ORIGINAL ARTICLE

FOSIDIAL: a randomised placebo controlled trial of the effects of fosinopril on cardiovascular morbidity and mortality in haemodialysis patients. Study design and patients' baseline characteristics

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ABSTRACT

The prevalence of end stage renal disease (ESRD) is growing in western countries. Patients with ESRD are more frequently elderly and diabetic and are exposed to very high cardiovascular morbidity and mortality. The main aim of the FOSIDIAL study is to assess the efficacy and safety of fosinopril, an angiotensin converting enzyme (ACE) inhibitor, in reducing the mortality and cardiovascular events in haemodialysis patients presenting with left ventricular hypertrophy. A total number of 397 patients are included in the study. They are aged 50–80 years (average 66.7 years) and have been undergoing haemodialysis for 4.8 years. All have left ventricular hypertrophy with cardiac mass index > 100 g / m^2 in women and > 130 g / m^2 in men, measured within 3 months prior to inclusion. Baseline cardiac mass index is 174 g / m^2. After a 2 week placebo period, the patients are randomised into two groups receiving either fosinopril 5–20 mg / day, or a placebo for a duration of 24 months. The target dose is reached at the sixth, seventh or eighth week of treatment. Depending on tolerance, 300 patients reached the maximum recommended dose. Patients are subsequently assessed clinically every 3 months until the end of the study. The primary outcome is a composite endpoint of fatal and nonfatal major cardiovascular events. Secondary endpoints are individual cardiovascular events, event-free survival, overall mortality and all-cause hospitalisations. The trial began in October 1998. All patients were included by December 2000 and follow-up is ongoing. The last visit for the last patient is scheduled for 30 December 2002. We report here on the study design and the baseline characteristics of the study population.

INTRODUCTION

Although cardiovascular mortality has to a great extent decreased in western countries during the last decades, this does not apply to the population of end stage renal disease (ESRD) patients. Mortality is 20–40 times greater in the latter and 72% of ESRD patients experiencing acute myocardial infarction die within 2 years [1].

Cardiac events are the primary cause of death in haemodialysis (HD) patients, as indicated by registeries

and the few available cohort studies. They represented 38% of mortality occurring among this population in Canada in 1990 [2] and 42% in Europe in 1991 [3]. In the 2001 annual report of the USRDS [4], cardiovascular events represented almost 50% of the causes of death in HD patients and were mainly due to cardiac arrest (18.2% of total mortality), myocardial infarction (9.4%), arrhythmia (5.8%), cardiomyopathy (4.3%), coronary disease (4.1%) and stroke (6.1%).

Compared to the general population, ESRD patients have an increased rate of coronary deaths [5–8]. Age, blood pressure (BP), anaemia and hyperparathyroidism contribute to the development of left ventricular hypertrophy (LVH) in HD patients [9–14]. Alongside the direct role of hypertension, it is established that angiotensin II, parathormone, aldosterone, cathecholamines and endothelin influence the structural changes in the heart including myocardial fibrosis [15,16]. Coronary death rate is 2–3 times greater in diabetic as compared to nondiabetic ESRD patients [3,17]. Furthermore, 30% of the patients presenting with angina may have no angiographically-detectable coronary stenosis [18]. Microcirculatory factors and endothelial dysfunction, in addition to cardiac hypertrophy, may also contribute to left ventricular dysfunction and ischaemia [15].

