JNEPHROL 2007; 20: 646-655

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Protocol of the Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) randomized trial

Ausilia Maione[1], Antonio Nicolucci[1], Jonathan C. Craig[2,3], Giovanni Tognoni[1], Antonio Moschetta[4,5], Giuseppe Palasciano[4], Giuseppe Pugliese[6], Deni A. Procaccini[7], Loreto Gesualdo[8], Fabio Pellegrini[1], Giovanni F.M. Strippoli[1,2,3]

For the LIRICO study group

[1] Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti - Italy
[2] Centre for Kidney Research, NHMRC Centre for Clinical Research Excellence in Renal Medicine, School of Public Health, University of Sydney, Sydney - Australia
[3] Cochrane Renal Group, Sydney - Australia
[4] Department of Internal Medicine, University of Bari, Bari - Italy
[5] Department of Translational Pharmacology (DTP), Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti - Italy
[6] Department of Clinical Sciences, Diabetic Nephropathy Study Group, Società Italiana di Diabetologia, Policlinico Umberto I, Roma - Italy
[7] Department of Nephrology, Ospedali Riuniti, Foggia - Italy
[8] Department of Nephrology, University of Foggia, Foggia - Italy

ABSTRACT

Microalbuminuria is a strong, consistent and independent risk factor for cardiovascular and renal disease in patients with diabetes and/or hypertension and in the general population. Several randomized trials have shown the efficacy of inhibiting the renin-angiotensin system (RAS) with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) to prevent cardiovascular events and the progression of kidney disease. These 2 classes of drugs are equally effective for renal outcomes in patients with diabetic nephropathy, but only ACEIs have been found to significantly impact the risk of all-cause mortality, predominantly cardiovascular, in patients with diabetic nephropathy. Studies on the cardiorenal efficacy of combined therapy with ACEIs and ARBs in individuals with microalbuminuria or macroalbuminuria and other cardiovascular risk factors have been inconclusive. The Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) study aims to address existing questions in this setting. This is a phase III, randomized, comparative, pragmatic trial with prospective randomized open blinded endpoint (PROBE) design. It will evaluate the comparative efficacy of combined therapy with ACEIs and ARBs versus monotherapy with either ACEIs or ARBs in improving cardiovascular and renal outcomes in microalbuminuric or macroalbuminuric individuals at cardiorenal risk. The study will enroll 2,100 patients, selected in a network of internal medicine, diabetology or nephrology outpatient clinics. Patients will be randomly allocated to ACEIs, ARBs or their combination. The study has been approved and funded by the Agenzia Italiana del Farmaco (A.I.F.A.) within the 2005 funding plan for independent research on drugs.

Key words: *Angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers, Cardiovascular risk factors, Combined therapy, Microalbuminuria, Urinary albumin-creatinine ratio*

INTRODUCTION

Microalbuminuria is a strong, consistent and independent risk factor for cardiovascular and renal disease in patients with diabetes and/or hypertension and in the general population (1). Recent studies, including the third National Health and Nutrition Examination Survey (NHANES III) (2), the Prevention of Renal and Vascular End Stage Disease (PREVEND) study (3) and the AusDiab Kidney Study (4), have found that the prevalence of microalbuminuria is about 6%-8% in the general population and increases up to a level of 20%-30% in individuals with additional comorbidities (either diabetes or hypertension).

Results of available studies confirm that in patients with diabetes and/or hypertension, the risk of cardiovascular and all-cause mortality is 2-8 times higher in the presence of microalbuminuria (5-8). On the other hand, prospective studies confirm that microalbuminuria, independent of other recognized cardiovascular risk factors (i.e., diabetes, hypertension, dyslipidemia, obesity, smoking), is associated with an increase in the risk of cardiovascular and renal morbidity and mortality. A population-based British cohort study (n=22,368) shows that microalbuminuria compared with normoalbuminuria is consistently associated with about a 40% increase in the risk of coronary heart disease (9), independent of other risk factors (i.e., age, sex, smoking, systolic blood pressure, total cholesterol, diabetes, body mass index).

