SEMINARS IN
NEPHROLOGY

Treatment of Hypertension in Italian Nephrology Out-patient Clinics: The THIN Study

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Optimal pressure control is crucial to prevent cardiovascular events in hypertensive patients. However, well-controlled blood pressure is encountered only in a small percentage of hypertensive patients managed by general practitioners, cardiologists, diabetologists, and hypertension specialists. This study aimed to evaluate the target of blood pressure obtained in Italian nephrology out-patient clinics. Data were collected by questionnaire sent to nephrology out-clinics. Questions were pertinent to patient's clinical characteristics, lifestyle, biochemistry, blood pressure at the first and last visit, and antihypertensive medications. Data pertinent to 1,632 patients were collected. More frequent causes of hypertension were essential hypertension (26%), hypertension secondary to renal insufficiency (16%), and diabetes (10%). At admission the systolic blood pressure was more than 140 mm Hg in 98% and diastolic blood pressure was more than 90 mm Hg in 95% of patients; at the last visit a normalized systolic and diastolic blood pressure was found in 38% and in 75% of patients. A higher normalization rate was achieved in essential hypertensive patients compared with patients with hypertension secondary to chronic renal insufficiency and diabetes. These data indicate that improvement is obtained by nephrologists in controlling essential hypertension although more effective strategies in the management of hypertension in patients with reduced renal function and in diabetic patients still are required.
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Optimal blood pressure control is one of the most effective ways to retard the onset and/or progression of renal diseases and to prevent cardiovascular events in hypertensive patients. Despite the well-recognized need to decrease blood pressure, hypertensive patients with controlled blood pressure represent only a small percentage of the nonselected hypertensive population; and these data differ from the rather high rate of normalized blood pressure obtained in hypertensive patients enrolled in clinical trials.[1-5]

This multicenter retrospective study aimed to evaluate the target blood pressure obtained by Italian nephrologists in hypertensive out-patients. In addition, the study aimed to answer whether hypertensive patients who are examined at nephrology clinics are only those with concomitant renal diseases or also patients with essential hypertension.

Materials and Methods

Data were collected by questionnaire sent to nephrology clinics based at hospitals and/or universities of many Italian cities. Consecutive patients followed-up for at least 1 year were enrolled.

Questions were pertinent to patients' clinical characteristics and lifestyle: age, sex, body weight, height, habits (smoke, alcohol, coffee), systolic and diastolic blood pressure, cause and onset of hypertension, and antihypertensive medications. Biochemical data collected were as follows: urea, creatinine, creatinine clearance, glucose, cholesterol,

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triglycerides, serum sodium, plasma potassium, 24-h urinary sodium and potassium excretion, and urinary protein excretion levels. Because the study started before the guidelines of the International Society of Hypertension were released,[3] values for systolic and diastolic blood pressure of 140/90 mm Hg were regarded as normal limits. The diagnosis of chronic renal failure was made when the serum creatinine concentration was greater than 1.2 mg/dL and 1.4 mg/dL in women or men, respectively. Data recorded at the first admission to the clinic and at the last visit were collected and used for statistical analysis. Data were analyzed in aggregate and further according to cause of hypertension.

Results

A total of 102 nephrology out-clinics were contacted and 35 (35%) responded to the questionnaire. Data pertinent to 1,632 patients were collected. The causes of hypertension are reported in Table 1.[1] Most patients had essential hypertension (26%); in the remaining patients hypertension was secondary to reduced renal function (16%), diabetes (10%), glomerulonephritis (9.6%), polycystic kidney disease (6.7%), interstitial nephritis (5%), and miscellaneous renal diseases (26.7%) (eg, nephrovascular hypertension, systemic diseases, posttransplant hypertension, and so forth). At admission almost all patients had poor control of hypertension, with a systolic blood pressure of more than 140 mm Hg in 98% and a diastolic blood pressure of more than 90 mm Hg in 95%. In contrast, at the last visit normalized systolic and diastolic blood pressure was found in 38% and in 75% of all patients, respectively.

Patients With Essential Hypertension

There were 429 patients with essential hypertension (26% of the screened population). Clinical characteristics, lifestyle, and biochemical data are shown in Table 2.

At study entry very few patients with essential hypertension (1.5%) had systolic and diastolic blood pressure of 140/90 mm Hg or less; in contrast, at the last visit systolic blood pressure of 140 mm Hg or less and diastolic blood pressure of 90 mm Hg or less was attained in 52% and in 75% of patients, respectively. A positive correlation ($P < .01$) was observed between age and systolic blood pressure and between triglyceride level and alcohol consumption ($P < .01$). The diastolic blood pressure was correlated significantly ($P < .05$) with the number of cups of coffee the patient drank per day. No correlation was found between systolic and diastolic blood pressure and total cholesterol level, triglyceride level, smoke, alcohol, urinary sodium, and potassium excretion.

Single-drug and combination therapy were given to 42% and 58% of patients, respectively. Angiotensin converting enzyme inhibitors (ACEi) were the most frequently administered antihypertensive drugs both in single-drug (36%) and combination therapy (31%). The most frequent association was ACEi and calcium channel blockers. Among the several classes of antihypertensive medications, the most frequently prescribed drugs were hydrochlorothiazide (HCTZ), atenolol, amlodipine, enalapril, and clonidine.

