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**A double-blind randomised, multicentre clinical trial to evaluate the efficacy and safety of two doses of etomoxir in comparison with placebo in patients with moderate congestive heart failure: The ERGO (etomoxir for the recovery of glucose oxidation) study**

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**A Double-Blind Randomised, Multi-Centre Clinical Trial to Evaluate the Efficacy and Safety of Two Doses of Etomoxir in Comparison to Placebo in Patients with Moderate Congestive Heart Failure:**

**The ERGO-Study  
Etomoxir and Ergometry**

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## **Abstract:**

Etomoxir is an inhibitor of mitochondrial carnitine-palmitoyl-transferase 1 (CPT1) and thereby switches the energy metabolism from fatty acids to glucose oxidation. For two reasons such a metabolic change may be beneficial in heart failure: (1) Energy production (generation of ATP molecules per oxygen consumption) is more economical in case of glucose oxidation. (2) Glucose oxidation is associated with altered gene expression of important myocardial proteins that are related to function (sarcoplasmic reticulum calcium ATPase and myosin isoenzymes).

Etomoxir was planned to be tested in a dose of 80 and 40 mg versus placebo for a period of six months in patients with heart failure. As principle measures of efficacy a maximal exercise tolerance test using an exercise bicycle and a sub-maximal six minute corridor walk test were used. Secondary endpoints were echocardiographical dimensions and scores of quality of life assessments. 350 patients were planned to be screened with the expectation that endpoint data will be available for approximately 260 patients.

This study had to be stopped prematurely, because unacceptably high values for liver transaminases were detected in four patients taking 40 mg or 80 mg etomoxir. At the time of the end of the study, 121 patients were randomised to placebo, 118 to 40 mg etomoxir and 108 to 80 mg etomoxir. 21 patients in the placebo group, 17 and 14 patients in the 40 mg etomoxir and the 80 mg etomoxir group respectively, had completed the study at that time. The mean increases in exercise time were 3.3 sec, 10.2 sec, and 19.4 sec for the placebo, the 40 mg Etomoxir and 80 mg Etomoxir groups, respectively (N.S.) Neither changes were obvious in the six-minute corridor walk test from baseline nor in echocardiographical parameters.

Due to hepato-toxicity of etomoxir the study had to be stopped for safety reasons. The number of patients that completed the study was too small to demonstrate significant increases in exercise time. However, there was a tendency for increased exercise time. Therefore, before rejecting the hypothesis that fatty-acid-oxidation-inhibition might be beneficial in congestive heart failure, similar studies have to be performed using different fatty-acid-oxidation-inhibitors targeting CPT1 and other enzymes of this metabolic pathway.

**Five key words:** drugs, fatty acids, glucose, heart failure, metabolism

## **Introduction:**

Congestive Heart Failure (CHF) is a major public health problem afflicting up to 3% of the population in western countries and is associated with high morbidity and mortality rates [1,2,3] Heart failure can be viewed upon as the end-stage of various forms of heart disease [4]. The prognosis for patients with heart failure is poor and is in fact even worse than the survival chances in patients suffering from various malignancies [5] Various surveys have shown that medical management of CHF is characterized by polypharmacy and by the underuse of recommended medications [6,7].

The conventional medical therapy for CHF has been extensively outlined [8]. The following classes of agents are used: Diuretics are used to control the symptoms of volume overload. When these symptoms are absent, diuretics, in form of loop diuretics, have no proven benefit [9]. However, spironolactone [10] and eplerenone [11] have shown a clear benefit for heart failure patients regarding survival. The second class of agents useful in CHF includes digitalis glycosides, which have been shown to improve symptoms but not to prolong life [12]. The next class of agents used in the pharmacological therapy of CHF is the vasodilators. The angiotensin-converting enzyme (ACE) inhibitors have the most beneficial effect on mortality and are the most commonly used [13,14,15,16]. The most recent class to be recommended for heart failure patients is the beta-blockers, which provide a number of beneficial effects: Decrease in heart rate, decrease in overall work load, reduction in oxygen consumption, prolongation of diastolic myocardial perfusion, protection against toxic effects of catecholamines. These effects may work in common and thereby increase survival [17,18,19].

Despite the use of recent therapeutic regimens, many patients remain symptomatic and are at high risk of cardiac death. There remains a need to develop new treatments for heart failure which extend survival, reduce symptoms and provide patients with an improved capacity to conduct daily activities.

Etomoxir is an inhibitor of mitochondrial carnitine-palmitoyl-transferase 1 (CPT1), developed originally for the treatment of diabetes mellitus [20]. This inhibition of mitochondrial CPT1 is common to a number of oxirane carboxylic acid

derivatives and is both irreversible and stereospecific. Etomoxir effectively blocks long-chain fatty acid oxidation in heart, skeletal muscle and liver and thus switches the metabolism to glucose oxidation. Such a switch has been shown to induce expression of sarcoplasmic reticulum calcium ATPase and redistribution of myosin isoenzymes in experimental animal studies – alterations which may be beneficial in chronic heart failure [21,22,23,24,25].

In a first clinical trial with etomoxir in patients with chronic congestive heart failure, clinical improvement has been reported for 80 mg etomoxir per day [26].