Several randomized trials have found that use of different antihypertensive agents affecting urinary albumin excretion is associated with a significant decrease in the risk of all-cause

and cardiovascular mortality, cardiac events and progression of renal damage (10). In particular, in patients with diabetes and microalbuminuria or macroalbuminuria, key guideline agencies recommend the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) as first-line therapy, in preference to other antihypertensive agents (11-15). These agencies have clearly stated that ACEIs and ARBs may be considered equivalent in patients with diabetic kidney disease and hypertension. Despite these statements, existing uncertainty was brought up in a recent systematic review that explored the benefits and harms of ACEIs, ARBs and combined therapy with ACEIs and ARBs in diabetic kidney diseases (16). This systematic review identified only 3 comparative "head to head" trials of ACEIs versus ARBs (n=206), which were clearly underpowered to detect comparative effects on all-cause or cardiovascular mortality and on progression of renal disease of 1 of these agents over and above the others. ACEIs compared with placebo were found to significantly reduce the risk of all-cause mortality, while ARBs compared with placebo were not. Effects of ACEIs and ARBs on renal outcomes were comparable, although the data were weak. In comparison with placebo, both classes of agents significantly reduced the risk of end-stage kidney disease (ESKD), doubling of serum creatinine concentration and progression from microalbuminuria to macroalbuminuria, and they increased the likelihood of regression from microalbuminuria to normoalbuminuria.

Combined treatment with ACEIs and ARBs causes a complete blockade of the renin-angiotensin system (RAS) and on biological grounds could be potentially more effective than monotherapy for cardiovascular and renal protection. Only 2 studies have found an additive effect of combined treatment with ACEIs and ARBs compared with monotherapy for reduction of urine albumin excretion levels (17) and a reduction in the risk of ESKD (18). However, studies on the cardiorenal efficacy of combined therapy with ACEIs and ARBs are not available in the specific population of individuals with microalbuminuria and 1 or more cardiovascular risk factors, despite the fact that these are the most commonly seen in general practice and in internal medicine, endocrinology and nephrology outpatient clinics.

In this paper, we outline the protocol of an ongoing large-scale randomized controlled trial of ACEIs, ARBs or their combination in patients with microalbuminuria or macroalbuminuria and 1 or more cardiovascular risk factors. The trial has been funded by Agenzia Italiana del Farmaco (A.I.F.A., 2005 funding program for independent research to be conducted in Italy) and is due to start enrollment in 2007.

The Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) randomized trial is designed with the primary aim of assessing the comparative efficacy on cardiovascular outcomes of combined therapy with ACEIs and ARBs versus monotherapy with ACEIs or ARBs alone in patients at cardiorenal risk. The secondary objective of the study is to assess the comparative efficacy of ACEIs, ARBs or combined treatment with ACEIs and ARBs with regard to renal endpoints. The trial will address existing uncertainties in the area of direct comparison of different RAS inhibitors (ACEIs, ARBs and ACEIs plus ARBs) in a specific subset of the general population that is broadly seen in current medical practice. The study has been approved by a coordinating ethics committee and will be carried out according to the Declaration of Helsinki.

METHODS AND PATIENTS

Study population

The LIRICO study will be conducted in Italy and will enroll male and female consenting individuals aged 18 years or more who fulfill the following criteria:

1. presence of microalbuminuria (urinary albumin to creatinine ratio [ACR] =30-299 mg/g) or macroalbuminuria (ACR ≥300 mg/g), detected by measurement of ACR on a morning urine spot on 2 separate occasions; urinary dipstick and patient interview will be collected to exclude potential confounding by other causes of temporary increase in urinary albumin excretion rate (urinary tract infections, menstrual cycle, fever, intense physical activity, uncontrolled hypertension and hyperglycemia);
2. presence of 1 or more of the following cardiovascular risk factors:
   a. cigarette smoking: current smoker or somebody who quit smoking less than 12 months before enrollment;
   b. type 1 or type 2 diabetes (American Diabetes Association ADA-2006 criteria) (12): fasting glucose ≥126 mg/dL or glucose levels 2 hours after oral glucose tolerance test (OGTT) ≥200 mg/dL, or individuals being treated with oral antidiabetic agents or insulin;
   c. hypertension (Joint National Committee JNC-VII diagnosis criteria) (11): systolic blood pressure ≥140

