Atherosclerotic renovascular disease: Medical therapy versus medical therapy plus renal artery stenting in preventing renal failure progression. The rationale and study design of a prospective, multicenter and randomized trial (NITER)

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ABSTRACT: Background: Many studies suggest a major prevalence of atherosclerotic renovascular disease (ARVD), caused by mono or bilateral renal artery stenosis (RAS). Unfortunately, there is no definite therapy to cure this disease to date; therefore, ARVD is burdened by important clinical complications with high social and economic costs. The last few years have seen important advancements in both medical therapy and in interventional radiology (for example, percutaneous transluminal renal artery stenting (PTRS)). All of them could affect, in some way, the natural history of ARVD, but to date the optimal strategy has not been established.

Methods: The protocol of a prospective, multicenter, randomized trial “Nephropathy Ischemic ThERapy (NITER)” is presented. It enrolls patients with stable renal failure (glomerular filtration rate (GFR) ≥30 ml/min) and hypertension, and hemodynamically significant atherosclerotic ostial RAS (≥70%) diagnosed by duplex Doppler (DD) ultrasonography and confirmed by magnetic resonance angiography (MRA). This study aims to evaluate whether medical therapy plus interventional PTRS is superior to medical therapy alone according to the following combined primary endpoint: death or dialysis initiation or reduction by >20% in estimated GFR after 0.5, 1, and 2 yrs of follow-up and an extended follow-up until the 4th year. Medical therapy means drugs to control hypertension, improve dyslipidemia and optimize platelet anti-aggregant therapy. The sample size is estimated in 50 patients per group to achieve a statistical significance of 0.05 in case of a reduction by 50% in the combined endpoints.

Key words: Atherosclerotic renovascular disease, Renal artery stenosis, Ischemic nephropathy, Percutaneous transluminal renal artery stenting, Angioplasty, Hypertension, Renal insufficiency, End-stage renal disease, Cardio- and cerebro-vascular comorbidity, Randomized controlled trial

INTRODUCTION

Atherosclerotic renovascular disease (ARVD), due to renal hypoperfusion caused by mono or bilateral renal artery stenosis (RAS), is a well-known cause of renal failure, as demonstrated, many years ago, by the experimental studies of Goldblatt in dogs (1). In the twenty-first century, the burden of ARVD in nephrology is progressively growing, above all in diabetics (2), in patients with atherosclerotic vascular...
lesions in other regions (3-5), as demonstrated by its high prevalence in elderly patients starting dialysis (6, 7).

The real prevalence of ARVD in the general population is not clearly defined, but many reports (3-7) suggest that nephrologists are now seeing only the tip of the iceberg. If ARVD diagnosis is denied or late, inevitably, therapy will be denied or late, leading to a high complication rate with high social and economic costs. The importance of an early diagnosis is supported by many considerations.

- Atherosclerosis is a progressive disorder; therefore, the risk of vascular obstruction increases linearly according to the stenosis degree (8, 9).
- More than 15% of elderly patients start dialysis due to ARVD (6, 7).
- ARVD reduces life-expectancy more than any other cause of end-stage renal disease (ERSD) (10).
- Patient survival decreases as ARVD severity increases: patients with 75 and 95% RAS, have a 4-yr adjusted survival of 68 and 48%, respectively, as seen in a large sample of 3987 patients submitted to diagnostic coronary angiography (11).
- The mortality rate is higher in ARVD patients than in patients with stable angina and it is similar to that of patients undergoing surgery for colon cancer (12). Even in patients already on dialysis, ARVD has a tendency for a higher mortality risk than other diseases (7). Unfortunately, an optimal therapy for ARVD is not well established, despite the fact that percutaneous transluminal renal artery stenting (PTRS) for renal artery lumen restoration has been widely used since the early 1990s. The few prospective randomized studies (13-15) did not demonstrate any significant differences between interventional radiological therapy and medical therapy.

**Study design**

This is a multicenter, prospective, randomized trial in patients with renal failure (serum creatinine (Cr) ≤3 mg/dL and/or Cr clearance ≤30 ml/min), blood hypertension and hemodynamically significant atherosclerotic ostial RAS (with a luminal reduction ≥70%). The RAS diagnosis will be made by duplex Doppler (DD) ultrasonography and confirmed by magnetic resonance angiography (MRA) of the renal arteries. This study aims to investigate whether PTRS of the renal artery offers more, in terms of both preventing renal failure progression and controlling hypertension, compared with medical therapy alone to control hypertension, improve the dyslipidemic profile and optimize the platelet anti-aggregant therapy.