The purpose of this study was to reconfirm the efficacy of 80 mg etomoxir per day in a double-blind setting and to study the risk/benefit ratio of 40 mg and 80mg etomoxir in comparison with placebo based on clinical findings, exercise testing, echocardiography and Holter monitoring in patients with moderate congestive heart failure (CHF NYHA class II-III).

### **Methods:**

**Rationale:** The hypothesis to be tested in the ERGO-Study was an increase in cardiopulmonary capacity by 10% as induced by etomoxir at a dosage of 40 or 80 mg compared to placebo during a period of three or six months.

**Patients:** Investigations were performed in Poland, Germany and Italy. 347 patients were randomised, 193 patients in Poland, 127 patients in Germany, and 27 patients in Italy. Age of patients was between 21 and 84 years (mean 66.6 years). Patients were suffering from moderate congestive heart failure (NYHA II – III).

A total of 230 (66%) patients had ischemic heart disease of which 80 (35%) had current angina and 182 (79%) reported at least one previous myocardial infarction. 189 (57%) patients had hypertension, 84 (24%) had dilated cardiomyopathy, 21 (6%) had valvular heart disease, and 14 (4%) had other etiologies.

59 (17%) of the patients had diabetes mellitus type 2.

All patients gave written consent. The protocol was reviewed and approved by competent Ethic Committees

**Study protocol:** A double-blind study design was used. Etomoxir was provided in soft gelatine capsules containing 40mg compound dissolved in a mixture of medium chain triglycerides derived from coconut and palm oil. The daily dose for one patient was packed into blister strips, each strip containing two capsules for each seven days; as one of the following three forms: 80mg etomoxir (two 40mg capsules), 40mg etomoxir (one verum and one placebo capsule), or placebo (two placebo capsules). All patients were given two capsules once daily prior to their evening meal.

**Examination:** Before randomization, patients completed a baseline six-minute-corridor-walk-test, two quality of life questionnaires (Minnesota 'Living with heart failure' and EUROQOL 'EQ-5D') and a 24 hour Holter ECG. The treatment phase was thought to contain visits at 3, 6, 12, 18 and 24 weeks following randomization. The visits consisted of physical examination, 12-lead ECG, urinalysis, bicycle protocol and a six- minute-corridor-walk-test. The patients underwent laboratory examinations including electrolytes, liver and renal function and hematology profile with platelet count at 3, 6, 18 and 28 week visits and biochemistry and hematology at 12 and 24 week visits. At 3 and 24 week visits 24-hour Holter monitoring was performed.

**Exercise testing:** Bicycle protocol and the six-minute-corridor-walk-test were performed at baseline, 12 and 24 week visit (bicycle protocol was optional at 3, 6 and 18 week visits). At baseline at least two exercise tests were postulated with exercise-times within  $\pm 20\%$ .

The bicycle protocol consisted of two minutes stages with an initial work load of 25 watts, increasing by 25 watts each successive stage.

All bicycle tests for a particular patient were scheduled for the same time of day throughout the study. The following test measurements were determined: date and time of start test; total exercise time; ECG at the end of every minute and at 1, 2, and 5 minutes post exercise; systolic and diastolic blood pressure; heart rate at the end of each two minute stage, at the end of exercise and at 1, 3, and 5 minutes post

exercise; Borg score (end of each stage; at end of exercise); reason for stopping if needed.

The six minute corridor walk test was thought to be a simple and objective measure of submaximal exercise capacity. On all occasions this test was performed during a visit where the bicycle test has previously been performed.

**Echocardiography:** Echocardiographical measurements were made as follows: the left ventricular ejection-fraction LVEF, left ventricular end-diastolic diameter LVEDD, fractional shortening and left ventricular wall thickness at the septum and the posterior wall. Echocardiograms were performed at baseline and at the 24-week-end-point.

**Holter monitoring:** Twenty-four hour Holter monitoring was performed at 3, 12 and 24 week visits. All evidences of torsade de pointes and ventricular fibrillations, asystoles, runs of ventricular tachycardia, AF, flutter or supraventricular tachycardia, number of ectopic beats, number of ectopic couplets and mean heart rate were printed out and validated by a cardiologist.

#### **Sample size calculation:**

The proposed recruitment of 120 patients per treatment group (that is, a total of 360 patients who successfully complete the screening period and are eligible for randomisation) is motivated by the following considerations:

- An average baseline total exercise time for the bicycle protocol of 420 seconds (seven minutes).
- An anticipated increase over baseline by week 24 of 45 seconds for placebo, 67.5 seconds for 40 mg etomoxir and 90 seconds for 80 mg etomoxir. Some placebo effect is anticipated as the baseline value will be obtained prior to the commencement of study medication.
- A within-patient standard deviation for change from baseline with respect to the primary endpoint of 90 seconds. This figure is consistent with the requirement that prior to randomisation each patient must achieve two exercise times within  $\pm 20\%$ .

- The direct comparison of 80 mg etomoxir with placebo, to be investigated using a two sided parametric test at the experimentwise 5% significance level should have at least 90% power.

