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A double-blind randomized 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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ABSTRACT

Etomoxir is an inhibitor of mitochondrial CPT1 (carnitine palmitoyltransferase 1) and thereby switches energy metabolism from fatty acids to glucose oxidation. Such a metabolic change may be beneficial in CHF (congestive heart failure). The ERGO (etomoxir for the recovery of glucose oxidation) study was designed in which etomoxir was tested at a dose of 80 and 40 mg compared with placebo for a period of 6 months in patients with CHF. As the principle measure of efficacy, a maximal exercise tolerance test and a submaximal 6-min corridor walk test were used. Secondary end points were echocardiographical dimensions and quality-of-life assessment scores. A total of 350 patients were planned to be screened, with the expectation that end point data would be available from approx. 260 patients. However, the study had to be stopped prematurely, because unacceptably high liver transaminase levels were detected in four patients taking etomoxir. At the termination of the study, 121 patients were randomized to placebo, 118 to 40 mg of etomoxir and 108 to 80 mg of etomoxir. At that time, 21 patients in the placebo group, 16 in the 40 mg of etomoxir group and 14 patients in the 80 mg of etomoxir group had completed the study. The mean increases in exercise time were 3.3, 10.2 and 19.4 s for the placebo, 40 mg of etomoxir and 80 mg of etomoxir groups respectively (*P* value was not significant). No changes were obvious in the 6-min corridor walk test or in echocardiographical parameters from baseline. The number of patients that completed the study was too small to demonstrate significant effects on exercise time, although there was a tendency towards an increase in exercise time. Therefore, before rejecting the hypothesis that inhibition of fatty acid oxidation might be beneficial in CHF, similar studies have to be performed using different inhibitors of fatty acid oxidation targeting CPT1 and other enzymes in this metabolic pathway.

Key words: carnitine palmitoyltransferase 1 (CPT1), congestive heart failure, energy metabolism, etomoxir, fatty acid, glucose.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; ANP, A-type natriuretic peptide; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; CHF, congestive heart failure; CPT1, carnitine palmitoyltransferase 1; EF, ejection fraction; ERGO, etomoxir for the recovery of glucose oxidation; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVWT, LV wall thickness; NYHA, New York Heart Association; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase.

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INTRODUCTION

CHF (congestive heart failure) 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 [1–3]. CHF can be viewed as the end stage of various forms of heart failure [4]. The prognosis for patients with CHF is poor and is, in fact, even worse than the survival chances in patients with various malignancies [5]. Various surveys have shown that medical management of CHF is characterized by polypharmacy and by the underuse of recommended medication [6,7].

Conventional medical therapy for CHF has been outlined extensively [8], and the following classes of agents are used. Diuretics are used to control the symptoms of volume overload. When these symptoms are absent, diuretics, in the form of loop diuretics, have no proven benefit [9]; however, spironolactone [10] and eplerenone [11] have been shown to have a clear benefit for patients with CHF with regards to 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. ACE (angiotensin-converting enzyme) inhibitors have the most beneficial effect on mortality and are the most commonly used [13–16]. The most recent class to be recommended for patients with CHF is β-blockers, which provide a number of beneficial effects, including decreasing heart rate, decreasing overall work load, reducing oxygen consumption, prolonging diastolic myocardial perfusion and protecting against toxic effects of catecholamines. These effects may work via a common mechanism and thereby increase survival [17–20].

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 CHF which prolong survival, reduce symptoms and provide patients with an improved capacity to conduct daily activities.

Etomoxir is an inhibitor of mitochondrial CPT1 (carnitine palmitoyltransferase 1), which was developed originally for the treatment of diabetes mellitus [21]. 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 metabolism to glucose oxidation. Such a switch has been shown to induce the expression of SERCA (sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase) and redistribution of myosin isoenzymes in experimental animal studies, alterations which may be beneficial in CHF [22–26].

In a first clinical trial with etomoxir in patients with chronic CHF, clinical improvement was reported with 80 mg of etomoxir/day [27]. The aim of the present study was to reconfirm the efficacy of 80 mg of etomoxir/day in a double-blind setting and to study the risk/benefit ratio of 40 and 80 mg of etomoxir in comparison with placebo based on clinical findings, exercise testing, echocardiography and Holter monitoring in patients with moderate CHF [NYHA (New York Heart Association) classes II and III].

MATERIALS AND METHODS

Rationale

The hypothesis to be tested in the ERGO (etomoxir for the recovery of glucose oxidation) study was an increase in cardiopulmonary capacity by 10 % as induced by etomoxir at a dosage of 40 or 80 mg compared with placebo during a period of 3 or 6 months.