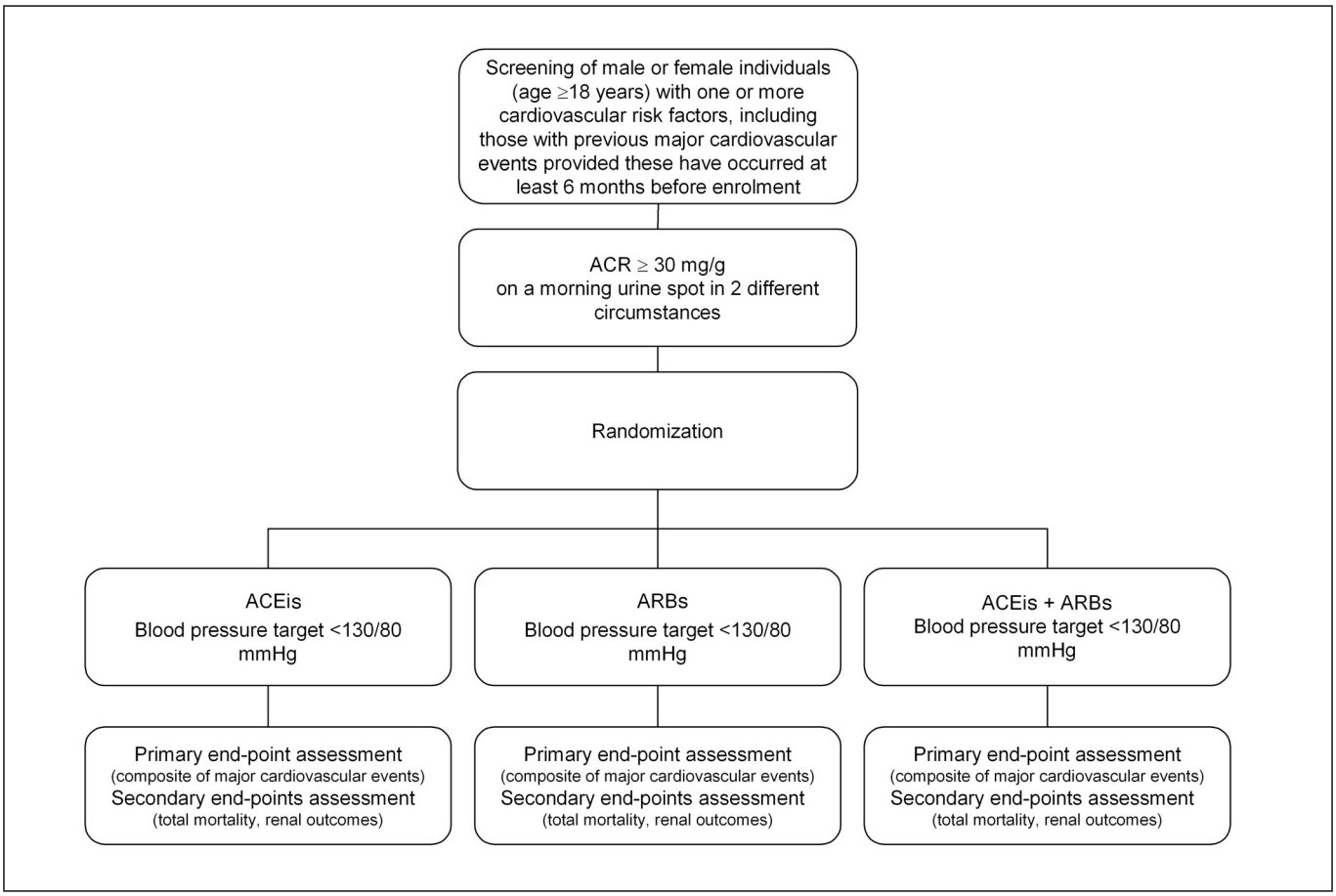


Fig. 1 - Flow-chart indicating the selection, randomization and follow-up process of the Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) trial.

mm Hg or diastolic blood pressure ≥90 mm Hg, or individuals being treated with antihypertensive agents;

d. visceral obesity: waist circumference ≥94 cm in males and ≥80 cm in females (19);
e. dyslipidemia (National Cholesterol Educational Program–Adult Treatment Panel III diagnostic criteria) (20): LDL cholesterol ≥130 mg/dL or total cholesterol ≥200 mg/dL, or individuals receiving lipid-lowering agents;
f. family history of cardiovascular disease: myocardial infarction or sudden death before the age of 55 years in the father or other first degree relative (male) or before 65 years in mother or other first degree relative (female).