Assuming equal numbers of patients per group, it can be shown via simulation that the ANOVA F test for the equality of the three treatment means has 90% power if a minimum of 103 patients are recruited to each group and the underlying group means are as described. This is a “worst-case” scenario and it can be shown that in this case the comparison of 80 mg etomoxir with placebo will also be significant with a power of at least 90%

#### **Statistical analysis:**

Comparability of treatment groups at baseline has been assessed and summarized using descriptive statistics. Hypothesis testing to determine differences between treatments were two-sided, with differences being declared statistically significant if the observed significance level is less than 0.05. The two pairwise comparisons of 80mg etomoxir with placebo and 40mg etomoxir with placebo with respect to the primary endpoint constituted the only confirmatory analysis and the type I error for this analysis was controlled to be 0.05 by adjusting the statistics using the method of Dunnett. All other analyses were secondary and were reported without adjustment of significance levels.

Data collection and the statistical analysis were conducted on a collaborative basis by the Study Statistician and the Statistic Department of Nottingham Clinical Research Limited who jointly prepared the Statistical Analysis Plan.



## **Results:**

### **Characteristics of the treatment groups.**

A total of 375 patients had some data entered into the study data base with 347 patients randomised with 121 receiving placebo, 118 patients receiving 40 mg and 108 receiving 80 mg etomoxir. Table 1 gives details on entry and completion for randomised patients for each country. Therefore at the end of the prematurely stopped study, 52 patients had completed the study, 21 in the placebo group, 17 in the 40 mg etomoxir and 14 in the 80 mg etomoxir group respectively.

The treatment groups were balanced with respect to age, gender, smoking history and race. Table 2 summarizes demographics information about treatment groups.

A total of 209/347 (60%) patients were graded NYHA grade II at screening. The corresponding number of patients graded NYHA III was 137 (40%), see also Table 2.

### **Concomitant Medication:**

81% of the patients were on ACE-inhibitors or angiotensin-receptor-blockers, 52% on  $\beta$ -blockers, 23% on spironolactone, 7% on amiodarone, 32% on nitrates, and 24% digitalis-preparations.

### **Bicycle Exercise testing and echocardiographical data:**

A total of 234 patients were included in the randomised set for the principal measure of efficacy of the change from baseline in total exercise time (sec) at week 24 endpoint. There was a clear tendency regarding increases in bicycle exercise testing (Figure 1; Table 3). The mean increases in exercise times were 3.3 sec, 10.2 sec and 19.4 sec for the placebo, etomoxir 40 mg and etomoxir 80 mg groups, respectively (Table 3). However, none of these were statistically significant. The number of patients that reached the 24 week endpoint and thus could be included in the pairwise comparisons were  $n = 21$  in the placebo group,  $n = 16$  in 40 mg and  $n = 14$  in the 80 mg etomoxir groups respectively (Table 3). This may be due to the premature study end resulting in a too small number of patients having

finished the study. There were no statistically significant differences between any of the three pairwise comparisons for the change from baseline in total distance covered in the six-minute-corridor-walk test at week 12 endpoint and week 24 endpoint (table 4 A). Also, no statistically significant differences were found for LVEF (table 4 B), LVEDD, fractional shorting and left ventricular wall thickness at week 12 and week 24 endpoint.

Unfortunately, there is no data available from the 24 hours Holter monitoring.

### **Cardiac deaths and serious adverse events:**

Six patients died during the study. One patient died during the run-in phase. Five patients died during the randomisation phase, three in the placebo group all of whom had sudden cardiac death, one in the etomoxir 40 mg group who died due to cardiogenic shock, and one patient in the 80 mg etomoxir group who died due to myocardial infarction.

Serious adverse events are listed in table 5. There were four patients with elevations of liver enzymes all of them were either in the 40 mg etomoxir or in the 80 mg etomoxir group ( see table 6).

### **Using the Minnesota questionnaire:**

The pairwise comparison between 40 mg etomoxir and placebo was statistically significant ( $p < 0.05$ ) in favour of 40 mg etomoxir for the following questions and timepoints:

Making him/her sit or lie down to rest during the day at week 24 endpoint, making going places away from home difficult at week 12 endpoint, and making them stay in a hospital at week 24 endpoint.

The pairwise comparison between 80 mg etomoxir and placebo was statistically significant ( $p < 0.05$ ) in favour of 80 mg etomoxir for making them stay in a hospital at week 24 endpoint.

## **Discussion:**

Molecular changes of the myocardium in congestive heart failure

Left ventricular systolic dysfunction and chronic congestive heart failure are known to be associated not only with a quantitative increase in muscle mass, but also with subtle qualitative changes in gene expression and subsequent district functional consequences of the myocardium. At least four major phenotypic changes have been reported: (1) Increased production and release of natriuretic peptide type A and type B (ANP and BNP), (2) a shift in the myosin heavy chains from  $\alpha\alpha$  to  $\beta\beta$  dimers, (3) up-regulation of the gene encoding the sodium-calcium exchanger, and (4) downregulation of SERCA-2.

The former two alterations may be judged to be beneficial, in as far as they compensate for increased wall stress. Due to the vasodilating, diuretic, and angiotensin-converting-enzyme blocking properties of ANP and BNP, these peptides ameliorate increased workload, and salt and water retention [27,28,29,30,31]. The shift of myosin heavy chains from  $\alpha\alpha$  to  $\beta\beta$ -dimers leads to slower actomyosin cross-bridge cycling rates and thereby improved economy of force generation as shown in animal experimental studies [32,33,34,35,36]. Such a shift may also play a role in human myocardium [37,38,39,40] which may also be interpreted to be beneficial because of more economical contraction.

