for patients within the first 24 hours of myocardial infarction with anterior ST elevation or clinical heart failure, and a class IIa recommendation, a condition in which there is conflicting evidence or divergence of opinion about the usefulness and/or efficacy of a treatment, but one in which the weight of evidence and/or opinion is in favor of usefulness and/or efficacy for all other patients within the first 24 hours of a suspected or established acute myocardial infarction.\textsuperscript{22} Both of these recommendations assume the absence of significant hypotension or a clear-cut contraindication to the use of an ACE inhibitor.

In my opinion, ACE inhibitors should be considered in every patient with acute myocardial infarction soon after the decisions on the use of aspirin, reperfusion, and \( \beta \)-blockers have been made. Patients at augmented risk for early death, such as those with a past history of hypertension, diabetes, or prior infarcts, or who present with higher heart rates, anterior ECG involvement, manifest pulmonary congestion, or left ventricular dysfunction on an assessment of ventricular performance have the most to gain from the early initiation of an ACE inhibitor. These patients are also likely to continue to benefit from the long-term use of this therapy. ACE inhibitor use in acute myocardial infarction has shifted from investigational to standard therapeutics. The implementation of this therapy to reduce mortality and morbidity rates will now be determined by the treating physician. The luxury of adopting alternative strategies applies to committees but not to the frontline physician, who has to make a decision for a specific patient.

**References**


**Key Words:** Editorials ■ angiotensin ■ myocardial infarction