showing a parallel course for both, low- and high-risk populations after 14 months until the end of follow-up. Unfortunately, data on the incidence of sudden cardiac death and serious arrhythmic events in this long-term followed population have not been presented. This would provide a better understanding of the pathophysiological mechanisms leading to the decreased predictive power of heart rate variability after one year of survival.

The predictive value of heart rate variability described by Quintana et al. [5] differs considerably from previously published data. This may be based on obvious differences in mortality and event rates compared to previous studies, but not necessarily on the extended follow-up period, as mentioned by the authors. These findings need further explanation with regard to the amount of thrombolysis, beta-blocker therapy or a potential bias due to the large proportion of screened but lost patients.

Despite the valuable results obtained by the study of Quintana et al. [5] the evaluation of the independent prognostic value of heart rate variability for long-term risk stratification still needs further investigation.

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References


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Treatment of mild heart failure: the place of diuretics and ibopamine

See page 852 for the article to which this Editorial refers

Chronic heart failure is a progressive disorder which carries high morbidity and mortality. In recent years, it has become increasingly clear that disease progression in chronic heart failure is not only related to haemodynamic, but also to neurohumoral factors [1]. Treatment which favourably affects both factors is attractive and should be initiated as early as possible. In the present issue, Andrews et al. [2] emphasize (again) the importance of diuretics in this patient group and provide new clinical information on the oral dopamine agonist, ibopamine, which was recently found to increase mortality in severe chronic heart failure (ref. [21] of Andrews et al.).

As fluid retention and congestion are hallmarks of chronic heart failure, diuretics are often the first drugs to be prescribed. In the acute phase of cardiac decompensation with pulmonary congestion, the value of these agents, particularly loop diuretics such as furosemide and bumetanide, is unquestioned. During long-term use in chronic heart failure, however, monotherapy with these drugs may be less appropriate, because of activation of neurohumoral systems, induction of electrolyte disturbances, and other side effects (refs [4] and [5] of Andrews et al.).
Further, the effect of diuretics on the progression of chronic heart failure and survival is unknown\cite{3}. Angiotensin converting enzyme (ACE) inhibitors have been shown to reduce morbidity and mortality in patients with chronic heart failure. In most studies, however, ACE inhibitors were added to a regimen that included diuretics (and digoxin), and the results of ACE inhibitors when given as monotherapy, or as first-line treatment are less convincing (refs [3] and [15–17] of Andrews et al.).

In contrast to furosemide, ibopamine was not effective in the present 8-week study\cite{2} in preventing the exacerbation of chronic heart failure. This finding is in contrast with three previous studies, in which ibopamine was comparable to diuretics as monotherapy (refs [19], [22] and [23] of Andrews et al.) and in another, in which it was compared to digoxin monotherapy (ref. [24] of Andrews et al.). These four studies showed that ibopamine was at least equivalent to the reference drug\cite{2}, and more effective than placebo (refs [19] and [22] of Andrews et al.). This difference is probably due to the fact that patients in the present study\cite{2} were diuretic dependent, while in the previous four studies they were not.

Recently, ibopamine has received considerable attention because a large international survival study with this drug (PRIME-II) was prematurely discontinued after 1906 patients had been randomized (ref. [21] of Andrews et al.). In this study, ibopamine was found to increase mortality in patients with moderate to severe chronic heart failure (New York Heart Association class [NYHA] III–IV) during a mean follow-up of ± 1 year. Although a full paper has not yet been published, the data showed that the adverse effect was mainly found in the most severely ill patients, and that there was significant interaction with the use of antiarrhythmic drugs (± 90% amiodarone). Ibopamine had been available for all classes of chronic heart failure in a number of European countries, but the findings of the PRIME-II study have led to a restriction of the drug to patients with mild chronic heart failure, in combination with diuretics, in those countries.

In contrast to the disappointing findings of PRIME-II are the results of two recent studies in which the effect of ibopamine was compared to the ACE inhibitor captopril\cite{4,5}. In a placebo-controlled study of 150 elderly (>65 years) patients with mild to moderate chronic heart failure\cite{4}, ibopamine 3 × 100 mg was as equally effective as captopril during 6 months treatment, with regard to exercise time and quality of life, while safety parameters were also similar, and both drugs were better than placebo. In a more recent comparative study\cite{5} in 266 chronic heart failure patients of all ages, these findings on efficacy and safety were confirmed and the two drugs also had a similar effect on plasma neurohormones during 6 months treatment. The results of these two studies, performed in >400 patients with NYHA class II–III chronic heart failure, who had background therapy with diuretics, would thus suggest that ibopamine could be considered as an alternative for ACE inhibitors, in chronic heart failure patients who do not tolerate these drugs.