In contrast, a decrease of SERCA-2 on the one hand and an increase in sodium-calcium exchanger on the other may be associated with decreased calcium activity, and thereby impairment of diastolic and systolic function [37,38,39,40]. Therefore, to counteract the latter two alterations may be a therapeutic goal [41,42,43].

## **Experimental animal studies with etomoxir**

Etomoxir has originally been developed for treatment of diabetes mellitus [20]. Etomoxir blocks mitochondrial CPT-1 thereby switching the metabolism from fatty-acid-oxidation to glucose oxidation [20]. This metabolic switch may have some advantage regarding energy expenditure under ischemic conditions [44], but –

probably more importantly - influences gene expression of SERCA-2 and myosin isoenzymes [21,22,23] thereby counteracting the molecular mechanisms taking place in congestive heart failure [24,25]. Therefore, it was an attractive pharmacological approach to test etomoxir in patients suffering from congestive heart failure.

### **Clinical Studies with Etomoxir:**

In a first, non-placebo controlled study in a small number of patients, this pharmacological approach was judged to be positive and safe, when etomoxir was given over a period of three months [26]. In this earlier study, we demonstrated a significant increase in maximum workload, which was associated with an increased ejection fraction and improved hemodynamic parameters. On this basis, a placebo-controlled much larger trial, the ERGO-Study, was planned and conducted with two etomoxir dosages (40 mg and 80 mg ) over a period of six months.

In contrast to our earlier study, the present ERGO-Study did not show significant improvement in exercise time or in echocardiographic parameters. The reason for these discrepancies may be threefold:

- (1) In the earlier study, nine out of ten patients suffered from dilated cardiomyopathy, whereas in the present study 66% of the patients had ischemic heart disease. It may well be that etomoxir is more effective in patients with cardiomyopathy than in those with ischemic heart disease.
- (2) The degree of the disease was more advanced in the earlier study as indicated by a mean ejection fraction of only 21.5%, whereas in the present study mean ejection fraction was 31%. Therefore, the extent of possible improvement may be different between the two studies.
- (3) As shown in Figure 1 and Table 3, there was a tendency for an increase in exercise-time of about 20 seconds in the 80 etomoxir group. With a greater number of patients instead of only fourteen in the pairwise comparison this

beneficial effect might become significant. Unfortunately, due to the hepatotoxic effects of etomoxir, the ERGO-Study had to be stopped prematurely (see below).

- (4) Beside the fact that subjects had a tendency (NS) to exercise more, some issues of the Minnesota questionnaire were significantly different in favour of etomoxir.

#### **Hepatotoxicity of etomoxir and premature end of the study:**

The ERGO-Study was prematurely stopped because in four patients liver enzymes were found to be elevated. In the study protocol, blood tests including liver enzymes were planned at 3, 6, 12, 18 and 24 weeks following randomisation. In former studies, increases in transaminase activity were reported, however these occurred early, were mild (increase by a factor for two), and of transient character [20]. The following arguments were the most important for the responsible committee to stop the continuation of the study:

- (1) There was a clear relationship between increases in ALT and AST and study medication: None of the four patients with increased liver enzymes was in the placebo-group, one was in the 40 mg and three were in the 80 mg etomoxir group. Furthermore, in all patients ALT and AST returned to normal values after cessation of etomoxir.
- (2) A number of four patients with liver problems seems low at the first glance. However at the time the study was stopped, only 15% of the study population had already safely completed the study.
- (3) The increase in ALT and AST occurred relatively late, i.e., at week six after randomisation. Therefore many randomised patients of the study were still at risk.
- (4) The increase of ALT and AST were unexpectedly high and not at all transient. Therefore, these changes did not indicate an adaptation of a liver cell but rather cell toxicity and cell death.
- (5) Under these conditions, etomoxir was judged to be no candidate for further development for treatment of heart failure patients because of too severe adverse events.

(6) All together the risk-to-benefit-ratio did not justify the continuation of the study for the individuals being at risk.

However, despite of premature stop of the study, there was a tendency to increased exercise time, the primary endpoint of the study. Therefore, before rejecting the hypothesis that fatty-acid-oxidation-inhibition might be beneficial in congestive heart failure, similar studies have to be performed using different fatty-acid-oxidation-inhibitors targeting CPT-1 and other enzymes of the metabolic pathway.

Alteration of cardiac energy metabolism, i.e., switch from fatty acids to glucose oxidation, may be achieved by alternative medical approaches:

- (1) Trimetazadine has a similar metabolic effect like etomoxir by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase [46]. Cardioprotective effects of this compound have been described during coronary artery graft surgery [47], but no data are available regarding its effect in heart failure patients.
- (2) Glucagon-like peptide-1 (GLP-1) or a similiarly active substance - exenatide - are known to stimulate insulin release – dependent on actual glucose concentrations. Such a medical intervention may not only act to control serum glucose concentration, but also alter cardiac metabolism favourably.
- (3) So-called insulin-sensitizers like pioglitazone and rosiglitazone are currently used as anti-diabetics. Due to their cellular effects on glucose-availability, a positive effect on cardiac energy metabolism may also be present in heart failure patients, which needs to be studied.

In the light of future alternatives, the strategy to alter cardiac metabolic pathways by compounds other than etomoxir remains still an attractive and challenging pharmacological approach.

