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One-Year Renal and Cardiac Effects of Bisoprolol versus Losartan in Recently Diagnosed Hypertensive Patients

A Randomized, Double-Blind Study

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Abstract

Background and objectives: Hypertension is a significant cause of chronic renal injury and its effective treatment is capable of reducing the rate of renal failure. β-Adrenoceptor antagonists (β-blockers) have been reported to induce a deterioration in renal function, while several data have indicated a renoprotective effect of treatment with the angiotensin II type 1 receptor antagonist losartan. Previous studies of the interaction between the selective β_1-blocker bisoprolol and kidney function were performed only for short- and medium-term periods. The aim of this study was to compare the antihypertensive efficacy and renal and cardiac haemodynamic effects of bisoprolol with those of losartan over a 1-year time period in patients with essential hypertension.

Methods: Seventy-two patients (40 males) with recently diagnosed uncomplicated (European Society of Hypertension [ESH] criteria stage 1–2) hypertension (mean ± SD age 52 ± 12 years) were enrolled in the study. After a run-in period of 14 days on placebo, the patients were randomized in a double-blind, prospective study to receive either bisoprolol 5 mg or losartan 50 mg, administered once daily for 1 year. At recruitment and 12 months after treatment, cardiac output and renal haemodynamics and function were evaluated by echocardiography and radionuclide studies, respectively.

Results: There were no significant differences in baseline clinical data, including glomerular filtration rate and blood pressure, between the two treatment groups. At 1 year, blood pressure had decreased significantly ($p < 0.001$) with both treatments, and heart rate was reduced only in the group taking bisoprolol. The long-term effects on renal haemodynamics and cardiac function were similar with both drugs, the only change being a significant reduction in the filtration fraction for each group.

Conclusions: These data suggest that both bisoprolol and losartan are effective agents for the treatment of patients with recently diagnosed ESH stage 1–2 hypertension. Over a 1-year period, both agents maintained good renal and cardiac performance and haemodynamics.

Background

Hypertension is characterized by the progressive impairment of renal function related to the patient's age and severity of disease.[1-3] Experimental studies indicate that increased glomerular capillary pressure may be the major pathogenic factor underlying the development of glomerulosclerosis and renal impairment in patients with hypertension.[4,5] Ljungman and co-workers[6] have affirmed that patients with hypertension progress relatively slowly to kidney dysfunction when an effective antihypertensive treatment is used. β-Adrenoceptor antagonists (β-blockers) and angiotensin II type 1 (AT_1) receptor antagonists (angiotensin receptor blockers [ARBs]) comprise the more widely used classes of drugs in many cardiovascular (CV) diseases such as hypertension, coronary heart disease (CHD) and worsening heart failure (HF).[7] Non-selective β-blockers have been associated with a deterioration in renal function in patients with chronic renal failure.[8-10] Conversely, previous trials have demonstrated that selective β_1-blockers are effective antihypertensive drugs and have fewer adverse effects on renal function than non-selective β-blockers.[11,12] Bisoprolol, a highly selective β_1-blocker, is effective in reducing blood pressure (BP) and has favourable cardiac effects in patients with hypertension and HF.[13,14] However, few studies have investigated the interaction of bisoprolol with renal haemodynamics and any such studies have focused mainly on medium-term treatment.[15] On the other hand, ARBs have been shown to have favourable effects on renal haemodynamics in the treatment of essential hypertension. Indeed, various studies in humans suggest that these agents significantly protect against diabetic glomerulopathy and that they might maintain renal function by a mechanism other than simply lowering BP.[16,17] Losartan is the first ARB that has been extensively used in the treatment of hypertension.

In the light of this background, this study was designed to compare the efficacy and safety of long-term (12 months) administration of bisoprolol and losartan in relation to renal haemodynamics and cardiac function in recently diagnosed hypertensive patients (European Society of Hypertension [ESH] criteria stage 1–2)[18] and in particular to investigate the hypothesis that treatment with bisoprolol would be non-inferior to losartan in terms of preserving kidney function in patients without renal injury.