Left ventricular hypertrophy is a major independent mortality factor in HD patients [19–22]. Concentric LVH, left ventricular dilation and systolic dysfunction are independent risk factors for the subsequent occurrence of myocardial ischaemia [23]. The frequency of LVH has decreased over the last few years as a result of correction of anaemia by erythropoietin, but remains high and varies between 35 and 78% according to the type of study [21,24,25]. In the presence of LVH, the relative risk of death, adjusted for age, diabetes and BP level was shown to be 2.9 for overall mortality and 2.7 for cardiovascular mortality [26]. In a cohort study, the 2 year survival was 67% in the presence of LVH, whereas it was 90% in the absence of any abnormality [27]. It was as low as 40% in the most severely-affected group of patients. Consequences of LVH such as reduction in coronary reserve [18], systolic and/or diastolic cardiac dysfunction [28], sudden death and arrhythmia [25], mainly explain the observed increase in mortality [29]. London et al. recently showed in a cohort of 153 HD patients with a mean follow-up period of 54 months that partial but significant regression of LVH had a favourable effect on cardiovascular mortality [30]. Several studies of regression of LVH with angiotensin converting enzyme (ACE) inhibitors yielded contradictory results. In uraemic rats, Rambausek et al. [31] showed that LVH developed and progressed in spite of BP control with ACE inhibitors. Lisinopril, administered to hypertensive patients at a dose that did not modify BP, had no influence on left ventricular mass [32]. Conversely, in a study by Dyadyk et al. [33], a significant reduction in left ventricular mass was obtained after 6 months and 12 months of treatment with captopril or enalapril. The same observation was also made by Cannella et al. [34] after 12 and 24 months of treatment with lisinopril. LVH regression may be partially but not totally explained by the antihypertensive action of ACE inhibitors.

The efficacy of ACE inhibitors is now well established in a variety of cardiovascular disease and/or risk situations. However, in all available outcome trials, patients with ESRD are usually excluded [35,36]. Therefore, it remains unknown whether patients with ESRD may benefit equally. Conversely, the safety of long-term use of ACE inhibitors and the appropriate dosage have not been properly investigated in specifically designed clinical trials in HD. Therefore, the risk/benefit ratio of ACE inhibitors is still to be established in HD patients.

Fosinopril is a phosphonyl group ACE inhibitor, with specific pharmacokinetic advantages related to its elimination in equal proportions via the hepatic and renal routes when these functions are normal. Hepatic clearance increases as renal function is impaired. In patients with various degrees of renal dysfunction (including when creatinine clearance is below 10 mL/min), its total clearance is reduced by approximately 50%, but is not correlated to the degree of renal insufficiency [37]. Fosinopril accumulates less than enalapril or lisinopril in case of repeated administration in patients with renal failure [38] with or without heart failure [39]. In ESRD patients undergoing dialysis, the pharmacokinetic parameters of fosinopril remain similar to those observed in patients withslight, moderate or severe renal insufficiency [40,41].

Although a dose of 5 mg of fosinopril has little or no haemodynamic effect in congestive heart failure, there is a progressive reduction in preload and afterload at doses of 20 mg and 40 mg [42]. In CHF and myocardial infarction, fosinopril was well tolerated [43] and resulted in significantly less symptomatic orthostatic hypotension than enalapril. Therefore safety of fosinopril appears to be good, even in haemodynamically-unstable patients when BP is monitored after a test dose of 5 mg and at each titration and when dosage is gradually increased up to a maximum of 20 mg/day.

Given this body of data and in so far as no treatment has proved its efficacy to date in cardiovascular event reduction in ESRD haemodialysis patients, we decided to initiate the FOSIDIAL (FOSInopril in DIALysis) study. FOSIDIAL is a double-blind controlled randomised trial investigating the effects of fosinopril vs. placebo in HD patients with LVH on cardiovascular fatal and nonfatal events.

METHODS

Objectives and outcomes

FOSIDIAL is a phase III controlled, randomised, double-blind study, with two parallel groups of patients, one receiving fosinopril at a daily dose of 5–20 mg / day and the other receiving a placebo, for 24 months.

The objective of the trial is to evaluate the efficacy and safety of fosinopril in reducing the incidence of fatal and nonfatal major cardiovascular events in HD patients with LVH.