## References:

1. Ho, K., Pinsky, J., Kannel, W. et al. (1993) The epidemiology of heart failure: the Framingham study. *J. Am. Coll. Cardiol.* **22** (Suppl A), 6A-13A
2. McMurray, J., Hart, W., Rhodes, G. (1993) An evaluation of the cost of heart failure to the National Health Service in the UK. *Br. J. Med. Econ.* **285**, 99-110
3. Andrews, R., Cowley, AJL. (1995) Clinical and economic factors in the treatment of congestive heart failure. *Pharmacoeconomics* **7**, 119-27
4. Mostered, A., Hoes, AW., de Bruyne, MC. et al. (1999) Prevalence of heart failure and left ventricular dysfunction in the general population; The Rotterdam Study. *Eur. Heart. J.* **20**, 447-55
5. Murray, CJ., Lopez (1997) AD-Global mortality, disability and the contribution of risk factors: global burden of disease study. *Lancet* **349**, 1436-42
6. Cohen-Solal, A., Desnos, M., Delahaye, F. et al. (2000) for the myocardial and heart failure working group of the French Society of Cardiology, the National College of General Hospital Cardiologists and the French Geriatrics Society. A national survey of heart failure in French hospitals. *Eur. Heart. J.* **21**, 763-9
7. Taubert, G., Bergmeier, C., Andersen, H. et al. (2001) Clinical profile and management of heart failure: rural community hospital vs metropolitan heart center. *Eur. J. Heart Failure* **3**, 611-7
8. ACC/AHA Task Force. (1995) Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee on evaluation and management heart failure). *Circulation* **92**, 2764-2784
9. Packer, M., Gheorghade, M., Young, JB. et al. (1993) for the RADIANCE Study. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting (enzyme inhibitors). *N. Engl. J. Med.* **329**, 1-7
10. Pitt, B., Zannad, F., Remme, WJ. et al. (1999) RALES-study. *N. Engl. J. Med* **341**, 709-717
11. Pitt, B., Remme, WJ., Zannad, F. et al. (2003) Eplerenone post-AMI heart failure efficacy and survival study: primary results of the EPHEsus-trial. *N. Engl. J. Med.* **348**, 1309-1321
12. The Digitalis Investigation Group. (1997) The effect of digoxin on mortality and morbidity in patients with heart failure. *N. Engl. J. Med.* **336**, 525-33
13. Cohn, JN., Johnson, G., Ziesche, S. et al. (1991) A comparison of enalapril with hydralazineisosorbide dinitrate in the treatment of chronic congestive heart failure. *N. Engl. J. Med.* **325**, 303-310
14. The SOLVD investigators. (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N. Engl. J. Med.* **325**, 293-302
15. Pfeffer, MA., Braunwald, E., Moye, LA. et al: (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the survival and ventricular enlargement trial-the SAVE investigators. *N. Engl. J. Med.* **327**, 669-677
16. The Acute Infarction Ramipril Efficacy (AIRE) Study investigators. (1993) Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* **342**, 821-828

17. A., Packer, M., Bristow, MR., Cohn, JN. et al. (1996) The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N. Engl. J. Med.* 334, 1349-55
18. B., Packer, M., Coats, ASJ., Fowler, MB. et al. (2001) Effect of Carvedilol on Survival in Severe Chronic Heart Failure. *N. Engl. J. Med.* 344, 1651-1658
19. CIBIS-II Investigators and Committees. (1999) The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomized trial. *Lancet* 353,9-13
20. MERIT-HF Study Group. (1999) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 353, 2001-7
21. Wolf, HPO: (1990) Aryl-substituted 2-oxirane carboxylic acids: a new group of antidiabetic drugs. C.J. Bailey & P.R. Flatt, new antidiabetic drugs, Smith-Gordon 217-229
22. Vetter, R., and Rupp, H. (1994) CPT-1 inhibition by etomoxir has a chamber-related action on cardiac sarcoplasmic reticulum and isomyosins. *Am. J. Physiol.* 267, H2091-H2099
23. Vetter, R., Kott, M., and Rupp, H. (1995) Differential influences of carnitine palmitoyltransferase-1 inhibition and hyperthyroidism on cardiac growth and sarcoplasmic reticulum phosphorylation. *Eur. Heart. J.* 16 (Suppl.C), 15-19
24. Rupp, H., Schulze, W., and Vetter, R. (1995) Dietary medium-chain triglycerides can prevent changes in myosin and SR due to CPT-1 inhibition by etomoxir. *Am. J. Physiol.* 269, R630-R640
25. Rupp, H., Elimban, V., and Dhalla, N.S. (1992) Modification of subcellular organelles in pressure-overloaded heart by etomoxir, a carnitine palmitoyltransferase 1 inhibitor. *FASEB J.* 6, 2349-2353
26. Zarain-Herzberg, A., Rupp, H., Elimban, V., and Dhalla, N.S. (1996) Modification of sarcoplasmic reticulum gene expression in pressure overload cardiac hypertrophy by etomoxir. *FASEB J.* 10, 1303-1309
27. Schmidt-Schweda, S., Holubarsch, C. (2000) First Clinical trial with etomoxir in patients with chronic congestive heart failure. *Clin. Sci. (Lond)* 99 (1), 27-35
28. Takahashi, T., Allen, P.D., and Izumo, S. (1992) Expression of A-, B-, and C-type natriuretic peptide genes in failing and developing human ventricles, Correlation with expression of the Ca<sup>2+</sup>-ATPase gene. *Circ. Res.* 71, 9-17
29. Morita, E., Yasue, H., Yoshimura, M. et al. (1995) Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. *Circulation* 88, 82-91
30. Hama, No., Itoh, H., Shirakama, G. et al. (1995) Rapid ventricular induction of brain natriuretic peptide gene expression in experimental acute myocardial infarction. *Circulation* 92, 1558-1564.
31. Wiese, S., Breyer, T., Dragan, A. et al. (2000) Gene Expression of Brain Natriuretic Peptide in Isolated Atrial and Ventricular Human Myocardium. Influence of Angiotensin II and Fiber Length. *Circulation* 102, 3074-3079.
32. Nakao, K., Saito, Y., Itoh, H. et al. (1996) Roles of natriuretic peptides in heart failure. *J. Cardiac Failure* 2, 129-133
33. Alpert, N.R. and Mulieri, L. A. (1982) Increased myothermal economy of isometric force generation in compensated cardiac hypertrophy induced by pulmonary artery constriction in rabbit. A characterization of heat liberation in normal and hypertrophied right ventricular papillary muscle. *Circ. Res.* 50, 491-500