Patients and Methods

Patients

One hundred and three consecutive patients attending the hypertension centre of the Biomedical Department of Internal and Specialist Medicine at the University of Palermo, Palermo, Italy, were recruited from February to October 2006.

Inclusion criteria were a diagnosis of essential hypertension (ESH stage 1 or 2 hypertension) established by history and physical examination, together with the absence of clinical findings that would be suggestive of a secondary form of hypertension, according to ESH guidelines.[18] Exclusion criteria were: other cardiovascular diseases (defined as myocardial infarction or angina pectoris, heart block, valvular disease, heart failure and claudication); concomitant left ventricular hypertrophy (defined according to echocardiographic criteria); other target organ damage (including hypertensive retinopathy); micro- or macroalbuminuria or renal diseases, insulin-dependent or -independent diabetes mellitus, electrolyte imbalances, alcoholism and/or psychiatric

problems; currently taking antihypertensive drugs; and contraindications to β-blockers.

Each patient gave voluntary informed consent after receiving a detailed description of the study procedure. The study protocol was approved by the local medical ethics committee and carried out in accordance with the Declaration of Helsinki.

Study Protocol

Seventy-two patients (40 males, 32 females; aged from 29 to 63 years; mean ± SD age 52 ± 12 years) with recently diagnosed essential hypertension were assessed for eligibility and enrolled in the trial. The study profile is described in the CONSORT flow chart detailed in figure 1. After a 14-day run-in period on placebo, double-blind randomization was carried out using a computer algorithm designed prior to commencement of the study. Each patient was identified with an allocation number that was associated with treatment groups according to a computer-generated allocation schedule. The physicians were blinded to the treatment-associated allocation number. Patients were assigned to receive either bisoprolol 5 mg/day (36 patients) or losartan 50 mg/day (36 patients). Both drugs were given for 12 months at the same time each day, which varied from 7:00 to 8:00am. At the end of the run-in period and at the end of the treatment period (12 months), clinical characteristics were evaluated and renal haemodynamic, laboratory and biochemical tests were performed. In addition, BP was measured monthly; specifically, systolic (SBP) and diastolic (DBP) BP were measured in triplicate with a mercury sphygmomanometer after 5 minutes in a supine position. The Korotkoff phase V sound was used to determine DBP. Mean BP (MBP) was calculated as the sum of DBP plus one-third of the pulse pressure. Laboratory and instrument-based tests included: fasting blood glucose, sodium, potassium, chloride, urinary excretion of sodium (measured by the flame photometry method on 24-hour urine collection), serum creatinine and creatinine clearance (CL_{CR}) according to the Modification of Diet in Renal

