Can qualitative echocardiography be used to select patients for angiotensin-converting enzyme inhibitors following acute myocardial infarction?

Introduction

Four large multicentre studies (SAVE, AIRE, GISSI-3, ISIS-4)\(^1\)-\(^4\), have now reported beneficial effects of angiotensin converting enzyme (ACE) inhibitors after acute myocardial infarction. However, their relevance to current clinical practice remains unclear, largely because the populations randomized in these trials were very different due to variations in inclusion and exclusion criteria. Although the data may be interpreted as supporting the universal use of ACE inhibitors in patients following acute myocardial infarction, this ‘one size fits all’ approach dilutes the benefits, which are concentrated in higher risk subgroups such as those with anterior wall infarction, heart failure and prior infarction\(^5\). To use a more selective approach will require well defined and readily available criteria for identifying patients likely to benefit from ACE inhibitor therapy.

The AIRE study provides simple clinical guidelines for the treatment of a high risk group with clinical evidence of heart failure\(^2\). However, as shown in the SAVE study, if clinical signs alone are used to select patients for ACE inhibitor therapy, then many patients likely to benefit will be excluded\(^6\). The SAVE study selected patients with left ventricular ejection fractions ≤40% and found that the mortality benefit with ACE inhibitors was seen equally in those without clinically overt heart failure (Killip Class I) as in those with overt heart failure\(^1\). This means that as well as the 20–30% of post-acute myocardial infarction patients who show clinical evidence of heart failure, an additional 26% of patients with asymptomatic left ventricular dysfunction will also benefit from ACE inhibitor therapy\(^7\). The method most commonly used to identify this latter group is estimation of the left ventricular ejection fraction by any of several cardiac imaging techniques.

Radionuclide ventriculography is an accurate way of measuring left ventricular ejection fraction, but has limitations as a screening method. It is expensive, involves giving a radioactive agent and is not widely available in the U.K. With the severe shortage of resources, the provision of radionuclide studies in all patients after acute myocardial infarction would present a logistic challenge. Furthermore, there is considerable variation in radionuclide estimations of left ventricular ejection fraction between centres\(^8\). To apply a single, universal treatment threshold based on a left ventricular ejection fraction ≤40% would therefore be questionable\(^9\).

Two-dimensional echocardiography, on the other hand, is widely available, less expensive than radionuclide ventriculography and provides both quantitative and qualitative information\(^10,11\). Measurements of left ventricular ejection fraction by two-dimensional echocardiography have been validated in both angiographic and radionuclide studies\(^12-14\), but high quality echocardiograms are essential in order to visualize ≥70% of the left ventricle endocardium for border tracing on an off-line computer. Accurate measurement of left ventricular ejection fraction is made difficult by freeze-framing videotaped echocardiographic images for tracing, since significant image quality is lost. Despite computer use, off-line analysis methods are time consuming since they require careful manual tracing of the endocardial borders in at least two different views — most commonly the apical 2- and 4-chamber views\(^14\). However, recent advances in echocardiographic assessment of left ventricular function using on-line automated border detection techniques are promising, with preliminary results suggesting that they may be faster than manual tracing with improved accuracy and precision\(^15,16\).

Nonetheless, quantitative assessment of left ventricular function is used infrequently in clinical practice, due to the time consuming nature of the technique. Furthermore, time constraints may compromise measurement accuracy, and they certainly explain why left ventricular ejection fractions are not measured routinely in clinical echocardiography laboratories.
Qualitative ('eye-ball') estimates of left ventricular ejection fraction by experienced echocardiographers, in contrast, have been shown to be accurate in several studies with correlation coefficients ranging from 0.88–0.93 when compared to radionuclide ventriculography or contrast ventriculography\(^\text{[17-19]}\). Moreover, when a subjective estimation of left ventricular ejection fraction was compared with several quantitative echocardiographic methods in a non-selected population (including patients with poor acoustic windows), it was found to correlate better with radionuclide ventriculography\(^\text{[17]}\). The predictive accuracy, namely the percentage of both normal and abnormal ejection fractions detected correctly by subjective estimation, was also found to be very high (86–89\%). These data go some way towards reaching the objectives set by the American Society of Echocardiography for quantitation of the left ventricle by two-dimensional echocardiography\(^\text{[11]}\).