34. Holubarsch, Ch., Litten, R.Z., Mulieri, L.A., and Alpert, N.R. (1995) Energetic changes of myocardium as an adaptation to chronic hemodynamic overload and thyroid gland activity. *Bas. Res. Cardiol.* 80, 582-593
35. Holubarsch, Ch., Goulette, R. P., Litten, R.Z. et al. (1985) The economy of isometric force development, myosin isoenzyme pattern and myofibrillar ATPase activity in normal and hypothyroid rat myocardium. *Circ. Res.* 56, 78-86
36. Hasenfuß, G., Mulieri, L.A., Blanchard, E.M. et al. (1991) Energetics of isometric force development in control and volume-overload human myocardium. Comparison with animal species. *Circ. Res.* 68, 836-846
37. Berman, M.R., Lord, C.C., and Maughan, D.W. (1988) Force transient course in heart muscle with high and low  $V_1$  to  $V_2$  myosin isoenzyme ratio. *J. Mol. Cell. Cardiol.* 20, 679-687
38. Hasenfuss, G., Reinecke, S., Studer, R. et al. (1994) Relation between myocardial function and expression of sarcoplasmic reticulum  $Ca^{2+}$ -ATPase in failing and nonfailing human myocardium. *Circ. Res.* 75, 434-442
39. Holubarsch, Ch., Schneider, R., Pieske, B. et al. (1995) Positive and negative inotropic effects of DL-Sotalol and D-Sotalol in failing and nonfailing human myocardium under physiological experimental conditions. *Circulation* 92, 2904-2910
40. Pieske, B., Kretschmann, B., Meyer, M. et al. (1995) Alterations in intracellular calcium handling associated with the inverse force-frequency relation in human dilated cardiomyopathy. *Circulation* 92, 1169-1178
41. Feldmann, A.M., Weinberg, E.O., Rax, P. E., and Lorell, B.H. (1993) Selective changes in cardiac gene expression during compensated hypertrophy and the transition to cardiac decompensation in rats with chronic heart aortic banding. *Circ. Res.* 73, 184-192
42. Hajjar, R.J., Kang, J.X., Gwathmey, J.K., and Rosenzweig, A. (1996) Physiological effects of adenoviral gene transfer of sarcoplasmic reticulum calcium ATPase in isolated rat myocytes. *Circulation* 94, (Suppl.1), 89
43. Hajjar, R.J., Kang, J.X., Gwathmey, J.K., and Rosenzweig, A. (1997) Physiological effects of adenoviral gene transfer of sarcoplasmic reticulum calcium ATPase in isolated rat myocytes. *Circulation* 95, 423-429
44. Meyer, M., and Dillmann, W.H. (1998) Sarcoplasmic reticulum  $Ca^{2+}$ -ATPase overexpression by adenovirus mediated gene transfer and in transgenic animals. *Cardiovasc. Res.* 37, 360-366
45. Lopaschuk, G.D., Spaffort, M.A., Davies, N.J., and Wall, S.R. (1990) Glucose and palmitate oxidation in isolated working rat hearts reperfused after a period of transient global ischemia. *Circ. Res.* 66, 546-553
46. Kantor, P.F., Lucien, A., Kozak, R., Lopaschuk, P.D. (2000) The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long chain 3-ketoacyl coenzyme A thiolase. *Circ. Res.* 86, 580-588
47. Tynerir, B., Colak, O., Alatas, O., Besogul, Y., Kural, T., Aslan, R. (1999) Measurement of troponin T to detect cardioprotective effect of trimetazidine during coronary artery bypass-grafting. *Ann. Thorac. Surg.* 68, 2173-2176

**Table1. Patients entry and completion by country**

<b>Country</b>	<b>Placebo</b>		<b>Etomoxir 40mg</b>		<b>Etomoxir 80mg</b>	
	<b>Entered</b>	<b>Completed</b>	<b>Entered</b>	<b>Completed</b>	<b>Entered</b>	<b>Completed</b>
<b>Germany</b>	47	21	41	17	39	14
<b>Italy</b>	8	-	10	-	9	-
<b>Poland</b>	66	-	67	-	60	-
<b>Overall</b>	<b>121</b>	<b>21</b>	<b>118</b>	<b>17</b>	<b>108</b>	<b>14</b>