Individuals who have previously experienced a major cardio-cerebrovascular event (coronary heart disease, nonfatal stroke, hospitalization for any cardiovascular cause) may be enrolled in the trial provided the event has occurred at least 6 months prior to enrollment.

The following will be exclusion criteria from the study:

1. pregnancy;
2. women who intend to become pregnant during the 4 years from enrollment to end of study;
3. malignancies as identified at the time of collection of medical history and which have occurred within 5 years from assessment of eligibility for study; this includes leukemia and lymphoma (skin cell basalioma are excluded from the list);
4. clinically significant aortic obstruction (detected through an ankle/brachial index test) (21);
5. clear contraindications to use of RAS inhibitors, including previously documented intolerance to these agents;
6. any condition which significantly reduces life expectancy;
7. inability or unwillingness to comply with all study requirements.

Study design

This will be a multicenter, randomized, pragmatic, parallel phase III trial (Fig. 1). Eligible individuals will be identified through population mass screening programs for detection of microalbuminuria or via opportunistic screening at any institution running outpatient clinics in patients with microalbuminuria or macroalbuminuria (internal medicine, diabetology and nephrology outpatient clinics) within a collaborative national network. Presence of microalbuminuria or macroalbuminuria will need to be confirmed twice. In this scenario, patients who are already known to have microalbuminuria or macroalbuminuria and are being followed in an outpatient clinic, may be recalled for a visit to confirm this condition prior to entering the trial; patients who are identified via a mass screening program as being microalbuminuric or macroalbuminuric will need to be recalled for an outpatient clinic visit to confirm this finding. Patient must not only have microalbuminuria or macroalbuminuria but also 1 or more cardiovascular risk factors (cigarette smoking, diabetes, hypertension, visceral obesity, dyslipidemia, family history of cardiovascular diseases), factors which will be assessed by patient interview. Screening consists in the evaluation of the ACR in a morning urine spot on 2 separate occasions; the first detection will be performed at the time of the screening visit, the second will be performed at the time of a pre-randomization visit, 7 days before randomization and no later than 2 months from the first ACR measurement. After providing an informed consent, subjects with a value of ACR ≥30 mg/g (confirmed in 2 separate occasions) will be centrally allocated through stratified, permuted blocks randomization to 1 of the following experimental interventions: ACEIs (any commercially available formula), ARBs (any commercially available formula), combined treatment with ACEIs and ARBs (any commercially available ACEIs or ARBs). Randomization lists will be stratified according to the enrolling center (nephrology, internal medicine or diabetology).

Based upon this trial design, use of ACEIs or ARBs or their combination should be at their full dose. Should the full doses be insufficient to reach a target blood pressure level of <130/80 mm Hg, additional antihypertensive cointerventions (any other antihypertensive agent) may be administered in a nonrandomized fashion.

Enrollment will run for 12 months, and follow-up will be for 4 years. During the follow-up, patients will be recalled to their outpatient clinics similarly to what happens in normal clinical practice conditions for patients affected by these baseline disease characteristics. At the time of randomization, at months 1 and 3, and every 6 months thereafter, scheduled trial follow-up visits will be performed to assess the incidence of all events expected to occur in the trial and representing the primary and secondary outcomes; this includes clinical workup and laboratory indicators (Tab. I). Figure 2 shows a summary of the key practical aspects of this study.

Endpoints

This study will be based on use of the prospective randomized open blinded endpoint (PROBE) technique (22). This design is comparable to that of a typical double-blind study but allows us to avoid the use of placebo and has lower costs and better applicability to standard clinical practice settings. According to the PROBE design, an independent endpoint committee composed of medical specialists of the disease of interest will be established; these physicians will ignore allocated treatment and will have all documents available (including charts, death certificates etc.) to provide a blinded assessment of all of the following outcomes.

The primary endpoint of the LIRICO trial will be the composite of the following events:

1. cardiovascular mortality;
2. coronary heart disease;
3. nonfatal stroke;
4. hospitalization for any cardiovascular cause.