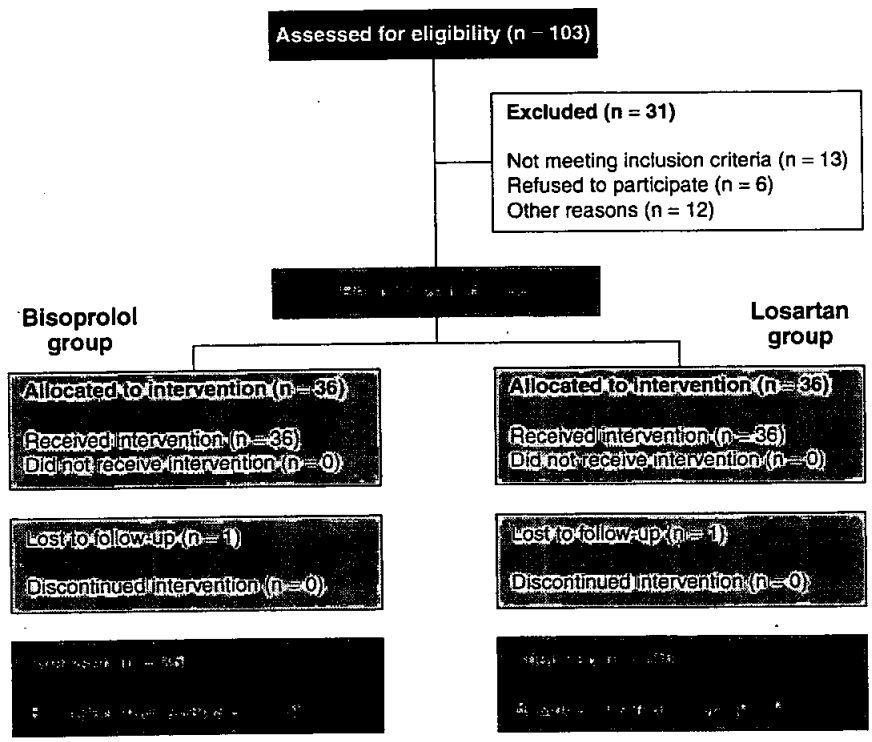

Fig. 1. CONSORT flow diagram for the study.

Disease (MDRD) formula, uric acid, chest x-ray, standard and ambulatory 24-hour ECG Holter recordings, 24-hour ambulatory BP monitoring (ABPM) and fundus oculi examination. If SBP or DBP remained above the BP target of 130/80 mmHg, hydrochlorothiazide 12.5 mg was administered.

ABPM was performed with a TM-2431® monitor (A&D, Tokyo, Japan). During ABPM, patients were allowed to continue their daily activities, including taking antihypertensive agents. The BP cuff was attached to the non-dominant arm, while the main monitor was attached to the waist. The ABPM data were obtained by the oscilloscopic method. The monitor was programmed to record BP every 15 minutes over a 24-hour period. The minimum criteria required to validate the recording were more than 60 successful readings from a total of 95 scheduled, with at least two efficient readings per hour. The device was removed after a minimum recording of 24 hours. Analysis of ABPM data collected from patients included: mean 24-hour SBP (SBP24), mean 24-hour DBP (DBP24), daytime mean SBP (DSBP), daytime mean DBP (DDBP), night-time mean SBP (NSBP), and night-time mean DBP (NDBP).

Ambulatory Holter ECG recordings were obtained from all patients using an Oxford two-channel or three-channel digital recorder (Oxford Instruments, Abingdon, UK; range 20–24 hours) with manual overhead by an experienced nurse. At least 20 hours of artefact-free recording time was required for patients to be eligible for this study. Analysis of data collected from patients included maximum, minimum and 24-hour mean heart rate (HR).

Renal haemodynamics were evaluated at baseline and after a 12-month follow-up period by radioisotope study, according to methods described by Schlegel and Haway[19] and Gates[20] that have been previously validated in our laboratory.[21-24] Effective renal plasma flow (ERPF; mL/min), effective renal blood flow (ERBF; [ERPF/(1 – haematocrit)]; mL/min), glomerular filtration rate (GFR; mL/min), and filtration fraction (FF; [GFR/ERPF; %]) were calculated using radioisotope techniques. Renal vascular resistance (RVR) was also calculated by the formula $RVR = MBP \times 80/ERBP$ dynes • sec • cm^{-5}. We used a non-invasive radionuclide technique as this is preferable to traditional methods utilized to evaluate ERPF or GFR. Isotopic methods can estimate GFR or ERPF without blood or urine samples. These techniques permit determination of measurements separately for each kidney and obtain values for global renal function. The accuracy and readability of this technique in the evaluation of global renal function or unilateral kidney function have been well reported.[18,19,21]

Transthoracic echocardiography was carried out at recruitment and after the treatment period of 12 months according to the standard procedure using a General Electric Vivid 7® Dimension.[25] Ejection fraction (EF) was obtained according to the modified Simpson rule, which uses two cross-sectional views (four- and two-chamber apical views). Cardiac output (CO) was derived from the formula: stroke volume (CSA LVOT × VLVOT) × HR, where CSA is cross-sectional area, LVOT is left ventricular outflow tract and V is the velocity integral of LVOT. Assuming a circular shape, the CSA LVOT was calculated as: $3.14 \times (D/2)^2$, where D is the inner diameter of the LVOT. VLVOT was obtained from use of pulsed-wave Doppler in the LVOT proximal to the aortic valve from the apical five-chamber view.