The enrollment of 100 patients will take place in various Italian centers, by involving the nephrologists and the radiologists from each center, with tight inter-specialist cooperation as this is the real key to success and good results.

Randomization started in January 2003 with completion expected by January 2007; there will be 2 yrs of follow-up with an extended 2yr follow-up.

**Baseline data**

Once the DD ultrasonography and MRA confirm the RAS diagnosis, the degree of stenosis will be recorded. The following blood and urinary laboratory tests will be performed: serum glucose, serum Cr, Cr clearance using the MDRD “four variable” abbreviated formula (16), total and high density lipoprotein (HDL) and low density lipoprotein (LDL) serum cholesterol, serum triglycerides, hemocromocytometry, serum homocysteine, serum C-reactive protein (CRP), total proteinuria and albuminuria 24-hr collection; for each patient a blood sample of 5 ml in EDTA will be stocked in every center for a possible future study.

The patients will be investigated with:

- Renal artery DD ultrasonography.
- MRA - standardized characteristics of MRA examination will be taken in all centers.
- Renal scintigraphy (for monolateral stenosis) for glomerular filtration rate (GFR) determination and the determination of the single kidney split.
- Cardiac ultrasonography (to mark left ventricular hypertrophy and the cardiac kinetic).
- Renal ultrasonography (to mark longitudinal ultrasonographic diameter of the stenotic kidney; mean of at least three measurements from an experienced operator).

The clinical history and the drug treatment will be recorded. All patients enrolled will be evaluated for the presence of risk factors such as smoking or past smoking history (number of cigarettes/day) and will be strongly advised to stop smoking.

A history of renal failure will be investigated (serum Cr ≥1.5 mg/dL) and/or GFR (16) <70 ml/min, history of hypertension, dyslipidemia (total serum cholesterol ≥220 mg/dL and/or serum triglycerides ≥170 mg/dL and/or LDL >160 mg/dL), or the presence of atherosclerotic diseases in other regions. Blood pressure (BP) values, expressed as the mean of three measurements in a sitting position after 5 min rest will be marked. The target for BP control is a systolic pressure of 140 mmHg and a diastolic pressure of 80 mmHg (17). Eligible patients must show stable BP levels (with the mean of at least three ambulatory measurements) and serum Cr concentration (mean of two serum Cr determinations) within the month before enrolment in the study; those will be considered as baseline values. A tight
glycemic control (with ideal serum HbA1c levels <7%) will be requested in diabetic patients, also encouraging particular attention to diet and increased physical activity.

Patients willing to participate, after giving their written informed consent, will be randomly allocated to medical therapy alone or to medical therapy plus renal artery stenting, after protocol approval by the ethical committee of each center participating in the study. The Study Secretariat in the Nephrology Department of Piacenza will centralize the randomization.

The enrolment period will be 4 yrs and the planned duration of follow-up is 2 yrs with an extended follow-up of 2 yrs. Each patient should leave the study 4 yrs after enrolment. Analysis will take place as intention-to-treat. Table I reports the inclusion and exclusion criteria.

**Treatment**

The eligible patients will be centrally randomized to:

- **a** - medical treatment with hypotensive drugs, lipid lowering therapy (statins, fibrates and omega-3 fatty acids) and anti-platelets (acetylsalicylate ASA plus ticlopidine, clopidrogel or others). Statins will be prescribed irrespective of the serum cholesterol levels in view of the protective role in reducing renal failure progression (18).
- **b** - the same medical therapy, as previously described in group A, associated with PTRS, according to a standardized protocol; every radiological procedure will be preceded by 0.45% saline solution intravenously at a rate of 1 ml/kg of body weight/hr for 12 hr and antioxidant acetylcysteine (600 mg orally twice daily), on the day before and on the day after contrast agent administration, to prevent the potential nephrotoxicity of iodinated contrast media (19).

Adverse outcomes during procedures will be recorded. Table II reports the study endpoints.