Secondary endpoints of the LIRICO trial will be the following:

1. each of the components of the primary endpoint;
2. all-cause mortality;
3. ESKD;
4. renal function (assessed as serum creatinine, glomerular filtration rate estimated with the Cockcroft-Gault equation (23) and the modified Modification of Diet in Renal Disease (MDRD) equation (24), and ACR).

Efficacy of experimental treatments will be assessed annually with relation to the primary study endpoint.

Statistical aspects

Sample size

The sample size for the LIRICO trial was calculated based on the following estimates and assumptions:

1. annual incidence of the primary composite endpoint: 5%;
2. expected risk reduction with combined ACEIs+ARBs

TABLE I
TIMETABLE OF THE LONG-TERM IMPACT OF THE RAS INHIBITION ON CARDIORENAL OUTCOMES (LIRICO) TRIAL

Indicators to be detected	Visit timelines												
	Screening (-1 or 2 mo)	Pre-randomization (-7 days)	Randomization time 0	1 mo	3 mo	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo
Lipid profile, blood glucose profile*, creatinine, potassium			X				X		X		X		X
ACR on morning urine spot after urine dipstick to exclude infection	X	X	X			X	X	X	X	X	X	X	X
GFR			X	X	X		X		X		X		X
Creatinine and potassium				X	X								
Blood pressure and heart rate		X	X	X	X	X	X	X	X	X	X	X	
Waist circumference and body weight			X			X	X	X	X	X	X	X	X
Written informed consent			X										
Patients' register	X	X	X										
Randomization visit form		X											
Follow-up form				X	X	X	X	X	X	X	X	X	X

Blood samples may be taken at 6, 18, 30 and 42 months at the discretion of the managing physician. If a patient has been already screened for microalbuminuria or macroalbuminuria before this study and has documented evidence of presence of microalbuminuria or macroalbuminuria through an ACR on a morning urine spot, rescreening may be avoided and the patient may be directly contacted for the prerandomization visit (-7 days).
ACR = albumin to creatinine ratio; GFR = glomerular filtration rate.
*This includes fasting glucose in nondiabetic patients and HbA1c in patients with type 1 or type 2 diabetes.

POTENTIALLY ELIGIBLE

- Male/female ≥ 18 years
- Presence of one or more cardiovascular risk factors (smoking, diabetes, hypertension, visceral obesity, dyslipidaemia, family history of cardiovascular diseases) including individuals with previous major cardiovascular events provided these have occurred at least 6 months before randomization

SCREENING VISIT

- Screening for micro/macroalbuminuria will be performed by means of an Albumin Creatinine Ratio (ACR) on a morning urine spot, after excluding presence of infection with a urine dipstick. During the screening visit the presence of cardiovascular risk factors will be investigated. The first screening visit may be avoided for patients who are already followed in an outpatient clinic and are known to be micro/macroalbuminuric (already existing first determination of ACR)

PRE-RANDOMIZATION VISIT (-7 DAYS FROM RANDOMIZATION VISIT)

- ACR will be assessed on a morning urine spot, after excluding presence of infection and other conditions affecting albumin excretion with a urine dipstick
- Eligibility criteria will be assessed again at this time

RANDOMIZATION VISIT (TIME 0)

- Written informed consent
- Collection and confirmation of indicators of cardiovascular risk (smoking, diabetes, hypertension, visceral obesity, dyslipidaemia, family history of cardiovascular diseases); if previous major cardiovascular events have occurred, in this visit the physician will reconfirm that these have occurred at least 6 months prior to randomization
- Blood chemistry: lipid profile , fasting glucose in non diabetic patients, HbA1c in diabetic patients (both type 1 and type 2 diabetes), serum creatinine, serum potassium
- Body weight, height, waist circumference
- Measurement of systolic and diastolic blood pressure, measurement of heart rate
- ACR on morning urine spot, following urinary dipstick to exclude presence of infection
- Assessment of glomerular filtration rate (Cockcroft-Gault and modified MDRD equation)
- Detailed assessment of concomitant medication use (trade name, dose, indication)
- Assessment of comorbidities
- Randomization and treatment allocation
- Definition of the next follow-up visit (1 month)

FOLLOW UP VISIT (MONTH 1)