Two observers, blinded to the clinical and ECG data, evaluated the two-dimensional echocardiographic images. When there were discrepancies, the two-dimensional echocardiographic images were again reviewed, and a decision was made by consensus; the mean of three measurements was used. The inter- and intra-observer coefficients of variation were 4% and 3%, respectively.

Statistical Analysis

The statistical analysis was performed by MedCalc® version 9.2.0.1 statistical software (MedCalc Software, Mariakerke, Belgium). Comparisons between baseline and end-of-treatment measurements were analysed by the t-test for paired data. The difference in SBP and DBP

between the treatment groups was analysed by the t-test for unpaired data. A p-value < 0.05 was considered statistically significant. All data are expressed as mean ± SD values. Sample size was calculated based on a non-inferiority hypothesis of the upper one-sided 98% boundary for the relative risk decrease in GFR for losartan versus bisoprolol. This boundary was chosen on the basis of the findings of previous studies[26] that consistently showed the benefit of losartan relative to placebo for decreasing GFR by about 10% or less. The sample size calculation was based on a β-value of 0.20 (80% power) and an α-value of 0.05. The maximum sample size obtained for this variable was 31 per group and this number was assumed as the minimum number for this study as well.

Results

All results are summarized in the accompanying tables and figures. Tables I and II show the clinical characteristics of patients at recruitment and after the 12-month follow-up period. Only two patients (one in each group) were lost to follow-up and none discontinued treatment. Age and sex ratios revealed no differences in distribution in groups taking bisoprolol or losartan. No significant differences were observed between the groups for any variable before treatment. The GFR measurements were similar with both methods (the MDRD equation and the radionuclide study). Treatment with bisoprolol and losartan significantly reduced SBP and DBP ($p < 0.001$) according to both office visit BP measurements (table I, figure 2) and 24-hour BP monitoring (table II). The BP target of <130/80 mmHg was obtained in 30 patients (86%) in the bisoprolol group and in 28 patients (80%) in the losartan group. A significant difference ($p < 0.01$) was observed between the two treatment groups in favour of bisoprolol for DBP (table I). A significant reduction ($p < 0.001$) in HR was observed in the bisoprolol group. Administration of hydrochlorothiazide 12.5 mg to achieve the BP target of 130/80 mmHg was necessary in only seven and five patients, respectively, in the bisoprolol and losartan groups. The numerical difference between the two groups in patients who received a diuretic was not statistically significant.

Table I. Clinical characteristics and biochemical measurements at baseline and at 1-year follow-up after administration of bisoprolol or losartan[a]

Characteristic	Losartan		Bisoprolol	
	baseline	1-year follow-up	baseline	1-year follow-up
Age (y)	51 ± 12		49 ± 11	
Sex (M/F) [no.]	19/17		21/15	
Height (cm)	166 ± 9		169 ± 10	
Weight (kg)	78 ± 15	77 ± 13	77 ± 16	76 ± 14
HR (beats/min)	84 ± 8	82 ± 6	81 ± 5	66 ± 4*
SBP (mmHg)	154 ± 16.5	128 ± 12*	156 ± 15.5	127 ± 12*
DBP (mmHg)	92.1 ± 11.6	79.3 ± 8.4*	94.7 ± 10.6	75.3 ± 8.8*,†
FBG (mg/dL)	91 ± 9	89 ± 7	89 ± 8	92 ± 9
BUN (mg/dL)	37 ± 10	38 ± 9.2	36 ± 8	35 ± 9.1
Creatinine (mg/dL)	0.80 ± 0.23	0.82 ± 0.24	0.85 ± 0.21	0.83 ± 0.22
CL_{CR} (mL/min/1.73 m²)	121.4 ± 31	111.2 ± 30	117.5 ± 29.4	109.5 ± 31.7
Uric acid (mg/dL)	4.7 ± 1.5	4.4 ± 1.4	4.5 ± 1.6	4.7 ± 1.5
Na^+ (mmol/L)	142 ± 2.3	143 ± 2.5	141 ± 1.8	140 ± 2.3
K^+ (mEq/L)	4.4 ± 0.6	4.8 ± 0.4	4.5 ± 0.7	4.3 ± 0.6
Haematocrit (%)	43.6 ± 3.1	43 ± 3.94	43.8 ± 3.3	42 ± 3.7