Sample size calculation

The proposed recruitment of 120 patients per treatment group (i.e. a total of 360 patients who successfully complete the screening period and are eligible for randomization) was prompted by the following considerations: (i) an average baseline total exercise time for the bicycle protocol of 420 s (7 min); (ii) an anticipated increase over baseline by week 24 of 45 s for placebo, 67.5 s for 40 mg of etomoxir and 90 s for 80 mg of etomoxir (some placebo effect was anticipated as the baseline value would be obtained prior to the commencement of study medication); (iii) a within-patient S.D. for change from baseline with respect to the primary end point of 90 s (this figure was consistent with the requirement that, prior to randomization, each patient must achieve two exercise times within $\pm$20 %); and (iv) the direct comparison of 80 mg of etomoxir with placebo, to be investigated using a two-sided parametric test at the experiment-wise 5 % significance level, should have at least 90 % power.

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

Patients

Investigations were performed in Poland, Germany and Italy. A total of 347 patients were randomized: 193 patients in Poland, 127 patients in Germany and 27 patients in Italy. The age of patients was between 21 and 84 years (mean, 66.6 years). Patients were suffering from moderate CHF (NYHA classes II and III).

A total of 230 (66 %) patients had ischaemic heart disease of which 80 (35 %) had current angina and 182 (79 %)

reported at least one previous myocardial infarction. A total of 189 (57 %) patients had hypertension, 84 (24 %) had dilated cardiomyopathy, 21 (6 %) had valvular heart disease and 14 (4 %) had other aetiologies. Of the patients recruited, 59 (17 %) had Type 2 diabetes mellitus.

All patients gave written consent, and 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 40 mg of compound dissolved in a mixture of medium-chain triacylglycerols (triglycerides) derived from coconut and palm oil. The daily dose for one patient was packed into blister strips, with each strip containing two capsules for each 7 days, in one of the following three forms: 80 mg of etomoxir (two 40 mg capsules), 40 mg 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 6-min corridor walk test, two quality-of-life questionnaires (Minnesota Living with heart failure and EuroQol EQ-5D questionnaires) and a 24 h Holter ECG. The treatment phase was proposed to have visits at 3, 6, 12, 18 and 24 weeks following randomization. Visits consisted of physical examination, 12-lead ECG, urine analysis, a bicycle protocol and a 6-min corridor walk test. Patients underwent laboratory examinations, including electrolytes, liver and renal function and haematology profile with platelet count at 3, 6, 18 and 28 weeks, and biochemistry and haematology at 12 and 24 weeks. At 3 and 24 weeks, 24 h Holter monitoring was performed.

Exercise testing

The bicycle protocol and 6-min corridor walk test were performed at baseline, and at 12 and 24 weeks (bicycle protocol was optional at 3, 6 and 18 weeks). At baseline, at least two exercise tests were performed with exercise times within ± 20 %. The bicycle protocol consisted of 2-min stages with an initial work load of 25 W, increasing by 25 W at 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 min post-exercise; systolic and diastolic blood pressure; heart rate at the end of each 2-min stage, at the end of exercise and at 1, 3 and 5 min post-exercise; Borg score (at the end of each stage and at the end of exercise); and reason for stopping if needed.

The 6-min corridor walk test was considered 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 had been performed previously.

Echocardiography

Echocardiographical measurements were made as follows: LVEF [LV (left ventricular) EF (ejection fraction)], LVEDD (LV end-diastolic diameter), fractional shortening and LVWT (LV wall thickness) at the septum and the posterior wall. ECGs were performed at baseline and at 24 weeks.

Holter monitoring

Holter monitoring for 24 h was performed at 3, 12 and 24 weeks. All evidence of torsade de pointes and ventricular fibrillations, asystoles, runs of ventricular tachycardia, atrial fibrilation, flutter or supraventricular tachycardia, number of ectopic beats, number of ectopic couplets and mean heart rate were printed out and validated by a cardiologist.

Statistical analysis

Comparability of treatment groups at baseline was assessed and summarized using descriptive statistics. Hypothesis testing to determine differences between treatments were two-sided, with differences being statistically significant if the observed significance level was < 0.05. The two pairwise comparisons of 80 mg of etomoxir with placebo and 40 mg of etomoxir with placebo with respect to the primary end point 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 database, with 347 patients randomized prior to the premature termination of the study, as shown in Table 1. Table 1 also gives details on entry and completion for patients randomized from each country. Therefore, when the study was prematurely stopped, 52 patients had completed the study, with 21 in the placebo group, 16 in the 40 mg of etomoxir group and 14 in the 80 mg of etomoxir group.