- Blood chemistry: serum creatinine, serum potassium
- Measurement of systolic and diastolic blood pressure, measurement of heart rate
- Assessment of glomerular filtration rate (Cockcroft-Gault and modified MDRD equation)
- Increasing dose of allocated treatment (titration) if blood pressure values <130/80 mmHg not targeted and in the absence of clinic counter-indications (e.g. in presence of serum potassium level >6 mEq/L and/or serum creatinine level >1.5 mg/dL or increased serum creatinine level >50% of baseline values if creatinine levels at baseline >1.5 mg/dL)

FOLLOW UP VISIT (MONTH 3)

- Blood chemistry: serum creatinine, serum potassium
- Measurement of systolic and diastolic blood pressure, measurement of heart rate
- Assessment of glomerular filtration rate (Cockcroft-Gault and modified MDRD equation)
- Titration drug if not already optimized at the previous follow up visit (month 1)

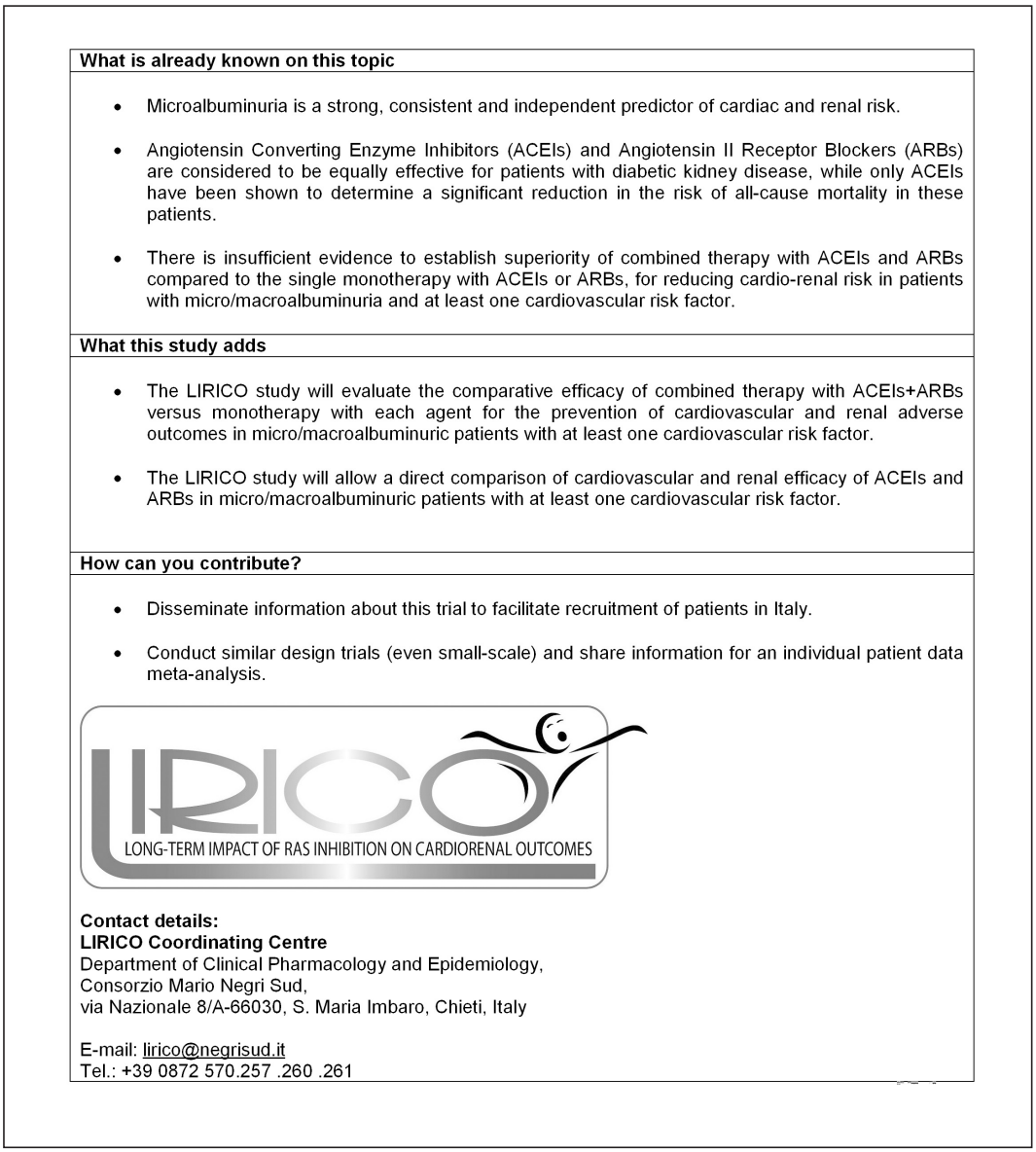
FOLLOW UP VISITS (months 6, 12, 18, 24, 30, 36, 42, 48)