a Values are given as mean ± SD unless specified otherwise.

BUN = blood urea nitrogen; **CL_{CR}** = creatinine clearance; **DBP** = diastolic blood pressure; **FBG** = fasting blood glucose; **HR** = heart rate; **NS** = nonsignificant; **SBP** = systolic blood pressure. * $p < 0.001$ vs baseline; † $p < 0.01$ vs losartan.

Table II. Blood pressure (BP) and heart rate average measurements assessed by ambulatory BP measurement and 24-hour ECG Holter monitoring[a]

Variable	Losartan			Bisoprolol		
	baseline	1-year follow-up	p-value	baseline	1-year follow-up	p-value
24-h SBP (mmHg)	144±9.1	124.2±10	<0.001	146.4±8.9	123.1±9.2	<0.001
24-h DBP (mmHg)	88.2±7.9	74.5±10.1	<0.001	87.4±9.8	72.5±8.9	<0.001
DSBP (mmHg)	147±10.1	129.4±11.1	<0.001	151±10.9	128.2±10.2	<0.001
NSBP (mmHg)	137±8.9	120±10.5	<0.001	137±9.2	119±11	<0.001
DDBP (mmHg)	91±9.2	78.7±9.4	<0.001	92±8.6	76.8±9.4	<0.001
NDBP (mmHg)	80±8.1	70.4±9.2	<0.001	79±8.7	70.2±9.9	<0.001
MaxHR (beats/min)	93.8±7.2	90±0.8.4	NS	92.5±7.8	77.4±9.4	<0.001
MinHR (beats/min)	67.1±6.5	65±0.4.4	NS	66.4±5.2	58.2±4.6	<0.01
Mean HR (beats/min)	83.8±9.1	80.1±9.5	NS	82.4±8.5	68.6±9.5	<0.001

a Values are given as mean±SD.

(D)(N)DBP = (daytime)(night-time) diastolic BP; **(D)(N)SBP** = (daytime)(night-time) systolic blood pressure; **HR** = heart rate; **Max** = maximum; **Min** = minimum; **NS** = nonsignificant.

Renal and cardiac function (including GFR calculated by the MDRD equation, proteinuria, EF and CO) were unchanged after 12 months of treatment in both groups. A slight increase in ERPF and a slight decrease in GFR were observed but values remained within the normal range except for a reduction in FF with both treatments; this was more marked in the losartan group ($p<0.001$) than in the bisoprolol group ($p<0.05$) [table III].

Discussion

Despite concerted efforts, BP is generally considered today to be poorly controlled. The relative risk of serious renal damage in uncontrolled essential hypertension is low compared with other CV complications. Nevertheless, given the huge prevalence of hypertension in the general population, the condition remains the second leading cause of end-stage renal disease.[27] To our knowledge, ours is the first study indicating that long-term treatment with bisoprolol is as effective as losartan, not only in controlling BP, but also in maintaining renal function in hypertensive patients. The sustained BP control in hypertensive patients treated with bisoprolol observed in this study is consistent with previous reports, and may be explained by the following haemodynamic effects: (i) a blocked increment in CO and a modest block of peripheral vascular resistance in hypertensive patients with high CO; and (ii) a peripheral vascular dilatation in patients