The primary outcome is a composite of the following events: cardiovascular death, nonfatal myocardial infarction, unstable angina or stroke, revascularisation, hospitalisation for heart failure and resuscitated cardiac arrest. Secondary endpoints are: rates of each of the individual events comprised in the primary endpoint, event-free survival and time-to-onset of the first event, total mortality and all-cause hospitalisations.

Study population

Men and postmenopausal women aged 50–80 and undergoing HD in France for at least 6 months for ESRD (regardless of origin and including diabetes), with at least three dialysis sessions per week and having given their written consent are eligible if they have LVH defined by a cardiac mass index exceeding 131 g/m^2 for men and 100 g/m^2 for women, measured during the 3 months prior to inclusion. Left ventricular mass is measured immediately before a dialysis session and cardiac mass index is calculated according to the recommendations of the Penn convention and the American Society of Echocardiography guidelines.

Exclusion criteria are: mandatory use of ACE inhibitors, interdialytic symptomatic hypotension, hypersensitivity to ACE inhibitors, latest kaliaemia ≥ 6 mmol / L, use of a high-permeability dialysis membrane (polyacrylonitrile), acute phase of a systemic disease, pheochromocytoma, uncompensated hypo or hyperthyroidism, comorbidity jeopardising the 2 year vital prognosis, heart transplant, severe uncontrolled arrhythmia, stroke or acute coronary syndrome in the 3 months before inclusion, coronary revascularisation and cardiovascular surgery, with the exception of vascular accesses for HD, either recent (3 months) or planned, poor compliance or legal incapacity.

Also excluded are patients with SBP > 200 mmHg and or DBP > 110 mmHg or with a clinically-significant biological abnormality not directly related to terminal renal failure.

The study protocol is approved by the Comité de Protection des Personnes se Prêtant à la Recherche Biomédicale (CCPPRB), the ethics review board of Lorraine, France.

Randomisation, treatment protocol and study schedule

The study schedule is presented in *Table I*.

After a 2 week run in single-blind placebo period, patients meeting all inclusion criteria are randomised to receive, double-blind, a test dose of 5 mg of fosinopril or placebo. Allocation of the treatment is centralised and

Table I Baseline characteristics of the patients.

Characteristic	
Age (years)	66.7 ± 8.04
Females (*n* / %)	190 (47.9)
Systolic BP (mmHg)	147.9 ± 21
Diastolic BP (mmHg)	77.4 ± 11.8
Heart Rate (beats / min)	75.2 ± 12.2
Left Ventricular Mass Index (g/m^2)	174.1 ± 53.5
History of stroke (*n* / %)	27 (6.8)
History of coronary artery disease (*n* / %)	52 (13.1)
History of peripheral vascular disease (*n* / %)	62 (15.6)
Current cigarette smoking (*n* / %)	46 (11.6)
Diabetes (*n* / %)	124 (31.2)
Dyslipidaemia (*n* / %)	156 (39.3)
History of renal transplant (*n* / %)	29 (7.3)
Waiting list for renal transplant (*n* / %)	26 (6.6)
Medications (*n* / %)	
Erythropoietin	313 (78.8)
Antidiabetic agents	15 (3.8)
Insulin	81 (20.4)
Lipid-lowering agents	100 (25.2)
Anti-hypertensive agents	210 (52.9)
Height (cm)	163 ± 9
KT / V	1.36 ± 0.39
Residual diuresis mL / day	270 ± 375
Predialysis weight (kg)	71.4 ± 15.6
Interdialytic weight gain (kg)	2.53 ± 1.56