Table 1 Causes of Hypertension

	%
Essential Hypertension	26
Chronic kidney insufficiency	16
Diabetes mellitus	10
Glomerulonephritis	9.6
Adult polycystic kidney disease	6.7
Interstitial nephritis	5
Miscellaneous	26.7

NOTE. n = 1,432.

Table 2 Patients With Essential Hypertension: Clinical Characteristics, Lifestyle, and Biochemical Data

Age (y)	51 ± 12
Sex (male/female; %)	52/48
Coffee %	95
Smoke %	51
Alcohol %	71
Body weight (kg)	76 ± 13
Plasma urea level (mg/dL)	31 ± 10
Serum glucose level (mg/dL)	91 ± 9
Triglyceride level (mg/dL)	258 ± 76
Serum sodium level (mEq/L)	141 ± 3
Serum potassium level (mEq/L)	4.2 ± 0.4
$U_{Na} \times V$ (mEq/24 h)	123 ± 48
$U_K \times V$ (mEq/24 h)	60 ± 15
C_{Cr} (mL/min)	106 ± 11
UAE (mg/24 h)	12 ± 40

Data are mean ± SD. N = 429.

$U_{Na} \times V$, urinary sodium excretion; $U_K \times V$, urinary potassium excretion; C_{Cr}, creatinine clearance; UAE, urinary albumin excretion.

Hypertensive Patients With Reduced Renal Function

There were 259 hypertensive patients with reduced renal function (16% of the screened population). Clinical characteristics, lifestyle, and biochemical data are shown in Table 3. Men were more likely than women to have reduced renal function (60% versus 40%, $P < .01$). At study entry, 99% and 91% of hypertensive patients with reduced renal function had systolic blood pressure greater than 140 mm Hg and diastolic blood pressure greater than 90 mm Hg, respectively. At the last visit a systolic blood pressure of 140 mm Hg or less and a diastolic blood pressure of 90 mm Hg or less was attained in 29% and in 82% of patients, respectively. A significant negative correlation ($P < .01$) was found between diastolic blood pressure and age, and between systolic blood pressure and creatinine clearance ($P < .05$). A positive correlation was observed between systolic blood pressure and age ($P < .05$), and serum creatinine level ($P < .01$). Diastolic blood pressure positively correlated ($P < .05$) with number of cups of coffee a patient drank per day. No correlation was found between systolic and diastolic blood pressure and alcohol, smoke, cholesterol, and triglyceride levels.

In 26% of patients a single antihypertensive medication

Table 3 Patients With Chronic Kidney Insufficiency: Clinical Characteristics, Lifestyle, and Biochemical Data

Age (y)	63 ± 14
Sex (male/female, %)	60/40*
Coffee %	91
Smoke %	66
Alcohol %	71
Body weight (kg)	71 ± 14
Plasma urea level (mg/dL)	89 ± 38
Serum glucose level (mg/dL)	92 ± 11
Serum creatinine level (mg/dL)	4.4 ± 2.7
Total cholesterol level (mg/dL)	218 ± 54
Triglyceride level (mg/dL)	175 ± 106
Serum sodium level (mEq/L)	141 ± 3
Serum potassium level (mEq/L)	4.6 ± 0.7
$U_{Na} \times V$ (mEq/24 h)	107 ± 59
$U_K \times V$ (mEq/24 h)	33 ± 14
C_{Cr} (mL/min)	37 ± 15
UAE	93 ± 107

Data are mean ± SD. N = 259.

$U_{Na} \times V$, urinary sodium excretion; $U_K \times V$, urinary potassium excretion; C_{Cr}, creatinine clearance; UAE, urinary albumin excretion.

*$P < .01$.

was prescribed; the most frequently prescribed medications were as follows ACEi (34%), calcium channel blockers (CCBB) (31%), and central acting agents (20%). Diuretics as a single antihypertensive drug were given to 9% of patients. Association therapy was prescribed in 74% of patients; the most frequent associations were as follows: ACEi and diuretics, ACEi and CCBB, and CCBB and diuretics. Two-drug regimen was found in 47% of patients. Among antihypertensive classes the most commonly prescribed medications were as follows: furosemide, enalapril, nifedipine (retard, gastro intestinal therapeutic system (GITS)), doxazosin, and clonidine.

Hypertensive Patients With Diabetes

There were 169 diabetic patients (10% of the screened population). Table 4 shows the clinical characteristics, habits, and biochemical data.

At study entry, no patient had systolic blood pressure less than 140 mm Hg and only 7% had diastolic blood pressure less than 90 mm Hg. At the last visit a systolic blood pressure of 140 mm Hg or less and a diastolic blood pressure of 90 mm Hg or less was attained in 27% and in 75% of hypertensive patients with diabetes, respectively. A significant negative correlation ($P < .01$) was found between diastolic blood pressure and age and between systolic blood pressure and creatinine clearance ($P < .05$). A positive correlation was observed between systolic blood pressure and age ($P < .01$) and serum creatinine ($P < .01$). No correlation was found between systolic and diastolic blood pressure and alcohol, smoke, cholesterol, and triglyceride level. Only 8.9% of patients had normal renal function (as creatinine clearance) and 18% of patients were without proteinuria.