Visual assessment of left ventricular ejection fraction by an experienced echocardiographer is derived from all possible views and is not limited by geometric assumptions. Wall motion analysis is made in real-time, which greatly aids endocardial detection compared to stop-frame images. In addition, subjective echocardiography is made attractive because it is neither time-consuming nor does it require an expensive computer, thus allowing assessment of left ventricular function 'on-line' with the study interpretation. It also allows an early assessment of left ventricular function to be made after myocardial infarction, without the need to move the patient from the coronary care unit. This may be important with data from the GISSI-3 and ISIS-4 trials suggesting that up to 30\% of the deaths saved with ACE inhibitor therapy occurred in the first 24\,h after acute myocardial infarction\(^\text{[3,4]}\). Hence subjective echocardiography, performed at the bedside early after myocardial infarction, would enable an early decision to be made with regards ACE inhibitor therapy.

Whether an exact measure of left ventricular ejection fraction is necessary when selecting patients for ACE inhibitor therapy following acute myocardial infarction remains an issue. Certainly, it is not clear what the threshold for treatment should be, although the 40\% threshold used in the SAVE study is most frequently chosen by clinicians. Therefore, a visual assessment of left ventricular function, carried out by an experienced echocardiographer and reported in terms of qualitative equivalents (such as mildly, moderately or severely diminished), may be adequate for the correct selection of patients for ACE inhibitor therapy. Importantly, a number of studies have shown that conventional 2-D echocardiography performed early after acute myocardial infarction can provide important prognostic information (e.g. ventricular dilatation) that may be independent of conventional patient descriptors such as left ventricular ejection fraction\(^\text{[20,21]}\). Nevertheless, in clinical practice, left ventricular ejection fraction remains the most widely accepted indicator of left ventricular performance.

Subjective echocardiography has a number of potential limitations. Firstly, it is a qualitative assessment and therefore observer-dependent. However, it has been reported that with a short period of training (<3 months) an echocardiographer can make reliable evaluations of left ventricular ejection fraction\(^\text{[18]}\), but it would be critical for the echocardiographer to validate his or her estimates of left ventricular ejection fraction against a series of known standards (such as biplane contrast left ventriculograms in patients with similar ejection fractions by radionuclide ventriculography or quantitative 2-D echocardiography). Only such comparisons can ensure accuracy and reliability.

One way to reduce the subjectivity of qualitative echocardiography may be to use a formalized scoring system to assess wall motion abnormalities rather than estimating left ventricular ejection fraction. The Trandolapril Cardiac Evaluation (TRACE) study used such an approach to select patients for a large multicentre study assessing the long-term benefits of an oral ACE inhibitor (trandolapril) in patients after myocardial infarction\(^\text{[22]}\). In this study, left ventricular function was visually assessed using the nine segment model originally described by Heger et al.\(^\text{[23]}\). Wall motion score was graded as −1 for paradoxical movement of a segment, 0 for akinesia, 1 for hypokinesia, 2 for normokinesia, and 3 for hyperkinesia. Total wall motion score was then indexed by dividing by the number of scorable segments. This method was highly efficient for identifying high risk patients (those with a wall motion index ≤1-2) who then benefited from ACE inhibitor therapy\(^\text{[24]}\). The study also showed that physicians and sonographers can be quickly trained to obtain images adequate for reproducible, wall motion scoring at the bedside early after acute myocardial infarction. An additional important finding from the TRACE study was the high rate of agreement between cardiologists in identifying patients with reduced left ventricular systolic function using the wall motion index\(^\text{[24]}\). For daily clinical practice, the wall motion index may therefore prove to be an extremely useful and rapid way to assess left ventricular function in post-infarction patients.