- Bloood chemistry (every 12 months): lipid profile, fasting glucose in non diabetic patients, HbA1c in diabetic patients (both type 1 and type 2 diabetes), serum creatinine, serum potassium
- Body weight, waist circumference
- Measurement of systolic and diastolic blood pressure, measurement of heart rate
- Assessment of glomerular filtration rate (Cockcroft-Gault and modified MDRD equation)
- ACR on morning urine spot, following urinary dipstick to exclude presence of infection and other conditions affecting albuminuria
- Detailed collection of information on randomized intervention (if any variation of dose)
- Detailed information on cointerventions (trade name, dose, indication)
- Compliance assessment
- Reporting of events, toxicity, tolerability

MONITORING OF SAFETY AND EFFICACY

- Open central monitoring of safety and efficacy by an independent Data Safety and Monitoring Committee (DSMC) and blinded qualitative monitoring of outcome by an End-point Committee

Fig. 2 - Summary of key practical aspects of the Long-Term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) trial.



What is already known on this topic

- Microalbuminuria is a strong, consistent and independent predictor of cardiac and renal risk.
- Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs) are considered to be equally effective for patients with diabetic kidney disease, while only ACEIs have been shown to determine a significant reduction in the risk of all-cause mortality in these patients.
- There is insufficient evidence to establish superiority of combined therapy with ACEIs and ARBs compared to the single monotherapy with ACEIs or ARBs, for reducing cardio-renal risk in patients with micro/macroalbuminuria and at least one cardiovascular risk factor.

What this study adds

- The LIRICO study will evaluate the comparative efficacy of combined therapy with ACEIs+ARBs versus monotherapy with each agent for the prevention of cardiovascular and renal adverse outcomes in micro/macroalbuminuric patients with at least one cardiovascular risk factor.
- The LIRICO study will allow a direct comparison of cardiovascular and renal efficacy of ACEIs and ARBs in micro/macroalbuminuric patients with at least one cardiovascular risk factor.

How can you contribute?

- Disseminate information about this trial to facilitate recruitment of patients in Italy.
- Conduct similar design trials (even small-scale) and share information for an individual patient data meta-analysis.

LIRICO
LONG-TERM IMPACT OF RAS INHIBITION ON CARDIORENAL OUTCOMES

Contact details:
LIRICO Coordinating Centre
Department of Clinical Pharmacology and Epidemiology,
Consorzio Mario Negri Sud,
via Nazionale 8/A-66030, S. Maria Imbaro, Chieti, Italy

E-mail: lirico@negrisud.it
Tel.: +39 0872 570.257 .260 .261

Fig. 3 - Why we need the Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) trial and what you can do to contribute.

treatment: 25% (hazard ratio = 0.75);
3. power: 80% (alpha = 0.05).

Given these assumptions, 2,100 individuals (700 per group) will have to be randomized. If fewer patients are randomized or the incidence rate of events is lower than expected, the duration of follow-up will be extended.

Data analysis

All efficacy assessments will be made based on the intention-to-treat principle. The incidence of events with ACEIs vs. ARBs vs. ACEIs+ARBs will be estimated using Kaplan-Meier curves, which will be compared using the log-rank test. Additional multivariate analyses will be performed using a Cox proportional hazards model.

Ancillary analyses will be performed for assessment of efficacy of study intervention on any of the secondary endpoints of this study. Treatment efficacy will be also evaluated based on the following potential effect modifiers (baseline collection of information): gender (male vs. female), age, presence or absence of diabetes, type of diabetes (1 or 2), presence or absence of hypertension, presence or absence of visceral obesity, cigarette smoking (yes or no), family history of cardiovascular disease (yes or no), type of cardiovascular risk factor, presence or absence of previous cardio-cerebrovascular event, type of ACEIs or ARBs or

their combination, dose of ACEIs or ARBs reached during the study, level of albuminuria (microalbuminuria or macroalbuminuria) at enrollment, glucose control (quartiles of HbA1c; only in patients with diabetes), baseline cholesterol (quartiles of LDL and total cholesterol), presence or absence of retinopathy, antihypertensive cointerventions or other cointerventions, baseline serum creatinine levels and baseline glomerular filtration rate.