performed by telephone, immediately before administration of the test dose. Following the test dose, BP is measured every 30 min throughout the duration of the dialysis session and for at least 4–6 h after administration of the study medication. Patients experiencing symptomatic hypotension or whose SBP falls below 95 mmHg have to discontinue study medication and are dropped out of the study. All the remaining patients are started on 5 mg fosinopril or placebo once a day and included in a 3–6 weeks up titration period. Treatment is administered in the presence of the investigator, at the earliest 2 h before and at the latest immediately before the beginning of dialysis. Subsequently, visits take place at least 48 h after the preceding dialysis session and in most cases immediately before the next dialysis session. Study medication dose is increased each week in 5 mg increments until the maximum dose of 20 mg once a day is reached. The investigator may delay a dose increment or temporarily or definitely decrease drug dosage. Follow-up visits subsequently take place at 8 weeks and at 3 months following inclusion and every 3 months thereafter; the dose of the study medication can no longer be increased. At each visit, BP is measured immediately before dialysis using a mercury sphygmomanometer, in accordance with WHO recommendations. Symptomatic hypotension or SBP ≤ 95 mmHg is handled first by dose adjustment or discontinuation of concomitant hypotensive treatments. If ineffective, this is followed by progressive 5 mg dose decrements of the study medication. In extreme cases the study medication must be discontinued.

Concomitant treatments, with the exception of ACE inhibitors and angiotensin II receptor antagonists (discontinued at least 6 weeks before inclusion in the study), are authorised throughout the duration of the study. Cardiovascular medications are maintained unchanged during the run-in preinclusion period.

BP changes are carefully monitored at each follow-up visit. Investigators are advised to ensure that BP is maintained below 160/90 mmHg using allowed antihypertensive medications. They are also instructed to maintain haemoglobin levels above 10 g/dL, using erythropoietin dose adjustments and to maintain a Kt/V value ≥ 1.2.

Compliance is assessed by pill count.

Sample size and statistical analysis

On the basis of published data, calculation of sample size is made with the following hypothesis: a 2 year duration of treatment; primary combined event rate of 50%; a 90% statistical power to detect a 33% reduction in this event rate with fosinopril; a bilateral alpha risk equal to 5%. The required sample is of 396 patients. Given the random occurrence of kidney transplant and the anticipated minor interaction of transplantation with the primary endpoint, it is decided that there is no need to modify the hypothesis. Occurrence of the first event is described using Kaplan–Meier survival curves. Cox model is used for adjustments for the time of event occurrence and patients' baseline characteristics. The main analysis is performed with the intention to treat rule, using a Chi-2 test. For each of the secondary endpoints, treatment effects are compared using a Chi-2 test (Fisher's exact test for low patient numbers). Cox methods may also be used, only for high event rate endpoints. No adjustment for the multiplicity of tests is performed.

Per protocol analysis, excluding patients with major deviations, and analysis taking account of the data after kidney transplant only up to 3 months after the transplant, is also performed.

Organisation of the study

Several committees (see appendix) supervise the study. The Executive Steering Committee examines the progress of the study, taking any decision appropriate to its proper conduct; it decides upon amending or stopping the study prematurely, following the recommendations of the Data Safety Monitoring Board (DSMB). Three blinded safety analyses by an independent Data Safety Monitoring Committee are planned. These analyses focus exclusively on a limited number of safety variables and must at the most remain descriptive, allowing no prior judgement of the results of efficacy. The committee may recommend appropriate amendments or discontinuation of the study in case of a statistically significant ($P < 0.01$) excess of serious adverse events.

The critical events are adjudicated by an *ad hoc* Critical Event Committee according to pre-established definitions.

Study status

The trial began in October 1998 in 47 French HD centres. The last patient was included by December 2000. Four-hundred-and-seventeen patients were selected initially. The remaining 397 patients were randomised into the study. Their baseline characteristics on inclusion are given in *Table I*.

At the end of the titration period, 300 patients (76%) reached the target dose of 20 mg. So far, compliance is excellent (98%).

By January 2002, 73 patients had died. Follow up is ongoing until December 2002. So far, the DSMB has raised no special safety concern. The main results are expected for the first quarter of 2003.