Recent advances in echocardiographic techniques such as Doppler tissue imaging\(^\text{[25]}\) and 3-D echocardiography\(^\text{[26]}\) may have potential applications for the assessment of myocardial function and
enhanced detection of regional wall motion abnormalities. The ability of digital tissue imaging to obtain quantitative myocardial velocity data may prove useful in understanding regional and global left ventricular function in both normal and diseased states. Three-dimensional echocardiography offers more accurate, global assessment of left ventricular systolic function and clearly improves upon 2-D methods of quantitation of left ventricular ejection fraction. However, incorporation of these techniques into routine clinical practice is not likely to occur for a number of years.

In the future, other (non-echocardiographic) methods may also supersede assessment of left ventricular ejection fraction as a means of predicting ventricular dilatation after acute myocardial infarction. Plasma concentrations of B-type natriuretic peptide have been shown to correlate with left ventricular dysfunction and may predict adverse ventricular remodelling. The presence of late potentials on high resolution electrocardiography early after acute myocardial infarction may also identify patients likely to benefit from ACE inhibitor therapy, since they may serve as subsequent predictors of ventricular enlargement. However, these and other methods have not been adequately correlated with left ventricular function, and until their value is known, qualitative echocardiography may be the most useful bedside technique for selecting patients for ACE inhibitor therapy.

In conclusion, many patients with left ventricular dysfunction will be missed if clinical signs of heart failure alone are used to select patients for ACE inhibitor therapy following acute myocardial infarction. Clearly, patients with significant systolic left ventricular dysfunction following myocardial infarction benefit from ACE inhibitor therapy. Although the SAVE trial treatment threshold of a left ventricular ejection fraction ≤40% is now being widely adopted in clinical practice, and is rapidly increasing the number of radionuclide ventriculograms being performed for this purpose, we would question this practice in two respects. First, left ventricular ejection fractions determined by radionuclide ventriculography are likely to be less accurate and reproducible in clinical practice than in research studies. Once validated in a clinical laboratory, visual assessment of left ventricular function (by subjective or semi-quantitative means) by a dedicated echocardiographer can provide a simple alternative to formal radionuclide ventriculography or quantitative echocardiography, which consume greater time and resources for only marginally greater accuracy. Second, selection of the 40% ejection fraction threshold is arbitrary and based only on the SAVE study. Other selection criteria have proved useful, such as the extent and severity of wall motion abnormalities after infarction, and new criteria are being developed. For the present, however, we favour echocardiographic assessment of ventricular function since it can be performed rapidly at the bedside early after myocardial infarction and has been proven to identify high risk patients who will benefit from ACE inhibitor therapy.

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Gender differences in clinical trials in coronary heart disease: response to drug therapy

Introduction

Clinical experience supported by an abundance of trial data indicate that the presentation, management, response to treatment and prognosis of coronary heart disease, differs in several important aspects between men and women. The large-scale clinical trials of the last decade present unique insights into these differences.

Outcome after myocardial infarction

As long as 9 years ago, the MILIS study group found that women, and in particular black women, had an adverse prognosis after myocardial infarction in comparison with their male counterparts, even after adjustment for risk score[1]; women were found to have a greater risk of subsequent stroke, early reinfarction, and cardiac rupture.

These observations were confirmed by the large-scale trials of therapy in acute myocardial infarction. In the early ISIS-1, placebo-controlled trial of atenolol, the 7-day mortality in the control group was much greater in women than in men (7.5% vs 3.7%)[2]. Similar gender differences were seen in the trials of thrombolysis. In the meta-analysis of nine large thrombolytic trials by the Fibrinolytic Therapy Trialists (FTT) collaborative group, women were shown to have a 60% greater mortality than men 35 days after presentation to hospital with acute myocardial infarction[3].