Any existing trends in the efficacy based upon these subgroup analyses will be tested with the Mantel-Haenszel test, while a chi-square test will be used to assess heterogeneity of observed effects of interventions.

Interim analysis

One interim analysis will be performed 2 years after completion of enrollment. Data will be analyzed to assess the correctness of study hypotheses for sample size calculations and a formal efficacy analysis.

The data safety and monitoring committee will inform steering committee members if they believe that there is "no further doubt" of an existing net difference between the experimental and control intervention with regards to efficacy for the primary endpoint or if there is any novel evidence indicating that the management of patients enrolled in the study should change. An existing net efficacy difference implies at least 3 standard deviations more or less in the interim analysis for the risk of the primary endpoint, which could justify interruption of the study or modification of the study protocol. The steering committee will then decide if the study needs to be modified or further data are necessary. In any other case, nobody, with the exception of those providing the confidential information, shall be made aware of the results of the analyses for the primary endpoint of the study.

Summary

The LIRICO study will evaluate if combined treatment with ACEIs+ARBs compared to monotherapy is associated with an additional cardiorenal benefit, in a well-defined group of subjects with microalbuminuria and 1 or more cardiovascular risk factors.

Recruitment of patients is due to start by 2007.

We welcome identical design trials to be conducted in other countries; results may be pooled with those of the LIRICO trial. Figure 3 outlines the importance of the trial and how further information about it may be obtained.

Appendix

Steering committee

Dr. Craig Jonathan, Centre for Kidney Research, NHMRC Centre for Clinical Research Excellence in Renal Medicine, School of Public Health, University of Sydney, Australia; and Cochrane Renal Group, Sydney, Australia;

Dr. Gesualdo Loreto, Department of Nephrology, University of Foggia, Italy;

Dr. Nicolucci Antonio, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy;

Dr. Palasciano Giuseppe, Department of Clinical Sciences, Diabetic Nephropathy Study Group, Società Italiana di Diabetologia, Policlinico Umberto I, Rome, Italy;

Dr. Pellegrini Fabio, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy;

Dr. Procaccini Deni, Department of Nephrology, Ospedali Riuniti, Foggia, Italy;

Dr. Pugliese Giuseppe, Department of Clinical Sciences, Diabetic Nephropathy Study Group, Società Italiana di Diabetologia, Policlinico Umberto I, Roma, Italy;

Dr. Strippoli Giovanni (principal investigator), Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy; Centre for Kidney Research, NHMRC Centre for Clinical Research Excellence in Renal Medicine, School of Public Health, University of Sydney, Australia; and Cochrane Renal Group, Sydney, Australia;

Dr. Tognoni Giovanni (chairman of the steering committee), Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, S. Maria Imbaro, Chieti, Italy.

Clinical research management and monitoring

Miriam Valentini and Celeste Pirozzoli, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy.

Trial coordinating center

Ausilia Maione (project manager)

Barbara Di Nardo, Sonia Ferrari, Marco Piaggione and Rosalia Di Lallo (database design, study and data management)

Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti, Italy.

Acknowledgements

This study has been approved and funded by the Agenzia Italiana del Farmaco (A.I.F.A.) within the 2005 funding plan for independent research on drugs.

The LIRICO study was supported by the Agenzia Italiana del Farmaco (A.I.F.A.) 2005 program for independent research, contract no. FARM537JNE. The LIRICO study has been registered in the Cochrane Renal Group trial registry with number CRG020700104 and in the Australian Clinical Trials Registry (ACTR) with number ACTRN012607000333415. Systematic reviews performed in preparation for the LIRICO trial have been funded by the Cochrane Renal Group.

Conflict of interest statement: None declared.

Address for correspondence:
Ausilia Maione, MScPharmChem
Consorzio Mario Negri Sud
Via Nazionale 8/A
I-66030, S. Maria Imbaro (CH), Italy
maione@negrisud.it
strippoli@negrisud.it

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