In 27% of patients a single antihypertensive medication was prescribed; the most frequently prescribed medications were as follows: ACEi (47%), CCBB (37%), and doxazosin (11%). Association therapy was prescribed in 73% of patients; the most frequent associations were as follows: ACEi and CCBB, CCBB and diuretics, and ACEi and diuretics. Among antihypertensive classes, the most commonly prescribed were as follows: furosemide, enalapril, nifedipine (retard, gastro intestinal therapeutic system (GITS)), doxazosin, and clonidine.

Discussion

The data from the present study indicate that essential hypertensive patients represent a large part of hypertensive outpatients managed by nephrologists; thus, nephrologists are regarded as hypertension specialists also for nonuremic hypertensive patients. In addition, the study shows that (1) a large number of patients had alarming uncontrolled arterial blood pressure at study entry, and this was independent of the cause of hypertension; and (2) a better control of systolic and diastolic blood pressure was obtained in all categories of patients by nephrologists. Nevertheless, the latter statement deserves some further comments. Although the control of blood pressure was excellent in essential hypertensive patients, it was rather disappointing in hypertensive patients with reduced renal function and in diabetic patients. In fact, systolic blood pressure equal to or lower than 140 mm Hg was attained in 52% and diastolic blood pressure equal to or lower than 90 mm Hg in 75% of patients was attained. These results are impressive considering that the current control rate of essential hypertension (140/90 mm Hg) is 34%[3,5] and that the Healthy People Program 2010 has a goal of 50% of normalized blood pressure.[3] In contrast, equal results were not achieved in hypertensive patients with chronic renal failure and in diabetic patients. In both groups control rates of

Table 4 Patients With Diabetes: Clinical Characteristics, Lifestyle, Biochemical Data

Age (y)	64 ± 12
Sex (male/female; %)	53/47
Coffee %	82
Smoke %	32
Alcohol %	54
Body weight (kg)	75 ± 15
Plasma urea level (mg/dL)	87 ± 53
Serum glucose level (mg/dL)	156 ± 57
Serum creatinine level (mg/dL)	2.60 ± 1.9
Total cholesterol level (mg/dL)	228 ± 66
Triglyceride level (mg/dL)	202 ± 140
Serum sodium level (mEq/L)	140 ± 3
Serum potassium level (mEq/L)	4.6 ± 0.5
$U_{Na} \times V$ (mEq/24 h)	140 ± 81
$U_K \times V$ (mEq/24 h)	42 ± 24
C_{Cr} (mL/min)	45.3 ± 30.2
UAE	119 ± 133

Data are mean ± SD. N = 169.

$U_{Na} \times V$, urinary sodium excretion; $U_K \times V$, urinary potassium excretion; C_{Cr}, creatinine clearance; UAE, urinary albumin excretion.

systolic blood pressure were 29% and 27%, respectively; better results were obtained in controlling diastolic blood pressure (82% and 75%). These figures suggest that normalization of systolic blood pressure is less easy to achieve than diastolic blood pressure in uremic and diabetic patients. More prominent volume expansion and/or atherosclerosis may explain the poor control of systolic blood pressure. Independent from likely pathogenetic explanations, better control of systolic blood pressure is a crucial point. Systolic blood pressure is correlated more strongly with coronary heart disease, congestive heart failure, and mortality than diastolic blood pressure.[6-9] In addition, systolic blood pressure is a strong predictor of decrease in kidney function among middle-aged people.[6]

It also is important to note that some 10% of patients followed-up at nephrology clinics were diabetic patients. However, almost all diabetic patients had proteinuria and reduced renal function, indicating that they had been referred to nephrologists too late. The concomitant presence of proteinuria and reduced renal function indicates overt diabetic nephropathy, which hampers any effort to prevent or retard progression of renal insufficiency. Several studies have examined the possible association between late referral to nephrologists and outcomes in patients with chronic kidney disease; these studies have pointed out that late nephrologist referral is an independent risk factor for early death.[10,11] Early referral to nephrologists mostly is helpful for patients with initial renal impairment in whom the proper management of comorbid conditions may improve long-term outcomes, as is the case in diabetic patients in whom renal homodynamics are impaired long before the index changes of kidney function take place. But referral of diabetic patients shortly before the start of renal replacement therapy to nephrologists is quite common and represents a widespread problem,[12-15] as the data of present study seem to indicate.

This study clearly indicates a need for nephrologists to develop more effective strategies to improve the management of hypertension in patients with reduced renal function and in diabetic patients to prevent or retard the progression of renal insufficiency. This need is even more compelling considering the strict goal for blood pressure recently suggested for hypertensive patients with chronic renal failure and diabetic patients.[3] Finally, we must recommend that general practitioners and clinicians be more aggressive in their approach to hypertension and to refer diabetic patients and patients with chronic kidney insufficiency to nephrologists early in the course of disease.

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