DISCUSSION

Because they have a number of comorbid conditions, and present several safety issues, not the least of them being related to changes in the pharmacokinetics of drugs, it is usually thought wise to exclude patients with significant renal failure when planning for clinical trials. As a consequence, far from being evidence-based, therapy in ESRD patients is presently arbitrary or based on the results of observational and / or non randomised studies. Nephrologists apply to their patients the results of trials performed in patients with little or no renal dysfunction. The HD population has also been neglected because it represents only a small 'niche' market, as compared to the sizeable populations included in cardiovascular trials. Yet, the number of patients undergoing HD for ESRD is rising. Such patients suffer from an alarmingly-high rate of cardiovascular events. Results of trials in non-ESRD patients cannot be extrapolated without hazard to patients with ESRD. Thus, one should feel compelled to develop and test specific cardiovascular protective strategies in this population.

The aim of FOSIDIAL study is specifically to address this issue. The selected patients are fairly representative of the general HD population. In daily clinical practice in western countries, ESRD patients are most frequently elderly patients, aged above 50 with a rising proportion of diabetics. In order to avoid possible confounding factors related to dialysis, we included patients on stable dialysis for more than 6 months with optimal quality dialysis based on a minimal rate of dialysis defined as three per week.

In order to target a high cardiovascular risk population, we selected patients with LVH. Actually, LVH is highly prevalent in ESRD HD patients [25]. In an observational pilot study to FOSIDIAL performed in 11 HD centres, among 300 patients aged above 50, 63% met the LVH FOSIDIAL inclusion criteria [44].

Only patients on HD are selected for our study. Unlike haemodialysis, peritoneal dialysis is not accompanied by variations in BP and in the extracellular volume. The prevalence of LVH appears to be less frequent in this population. Kidney transplantation markedly alters patients profile [45]. It is associated with a major regression in LVH and cardiac volume related to correction of anaemia and hypervolaemia and occlusion of the arteriovenous fistula.

In our study, metabolic and BP control is probably better than in daily practice in patients with ESRD. Mortality in HD patients is higher in the USA than in Europe and even more so in elderly and African American subjects [46,47]. The difference in dialysis techniques with shorter sessions and higher exchange volumes appears more detrimental to the cardiovascular system.

The primary endpoint in FOSIDIAL is a composite of cardiovascular death and all hard predefined cardiovascular and cerebrovascular nonfatal events. The expected high number of such events makes it possible to include a limited number of patients and still retain sufficient statistical power. Ideally, total mortality is the best primary endpoint in outcome clinical trials. Considering this outcome as the primary endpoint would have required a much larger sample size, approximating 1000 patients. Actually, FOSIDIAL should be considered as a proof of principle study and would open the way for larger trials. Because the sample size will not allow subgroup analysis, it is even more important to undertake further studies in order to answer a number of relevant questions raised by the complex intricate pathophysiology of morbidity of renal and cardiovascular origin.

A number of therapeutic agents are candidates for clinical trials in ESRD HD patients. ACE inhibitors are one of these agents, because their benefit has been shown in a variety of non ESRD cardiovascular risk conditions [36], as recently reiterated in the HOPE study [48]. In a small number of ESRD patients with LVH included in a double-blind randomised study, perindopril was shown to decrease left ventricular mass, independently from BP lowering and unlike calcium antagonists [49]. Because investigators are encouraged to use all therapeutic antihypertensive measures they may feel useful (except ACE inhibitors and angiotensin II receptor antagonists), we anticipate that BP will be balanced in the two study subgroups. Apart from FOSIDIAL, a small number of cardiovascular drugs are currently undergoing prospective randomised clinical trials in ESRD patients. Statins aim at acting on atherogenic factors and lipid disorders. They may act on endothelial function and have antiproliferative effects. The ALERT study currently investigates the effects of fluvastatin in ESRD patients after kidney transplantation [50]. The CHORUS study [51] was genuinely the first to examine the potential reduction of cardiovascular mortality and morbidity in HD subjects with another statin, cerivastatin.