**Follow-up**

Clinical follow-up is scheduled after 7 days, 1, 3, 6 months and every 6 months, until the end of the follow-up. Every 6 months DD, MRA (only in the medically treated group), renal radioisotope scanning (in monolateral stenosis) for GFR determination and to determine the single kidney split, cardiac ultrasonography and renal ultrasonography will be repeated. Chemical data (glycemia, in diabetic patients with HbA1c, serum Cr, GFR (MDRD formula) (16), serum total cholesterol, LDL, HDL, triglycerides, serum creatine kinase (CK), lactic dehydrogenase (LDH) and transaminase, hemocromocytometria, CRP, total proteinuria and albuminuria, will be measured after 7 and 30 days from the start and after every 6 months.

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**TABLE I - INCLUSION AND EXCLUSION CRITERIA**

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<th>Inclusion criteria:</th>
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<td>- Age ≤80 yrs</td>
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<td>- Presence of ostial RAS ≥70% (determined by DD ultrasonography and confirmed by MRA valuated by at least two experienced operators)</td>
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<td>- Serum Cr ≤3 mg/dl and/or Cr clearance (MDRD formula) (16) ≥30 ml/min</td>
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<td>- Longitudinal ultrasonographic diameter of the stenotic kidney ≥8 cm</td>
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<td>- BP values ≤150/90 mmHg with the use of less than four hypotensive drugs</td>
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<th>Exclusion criteria:</th>
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<tr>
<td>- Age &gt;80 yrs</td>
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<td>- Other well-known nephropathy cause of renal failure</td>
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<td>- DD ultrasonography resistive index values &gt;0.8</td>
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<td>- Total occlusion of renal artery lumen</td>
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<td>- Occurrence of cerebral or cardiac vascular diseases in the 6 months before the enrolment in the study</td>
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<td>- Malignancy with a life expectation &lt;1 yr</td>
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<td>- Previous documented cholesterol thrombo embolization episodes (clinically, bioptically or instrumentally)</td>
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<td>- Liver failure</td>
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<td>- Cardiac failure (NYHA IV class) or unstable angina</td>
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<td>- Well-known intolerance or contraindications to the use of iodinated contrast media, to statins or to antiplatelet drugs</td>
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<td>- Pregnancy</td>
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Inter-current diseases, as well as possible side effects, will be recorded at each visit, together with drug dosages, drug modification, possible post-PTRS complications, or hospitalization. If a patient needs to be shifted from the medical therapy to PTRS treatment, the follow-up will be similar as for the primary PTRS-treated patients. If the serum CK levels should increase more than five-fold, or serum transaminase three-fold, from baseline values, statins will be temporarily discontinued and then reintroduced at half the dose, if the control is normal. The goal of the lipid lowering therapy will be a serum total CHL level <200 mg/dL, HDL >40 mg/dL, LDL <160 (<100 preferable) or serum triglycerides <160 mg/dL. All the data will be sent to the coordinating group in Piacenza, Italy.

Statistical analysis

In order to calculate the sample size we assumed exponential distributions for both treatment groups. We used the George-Desu method along with the Schoenfeld (20) formulas that allow the estimation of the expected number of events in the two groups. To allow for drop-ins (non-compliance to control therapy, crossover to intervention) and for non-compliance of the intervention, the Lachin and Foulkes method (21) was used. A sample size of about 50 patients per group was estimated to provide >80% power at statistical significance of 0.05 to detect a 50% reduction in the combined endpoint in the stent group, given a drop-in rate of 5% and an approximate drop-out rate of 10%.

Interim analysis will be performed after the enrolment of the first 50 patients to verify the study plan assumptions. The Lan-DeMets (22) spending function approach will be used to adjust the probability of a type I error for testing the primary outcome for this interim analysis.

DISCUSSION

The management of patients with RAS has to address the normalization of BP, restore renal artery patency to restore, stabilize or avoid the progression to ESRD, without forgetting the associated diseases in these elderly patients (atherosclerotic diseases in other regions - coronary artery diseases, peripheral arterial disease, cerebral artery disease, dyslipidemia and diabetes).

To our knowledge, there are no prospective randomized studies in the literature, over the medium or long term, comparing the effects of medical therapy alone vs. medical therapy associated with PTRS. Despite the fact that renal artery stenting has been routinely used since the early 1990s for treating more severe atherosclerotic renal artery ostial lesions, clinical results are clearly not satisfactory for improving renal function or in controlling hypertension (23).