**Table 2. Patient groups characteristic**

Variable	Treatment group			Overall
	Placebo (n=121)	Etomoxir 40mg (n=117)	Etomoxir 80mg (n=108)	
Age (yr) (mean $\pm$ sd)	60.1 $\pm$ 11.1	60.6 $\pm$ 10.1	61.2 $\pm$ 10.2	60.6 $\pm$ 10.5
Gender (male/female)	101/20	92/26	88/20	281/66
% current smokers	15%	17%	11%	14%
% Caucasian	98%	96%	98%	97%
Systolic bp (mmHg) (mean $\pm$ sd)	124.1 $\pm$ 17.6	127.7 $\pm$ 17.5	126.2 $\pm$ 17.4	126.0 $\pm$ 17.5
Diastolic bp (mmHg) (mean $\pm$ sd)	79.4 $\pm$ 10.5	77.9 $\pm$ 8.7	78.7 $\pm$ 9.3	78.7 $\pm$ 9.6
Heart rate (bpm) (mean $\pm$ sd)	74.3 $\pm$ 13.7	74.0 $\pm$ 12.8	76.1 $\pm$ 15.0	74.8 $\pm$ 13.8
Weight (kg) (mean $\pm$ sd)	80.9 $\pm$ 11.1	79.6 $\pm$ 12.3	82.1 $\pm$ 17.4	80.9 $\pm$ 13.8
Height (cm) (mean $\pm$ sd)	170.9 $\pm$ 7.5	169.9 $\pm$ 7.6	168.6 $\pm$ 14.8	169.8 $\pm$ 10.4
LVEF (%)	30.5 $\pm$ 5.9 (121)	31.0 $\pm$ 6.3 (117)	30.5 $\pm$ 6.3 (107)	30.7 $\pm$ 6.1 (345)
LVEDD (cm)	10.1 $\pm$ 13.9 (121)	9.3 $\pm$ 12.8 (116)	11.0 $\pm$ 16.0 (104)	10.1 $\pm$ 14.2 (341)
Fractional shortening (%)	15.2 $\pm$ 4.4 (61)	16.9 $\pm$ 7.2 (68)	16.4 $\pm$ 5.9 (53)	16.2 $\pm$ 6.0 (182)
Left ventricular wall thickness at the septum (mm)	10.6 $\pm$ 2.3 (112)	11.3 $\pm$ 2.5 (107)	11.5 $\pm$ 2.7 (97)	11.1 $\pm$ 2.5 (316)
Left ventricular wall thickness at the posterior wall (mm)	10.6 $\pm$ 2.1 (111)	10.5 $\pm$ 2.1 (104)	10.9 $\pm$ 1.9 (95)	10.7 $\pm$ 2.1 (310)
NYHA II	70	75	64	209
NYHA III	51	42	44	137

The numbers in parenthesis indicate the numbers of patients from which data were available for analysis.

**Table 3:**

Change from baseline in total exercise test time at week 24 endpoint (sec)

	Placebo (n=83)	Etomoxir 40mg (n=74)	Etomoxir 80mg (n=77)	
Baseline (mean±sd)	388.8±134.2	435.2±134.6	414.0±154.3	
Week 24 endpoint (mean±sd)	392.1±149.3	445.4±150.6	433.3±152.8	
Change from baseline (mean±sd)	3.3±92.2	10.2±73.5	19.4±61.8	
Pairwise comparisons	Mean difference <sup>a</sup>	Se	95% CI	P
Placebo-etomoxir 40mg	-10.9	12.4	-35.3,13.5	0.38 n = 16
Placebo- etomoxir 80mg	-18.6	12.2	-42.5,5.4	0.13 n = 14
Etomoxir 40mg- Etomoxir 80mg	-7.7	12.5	-32.3,17.0	0.54 n = 14

A Estimated from ANCOVA model with factors for treatment and country with baseline value as a covariate. A negative difference indicates the latter treatment is favoured

**Table 4 A:**

**Change from baseline in six minutes walk test (m)**

	Placebo (n = 83)	Etomoxir 40 mg (n = 74)	Etomoxir 80 mg (n = 77)
Baseline	401.2	382.2	392.5
Change from baseline (mean ± sd)	30.4 ± 95.9 (n = 19)	22.7 ± 81.8 (n = 16)	30.6 ± 52.7 (n = 12)
	N.S.	N.S.	N.S.

**Table 4 B:**

**Change from baseline in left ventricular ejection fraction (%)**

	Placebo	Etomoxir 40 mg	Etomoxir 80 mg
Baseline	30.5 ± 5.9 (n = 121)	31.0 ± 6.3 (n = 117)	30.5 ± 6.3 (n = 104)
Change from baseline(mean±sd)	5.8 ± 10.6 (n = 21)	6.3 ± 11.1 (n = 17)	8.2 ± 11.6 (n = 13)
	N.S.	N.S.	N.S.