Unfortunately, the recent withdrawal of this drug from the market forced the discontinuation of the study. The 4D prospective double blind randomised placebo controlled study with atorvastatin is currently enrolling 1200 adult type 2 diabetic HD patients in 150 German centres [52]. With cardiovascular mortality as a primary endpoint, this trial will provide valuable information on the specific population of noninsulin-dependent diabetic dialysis patients.

CONCLUSION

There is a lack of evidence-based guidance for our medical practice in the capital area of cardioprotection in ESRD patients. Control of cardiovascular risk factors in these patients remain very inadequate with regard to the extent of the observed cardiovascular mortality and morbidity. FOSIDIAL should contribute to designing effective and safe therapeutic strategies in ESRD HD patients. Although coronary angioplasty, stenting and cardiac surgery are technically feasible in ESRD patients, the risk of all these 'curative' interventional therapies is excessively greater than that observed in non ESRD patients [53]. Research should be aimed to earlier non-invasive, preferably preventive therapeutic intervention. It is hoped that FOSIDIAL will prove that performing controlled randomised outcome clinical trials in ESRD HD patients is feasible and may be rewarding.

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APPENDIX

Executive Steering Committee

F. Zannad (Chairman; Nancy); M. Kessler (Nancy); JP Grunfeld (Paris); C. Thuillez (Rouen); E. Rougemond (Lyon) and B. Pelletier (Nogent sur marne).

Critical event Committee

P. Lechat (Chairman; Paris); M. Laville (Lyon); M. Ovize (Lyon).

Data Safety Monitoring Committee

A. Leizorovicz (Chairman; Lyon); X. Andre-Fouet (Lyon); P. Zaoui (Grenoble); JC Peyrieux (Study Statistician; Statmed, Lyon).

Investigators

Sainte Clotilde de la Réunion (D. Schohn); Lille (F. Wambergue); Annonay (E. Legrand); Strasbourg (T. Hannedouche, H. Bittar); Colmar (P. Brignon); St Quentin (W. Jaber, M. Albadawy, B. Coevoet); Saint Brieuc (P. Simon, K.S. Ang); Limoges (M. Rince); Beauvais (G. Lambrey, Z. Massy, P. Fohrer); Bayonne (D. Petregne); Haumont (J. Lebleu, C. Lamotte); Saint Pierre de la Réunion (P. Finielz); Toulon (O. Lavelle, M. Boukelmoune, C. Gautier); Vandoeuvre Les Nancy (M. Kessler, M. Zerrouki-Bellou); Boulogne Sur Mer (P. Bataille, N. Bouzernidj); Evreux (G. Majdalani, A. Bouffandeau); Figanieres (A. Robert, T. Merzouk); Mont De Marsan (C.D. Teboulle, H. El Ali); Pamiers (Ph. Dupuy, F. Dehais, J.P. Duchet); Albi (D. Verdier, I. Lauze); Chambery (J. Fourcade, B. Morel, D. Mercier); Ajaccio (A. Tifoura); Brest (J.M. Dueymes, A. Guerard); Macon (J.S. Virot); Tremblay En France (G. Bobrie); Orleans (R. Sharobeem); Vittel (E. Prenat); Dieppe (J.L. Bacri, C. Bessin); Harfleur (S. Geffroy, S. Martin); Evian Les Bains (K. Megri); Poitiers (M. Bauwens, P. Nolen); Nancy (J.C. Valdenaire); St Michel (L. Yver, D. Blanchier); Vichy (D. Aguilera, A. Guerraoui); Aubervilliers (P. Urena); Rueil Malmaison (O. Simons); Fleury Merogis (G. London, A. Guerin); Nîmes (B. Branger); Valenciennes (V. Lemaitre, D. Fleury, R. Binaut); Alencon (C. Quere); Toulouse (P. Bories); Toulouse (P. Bories); Montpellier (J.P. Rivory, F. Maurice); Paris (I. Reach, M. Luong); Besancon (G. Motte); Caen (J.P. Ryckelynck, B. Levaltier).