Chronic heart failure has become a major medical and public health care problem in the Western World\cite{6}. Neurohumoral inhibition or modulation appears to be a challenging concept to slow disease progression in chronic heart failure\cite{1}. Whether neurohumoral modulators, such as ACE inhibitors, β-blockers, but also ibopamine, can be given as monotherapy, is largely unknown and often difficult to predict, as both the present study with ibopamine\cite{2} and previous data on ACE-inhibitors (refs [3] and [15] of Andrews et al.) are disappointing in patients with signs and symptoms of fluid overload\cite{3}. However, in patients with mild chronic heart failure (NYHA I–II), who have no signs of fluid overload, the situation may be different, and monotherapy with neurohumoral modulators may be more beneficial, but this needs further investigation.

In conclusion, diuretics remain very important in the treatment of early or mild chronic heart failure, and in most, if not all, patients a diuretic should probably be the first drug prescribed. A neurohumoral modulating drug should be added soon or even immediately, and in virtually all patients this will be an ACE inhibitor. In a proportion of patients, an ACE inhibitor will have been started earlier to prevent ventricular dilatation and remodelling after myocardial infarction. Nevertheless, in patients with chronic heart failure who do not tolerate ACE inhibitors, because of their well-known side effects, ibopamine may be considered. It may also be useful in the earlier stages of chronic heart failure as an alternative in countries where the drug is registered, given the favourable results of two trials which have compared ibopamine with captopril\cite{4,5}. However, as chronic heart failure advances, the situation with regard to ibopamine becomes more difficult. In NYHA class III, the drug is no longer licensed, and in NYHA class IV it is even contraindicated. The clinical experience with ibopamine therefore shows again the importance of well-conducted, controlled studies, when a new drug for chronic heart failure is introduced. In addition, the present data show that one should not discard older drugs, such as diuretics, too quickly.

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Stress echocardiography and myocardial contrast echocardiography in viability assessment

See page 771 for the article to which this Editorial refers

The strongest predictor of prognosis in patients with ischaemic heart disease is left ventricular dysfunction which is caused by post-infarction scar or fibrosis as well as by asynergic but still viable myocardium. In the latter case left ventricular dysfunction can be reversible and can improve either spontaneously (stunning) or after coronary revascularization (hibernation). Thus, assessment of myocardial viability becomes an essential step in clinical decision making related to coronary revascularization procedures.

Diagnostic methods capable of predicting myocardial viability have been based on the detection of either metabolic activity or contractile reserve within dysfunctional segments. Myocardial perfusion and preserved metabolic activity are evaluated in the clinical setting by deoxyglucose or 201-thallium scintigraphy. Contractile reserve (usually elicited by dobutamine infusion) is currently detected by echocardiography and, more recently, by MRI or blood pool scintigraphy. Over the past ten years, myocardial contrast echocardiography has been extensively evaluated in experimental and clinical studies and has been proposed as a method to assess myocardial perfusion and, recently, viability. Myocardial opacification, produced by the presence of microbubbles in the coronary microcirculation, has been considered synonymous with preserved microvascular integrity.

Potentially, contractile reserve (by dobutamine echocardiography) and microvascular integrity (by contrast echocardiography) provide different information regarding functional recovery after coronary revascularization. The inotropic stimulus focuses on the final effect (the recovery of dysfunctional segments), while contrast echocardiography refers to a prerequisite for myocardial viability (microvascular integrity)\(^1\)\(^2\).

Dobutamine echocardiography and myocardial contrast echocardiography also have different intrinsic limitations. In fact, haemodynamic changes induced systemically by dobutamine infusion may potentially alter wall motion and left ventricular function in a way which is independent of viability, thus providing false-positive results. Alternatively, some coronary stenoses may be so severe that the short period of increased contractility, which takes place as expression of viability, may be missed because of the rapid onset of ischaemic asynergy induced by dobutamine, thus generating false-negative results. On the other hand, myocardial opacification might be seen even in islands of viable myocytes surrounded by predominantly fibrotic areas. This phenomenon has been described with 201-thallium imaging and may render perfusion imaging ‘too sensitive’ to detect viability in segments which are, on the contrary, incapable of functional recovery.

A previous study by de Filippi et al.\(^3\) compared dobutamine stress echocardiography with myocardial contrast echo in predicting the recovery of regional left ventricular function after coronary revascularization in patients with chronic ischaemic heart disease. When dealing with hypokinetic segments, the two techniques were not significantly different in predicting functional recovery. However, when dealing with akinetic segments, dobutamine...