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

Table 1 Patients entry and completion by country

	Number of patients					
			Etomoxir			
	Placebo		40 mg		80 mg	
Country	Entered	Completed	Entered	Completed	Entered	Completed
Germany	47	21	41	17	39	14
Italy	8	—	10	—	9	—
Poland	66	—	67	—	60	—
Overall	121	21	118	17	108	14

A total of 209 out of 347 patients (60 %) were graded in NYHA class II at screening. The corresponding number of patients graded in NYHA class III was 137 (40 %; Table 2).

With regard to medication, 81 % of the patients were on ACE inhibitors or ARBs (angiotensin receptor blockers), 52 % on β-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 randomized set for the principal measure of efficacy of the change from baseline in total exercise time (in seconds) at the week 24 end point. There was a clear tendency towards an increase in bicycle exercise testing (Table 3A), with the mean increases in exercise times being 3.3, 10.2 and 19.4 s for the placebo, 40 mg of etomoxir and 80 mg of etomoxir groups respectively (Table 3); however, none of these were statistically significant. A total of 21 patients in the placebo group, 16 in the 40 mg of etomoxir group and 14 in the 80 mg of etomoxir group reached the 24 week end point and were thus included in the pairwise comparisons (Table 3B). Again, no statistically significant differences were observed, which may be due to the premature termination of the study resulting in too few patients having completed 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 6-min corridor walk test at weeks 12 and 24 (Table 4). In addition, no statistically significant differences were found for LVEF (Table 4), LVEDD, fractional shorting and LVWT at weeks 12 and 24. Unfortunately, no data were available from the 24-h Holter monitoring.

Cardiac deaths and serious adverse events

During the study, six patients died. One patient died during the run-in phase and five patients died during the randomization phase (three patients in the placebo group, all of whom had sudden cardiac death, one in the

Table 2 Characteristics of the patient groups

Values are means ± S.D. The numbers in parentheses indicate the numbers of patients from which data were available for analysis.

	Treatment group			
		Etomoxir		
Variable	Placebo	40 mg	80 mg	Overall
n	121	118	108	347
Age (years)	60.1 ± 11.1	60.6 ± 10.1	61.2 ± 10.2	60.6 ± 10.5
Gender (*n*) (male/female)	101/20	92/26	88/20	281/66
Current smokers (%)	15	17	11	14
Caucasians (%)	98	96	98	97
Systolic BP (mmHg)	124.1 ± 17.6	127.7 ± 17.5	126.2 ± 17.4	126.0 ± 17.5
Diastolic BP (mmHg)	79.4 ± 10.5	77.9 ± 8.7	78.7 ± 9.3	78.7 ± 9.6
Heart rate (beats/min)	74.3 ± 13.7	74.0 ± 12.8	76.1 ± 15.0	74.8 ± 13.8
Weight (kg)	80.9 ± 11.1	79.6 ± 12.3	82.1 ± 17.4	80.9 ± 13.8
Height (cm)	170.9 ± 7.5	169.9 ± 7.6	168.6 ± 14.8	169.8 ± 10.4
LVEF (%)	30.5 ± 5.9 (121)	31.0 ± 6.3 (117)	30.5 ± 6.3 (107)	30.7 ± 6.1 (345)
LVEDD (cm)	10.1 ± 13.9 (121)	9.3 ± 12.8 (116)	11.0 ± 16.0 (104)	10.1 ± 14.2 (341)
Fractional shortening (%)	15.2 ± 4.4 (61)	16.9 ± 7.2 (68)	16.4 ± 5.9 (53)	16.2 ± 6.0 (182)
LVWT (mm)				
At the septum	10.6 ± 2.3 (112)	11.3 ± 2.5 (107)	11.5 ± 2.7 (97)	11.1 ± 2.5 (316)
At the posterior wall	10.6 ± 2.1 (111)	10.5 ± 2.1 (104)	10.9 ± 1.9 (95)	10.7 ± 2.1 (310)
NYHA class II (*n*)	70	75	64	209
NYHA class III (*n*)	51	42	44	137

Table 3 Total exercise test time at baseline and at the week 24 end point (A), and comparisons between the groups (B)

Values are means ± S.D. *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. CI, confidence interval.