In the literature both Harden (24) and Beutler (25) reported good results after renal stenting in patients with RAS, in terms of renal damage reduction; even in ESRD patients on dialysis, renal function recovery after stenting is also reported, suggesting an additional protective role of the stent. Nevertheless, the presence of the stent could contribute per se to promote neo-intima proliferation and progressive renal failure could occur despite successful revascularization, suggesting that ischemic nephropathy can be multifactorial (26).

Renal PTRS complications, such as high rates of restenosis, atheroembolic embolization, injury at the vascular access puncture site, artery dissection, in addition to higher costs, are also well known. Treatment of the stenosis alone may be not adequate and the optimal medical therapy remains undefined (27). Nevertheless, some authors suggest that long-term effective management of patients with unilateral RAS, in terms of protecting renal function and controlling hypertension, can be achieved with medical
intervention: however, overall mortality and renal function were worse in medically treated patients with bilateral RAS or RAS in a single kidney (28).

The few prospective randomized studies (13-15) published in 1990s did not demonstrate either a significant difference between PTRS or medical therapy, or a difference in BP control or in avoiding renal failure progression. The only result, reported by Plouin (14), the EMMA study, was a significant lowering of medication needs in percutaneous transluminal angioplasty-treated patients, in spite of a higher complication rate after procedures (13-15).

According to Ritz (10), one could suggest that those studies are not recent, having been planned and started several years ago when the new antihypertensive and antiplatelet drugs were unavailable, and lacking the recent knowledge about the effect of aggressive lipid lowering therapy in atherosclerotic diseases. Moreover, those studies involved a smaller number of patients, followed over a shorter period (6-12 months), had a high crossover rate from medical therapy to PTRS, often mixing patients treated with two different techniques, PTRS with and without stenting, when it is proven that generally atherosclerotic ostial lesions do not respond well to angioplasty alone.

Some other studies are ongoing, at least three around the world, and in 2004 a protocol study was published in this Journal (29). Some of these studies underline the importance of a “global” approach to patients with ARVD with high cardiovascular morbidity, often smokers, diabetics and dyslipidemics.

The necessity of a trial comparing medical therapy alone vs. medical therapy plus stenting, is based on the consideration that stenosis correction is only one factor in the problem, and the other major factors are gradient pressure through the lumen vessel, extension of the atherosclerotic process in renal artery branches, arteriolar thickness, tubular and glomerular atrophy, glomerular sclerosis, possible atheroembolic complications, a pre-existing hypertensive background and functionality stage of the kidney controlateral to the stenosis. Moreover, the chronic hypofiltration and the reduction in perfusion pressure distal to the stenosis can lead to the histological picture of tubular atrophy, interstitial fibrosis and glomerulosclerosis.

Previous studies compared treatment in patients with a wide degree of stenosis rates of 50 (not hemodynamically significant) to 90%. Inclusion criteria of our study are tighter, in order to compare homogeneous groups of patients with similar renal artery lumen reduction. Moreover, we will compare two groups of RAS patients diagnosed by the same diagnostic tools (in our case DD and MRA), and not, as in some previous studies, a 50% RAS determined by DD with 90% determined by arteriography.

The main methodological difference, however, is the method of evaluating single kidney function. The total GFR and the rate in each kidney can be used to assess baseline and serial function, before and after renal revascularization. In our study, single kidney function will be assessed by using renal radioisotope scanning instead of the whole kidney function by serum Cr, in contrast to many other studies and according to a previous report (30).

Therefore, many arguments indicate the necessity of comparing the ideal treatment of ARVD patients in a prospective, randomized, multicenter trial to cure, or to control hypertension better, following recent guidelines (17, 31), or to address the stability or avoidance of renal damage progression, and above all to reduce the cerebral and cardiovascular complications, the primary cause of death in ARVD patients (9-12).

APPENDIX

Participants of the NITER (Nephropathy Ischemic ThERapy) Study Group are:
Divisione di Nefrologia e Dialisi, Ospedale “Guglielmo da Saliceto” di Piacenza: Roberto Scarpioni, Luciano Cristinelli.
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Unità Operativa di Radiologia, Ospedale di Cremona: Gabriele Rozzi, Lucio Olivetti.

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REFERENCES