**Table 5. Serious adverse events leading to withdrawal during the randomised phase (\*according to the judgement of the local investigator)**

<b>Patient number</b>	<b>Adverse event</b>	<b>Severity *</b>	<b>Relationship to study medication</b>
<b><u>Placebo</u></b> 12503	ventricular tachycardia	Moderate	Possible
<b><u>Etomoxir 40mg</u></b> 12505	cardiac decompensation	Severe	Possible
13003	highly elevated liver enzymes	Moderate	Probable
13103	ventricular tachycardia	Severe	Unlikely
14107	neoplasma of testes	Severe	Not related
<b><u>Etomoxir 80mg</u></b> 10007	increase of transaminases, elevated liver enzymes	Moderate	Possible
11105	elevation of liver enzymes	Unknown	Possible
12504	arrhythmia	Moderate	Probable
14105	elevation of liver enzymes	Moderate	Probable
14106	angina pectoris	Moderate	Unlikely

**Table 6: Four patients with elevated liver enzymes:**

		Patient 1	Patient 1	Patient 3	Patient 4
t <sub>0</sub>	ALT [U/l]	N	N	N	N
	AST [U/l]	N	N	N	N
t <sub>1</sub>	ALT [U/l]	N	N	N	N
	AST [U/l]	N	N	N	N
t <sub>2</sub>	ALT [U/l]	519	456	261	227
	AST [U/l]	1189	1300	493	584

t<sub>0</sub> is the control value before randomisation,

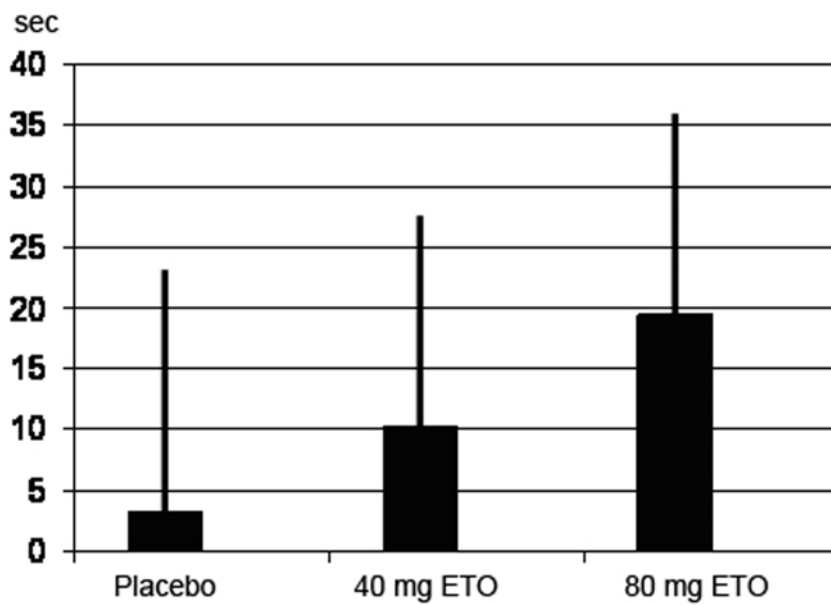
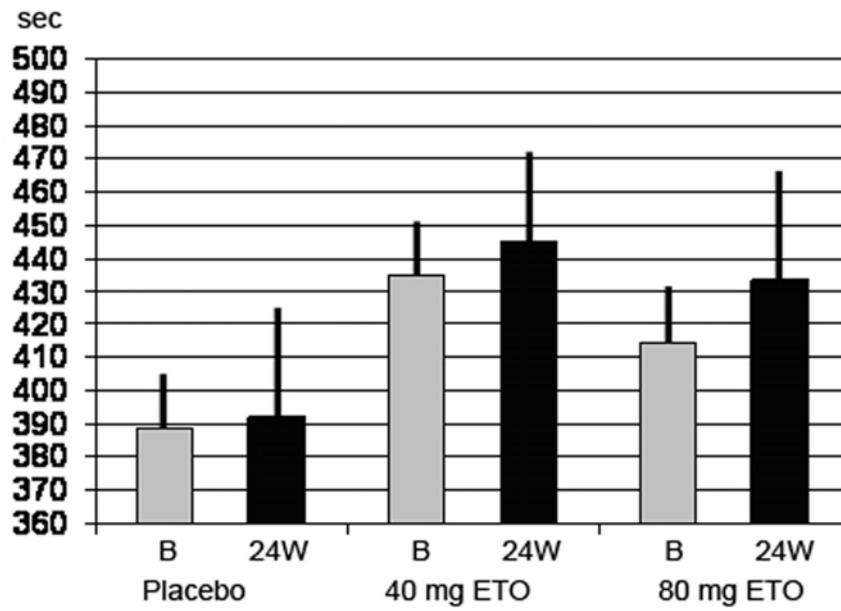
t<sub>1</sub> is the blood control after 3 weeks and

t<sub>2</sub> after 6 weeks of treatment

N means within the normal range.

Normal range for ATL is up to 35 U/l and for AST is up to 45 U/l.

Values for gamma-GT, Bilirubin, and Alcaline phosphatase remained in the normal range. After withdrawal of etomoxir, ALT and AST normalized gradually.





**Legends of Figure 1:**

Upper diagramm:

Mean times  $\pm$  SE in bicycle exercise testing at baseline (B) and at week 24 (24 w) for the placebo, 40 g etomoxir and 80 g etomoxir group, respectively.

The increases in bicycle exercise times were not statistically significant (see Table 3).

Lower diagram: Average increases in bicycle exercise times in the placebo, 40 mg etomoxir and 80 mg etomoxir groups.