(A) Exercise test

	Total exercise test time (s)		
		Etomoxir	
	Placebo	40 mg	80 mg
Baseline	388.8 ± 134.2 ($n = 83$)	435.2 ± 134.6 ($n = 74$)	414.0 ± 154.3 ($n = 77$)
Week 24 end point	392.1 ± 149.3 ($n = 21$)	445.4 ± 150.6 ($n = 16$)	433.3 ± 152.8 ($n = 14$)
Change from baseline	3.3 ± 92.2	10.2 ± 73.5	19.4 ± 61.8

(B) Pairwise comparisons

Group comparison	Mean difference*	S.E.M.	95% CI	*P* value
Placebo compared with etomoxir (40 mg)	− 10.9	12.4	− 35.3,13.5	0.38 ($n = 16$)
Placebo compared with etomoxir (80 mg)	− 18.6	12.2	− 42.5,5.4	0.13 ($n = 14$)
Etomoxir (40 mg) compared with etomoxir (80 mg)	− 7.7	12.5	− 32.3,17.0	0.54 ($n = 14$)

Table 4 Change from baseline in 6-min corridor walk test and LVEF

Values are means ± S.D. There were no statistically significant differences between any of the three pairwise comparisons for the change from baseline for either the 6-min corridor walk test or LVEF.

		Etomoxir	
	Placebo	40 mg	80 mg
6-min corridor walk test (m)			
Baseline	401.2 ($n = 83$)	382.2 ($n = 74$)	392.5 ($n = 77$)
Change from baseline	30.4 ± 95.9 ($n = 19$)	22.7 ± 81.8 ($n = 16$)	30.6 ± 52.7 ($n = 12$)
LVEF (%)			
Baseline	30.5 ± 5.9 ($n = 121$)	31.0 ± 6.3 (n = 117)	30.5 ± 6.3 ($n = 104$)
Change from baseline	5.8 ± 10.6 ($n = 21$)	6.3 ± 11.1 ($n = 17$)	8.2 ± 11.6 ($n = 13$)

40 mg of etomoxir group, who died due to cardiogenic shock, and one patient in the 80 mg of etomoxir group, who died from myocardial infarction).

A list of the serious adverse events are shown in Table 5. Four patients had elevated levels of liver enzymes, and all of them were either in the 40 mg or 80 mg of etomoxir groups (Table 6).

Minnesota questionnaire

The pairwise comparison between the 40 mg of etomoxir and placebo groups was statistically significant ($P < 0.05$) in favour of 40 mg of etomoxir for the following questions and time points: (i) making him/her sit or lie down to rest during the day at the week 24 end point, (ii) making going places away from home difficult at the week 12 end point, and (iii) making him/her stay in a hospital at the week 24 end point. The pairwise comparison between 80 mg of etomoxir and placebo was statistically significant ($P < 0.05$) in favour of 80 mg of etomoxir for the following question and time point: making them stay in a hospital at the week 24 end point.

DISCUSSION

Molecular changes of the myocardium in CHF

LV systolic dysfunction and chronic CHF 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 distinct functional consequences of the myocardium. At least four major phenotypic changes have been reported: (i) increased production and release of ANP and BNP (A-type and B-type natriuretic peptides respectively), (ii) a shift in the myosin heavy chains from $\alpha\alpha$- to $\beta\beta$-dimers, (iii) up-regulation of the gene encoding the sodium/calcium exchanger, and (iv) down-regulation of SERCA2. 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 ACE-blocking properties of ANP and BNP, these peptides ameloriate increased workload, and salt and water retention [28–32]. The shift

Table 5 Serious adverse events leading to withdrawal during the randomized phase

*As judged by the local investigator.

Group	Adverse event	Severity*	Relationship to study medication
Placebo			
Patient no. 12503	Ventricular tachycardia	Moderate	Possible
Etomoxir (40 mg)			
Patient no. 12505	Cardiac decompensation	Severe	Possible
Patient no. 13003	Highly elevated liver enzymes	Moderate	Probable
Patient no. 13103	Ventricular tachycardia	Severe	Unlikely
Patient no. 14107	Neoplasma of testes	Severe	Not related
Etomoxir (80 mg)			
Patient no. 10007	Increase in transaminases and elevated liver enzymes	Moderate	Possible
Patient no. 11105	Elevation of liver enzymes	Unknown	Possible
Patient no. 12504	Arrhythmia	Moderate	Probable
Patient no. 14105	Elevation of liver enzymes	Moderate	Probable
Patient no. 14106	Angina pectoris	Moderate	Unlikely

Table 6 Levels of elevated liver enzymes in four of the patients

Values for ALT and AST before randomization and after 3 weeks were within the normal range (up to 35 units/l for ATL, and up to 45 units/l for AST). Values for γ-glutamyltranspeptidase, bilirubin and alkaline phosphatase remained within the normal range throughout. After withdrawal of etomoxir, ALT and AST normalized gradually.

Liver enzyme	Patient 1	Patient 2	Patient 3	Patient 4
After 6 weeks of treatment				
ALT (units/l)	519	456	261	227
AST (units/l)	1189	1300	493	584

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 [33–37]. Such a shift may also play a role in human myocardium [38–41], which may also be interpreted to be beneficial because of more economical contraction.

In contrast, a decrease in SERCA2 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 [38–41]. Therefore counteracting the latter two alterations may be a therapeutic goal [42–44].

Experimental animal studies with etomoxir

Etomoxir was originally developed for treatment of diabetes mellitus [21]. Etomoxir blocks mitochondrial CPT1, thereby switching metabolism from fatty acid oxidation to glucose oxidation [21]. This metabolic switch may have some advantage in energy expenditure under ischaemic conditions [45], but, probably more importantly, influences gene expression of SERCA2 and myosin isoenzymes [22–24], thereby counteracting the molecular mechanisms taking place in CHF [25,26]. Therefore it was an attractive pharmacological approach to test etomoxir in patients suffering from CHF.

Clinical studies with etomoxir

In the 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 3 months [27]. In this earlier study, we demonstrated a significant increase in maximum workload, which was associated with an increased EF and improved haemodynamic parameters. On this basis, a much larger placebo-controlled trial, the ERGO study, was planned and conducted with two etomoxir dosages (40 mg and 80 mg) over a period of 6 months.

In contrast with our earlier study [27], the ERGO study did not have any significant improvement in exercise time or in echocardiographic parameters. The reason for these discrepancies may be 3-fold. (i) In the earlier study [27], nine out of ten patients suffered from dilated cardiomyopathy, whereas, in the present study, 66 % of the patients had ischaemic heart disease. It may well be that etomoxir is more effective in patients with cardiomyopathy than in those with ischaemic heart disease. (ii) The degree of the disease was more advanced in the earlier study, as indicated by a mean EF of only 21.5 %, whereas, in the present study, mean EF was 31 %. Therefore the extent of possible improvement may be different between the two studies. (iii) As shown in Table 3, there was a tendency for an increase in exercise time of approx. 20 s in the 80 mg of etomoxir group. With a greater number of patients, instead of only 14

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). (iv) Beside the fact that subjects had a tendency (although not significant) to exercise more, some issues of the Minnesota questionnaire were significantly different in favour of etomoxir.

Hepatotoxicity of etomoxir and the premature end of the study

The ERGO study was prematurely stopped because, in four patients, liver enzymes were found to be elevated (Table 6). In the study protocol, blood tests, including liver enzymes, were planned at 3, 6, 12, 18 and 24 weeks following randomization. In previous studies, increases in transaminase activity were reported; however, these occurred early, were mild (increased by a factor of two) and were transient in nature [21]. The following arguments were the most important for the committee responsible in stopping the continuation of the study. (i) There was a clear relationship between increases in ALT (alanine aminotransferase) and AST (aspartate aminotransferase) and study medication: none of the four patients with increased liver enzymes was in the placebo group, one was in the 40 mg of etomoxir group and three were in the 80 mg of etomoxir group. Furthermore, in all patients, ALT and AST returned to normal values after cessation of etomoxir. (ii) A total of four patients with liver problems may appear low at the first glance, but, at the time the study was stopped, only 15 % of the study population had already safely completed the study. (iii) The increase in ALT and AST occurred relatively late, i.e. at week 6 after randomization. Therefore many of the randomized patients in the study were still at risk. (iv) The increases in 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. (v) Under these conditions, etomoxir was judged not to be a candidate for further development of treatment of patients with CHF because of the too severe adverse events. (vi) Taken together, the risk-to-benefit ratio did not justify the continuation of the study for the individuals being at risk. However, despite the premature termination of the study, there was a tendency towards increased exercise time, the primary end point of the study. Therefore, before rejecting the hypothesis that inhibition fatty acid oxidation might be beneficial in CHF, similar studies have to be performed using different inhibitors of fatty acid oxidation targeting CPT1 and other enzymes in the metabolic pathway.

Alteration of cardiac energy metabolism, i.e. a switch from fatty acids to glucose oxidation, may be achieved by alternative medical approaches. Trimetazadine has a similar metabolic effect like that of etomoxir by inhibiting mitochondrial long-chain 3-ketoacyl CoA 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 patients with CHF. GLP1 (glucagon-like peptide 1) or a similarly 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. So-called insulin-sensitizers, such as pioglitazone and rosiglitazone, are currently used as antidiabetics. Due to their cellular effects on glucose availability, a positive effect on cardiac energy metabolism may also be present in patients with CHF, which needs to be studied. In the light of future alternatives, a strategy of altering cardiac metabolic pathways by compounds other than etomoxir still remains an attractive and challenging pharmacological approach.

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