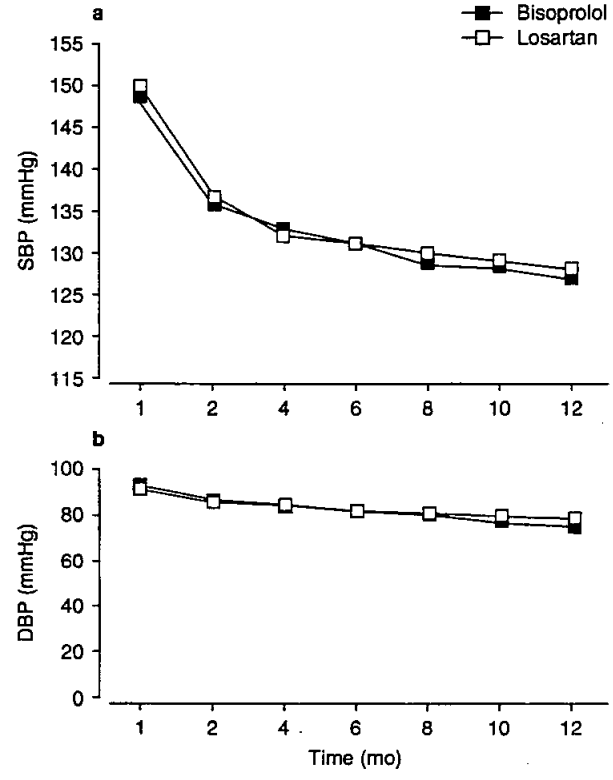

Fig. 2. Mean systolic (SBP) [a] and diastolic (DBP) [b] blood pressure values before and during 12 months of bisoprolol or losartan administration. Significant differences ($p<0.001$) for 12-month vs baseline measurements were seen for both SBP and DBP with both agents.

Table III. Effects of administration of either bisoprolol or losartan on renal and cardiac haemodynamic parameters in both groups[a]

Parameter	Losartan			Bisoprolol		
	baseline	1-year follow-up	p-value	baseline	1-year follow-up	p-value
GFR (mL/min)	131.3±38	119.1±39	NS	129.2±32.4	119.5±30	NS
ERBF (mL/min)	757±214	787±265	NS	747±125	753±167	NS
ERPF (mL/min)	519±99	569±112	NS	520.1±103	526.4 ±21	NS
FF (%)	25.2±5	20.9±6	<0.001	24.8±5	22.7±4	<0.05
RVR (dynes • sec • cm^{-5})	13.4±3.2	12.2±3.1	NS	12.8±1.9	12.1±2.1	NS
EF (%)	58.6±31	59.1±32	NS	60.8±33	60.3±32	NS
EDD (mm)[b]	50.3±8.3	49.4±8.1	NS	49.5±7.5	50.1±8.9	NS
ESD (mm)[b]	31.7±2.3	32.4±2.1	NS	30.6±2.2	32.1±2.1	NS
CO (L/min)	5.63±2.13	5.67±2.16	NS	5.46±2.34	5.39±2.26	NS

a Values are given as mean±SD.

b Measured in order to calculate EF.

CO = cardiac output; **EDD** = end-diastolic diameter; **EF** = ejection fraction; **ERBF** = effective renal blood flow; **ERPF** = effective renal plasma flow; **ESD** = end-systolic diameter; **FF** = filtration fraction; **GFR** = glomerular filtration rate; **NS** = nonsignificant; **RVR** = renal vascular resistance.

with high peripheral vascular resistance but low or normal CO.[28-33] However, the unchanged CO and EF at the end of the study indicate that the long-term antihypertensive effect of bisoprolol might be due to a reduction in sympathetic nervous activity, thereby inducing peripheral vascular dilatation rather than a negative inotropism. This mechanism has been partially explained by intrinsic sympathomimetic activity, blockade of calcium channels and α-adrenoceptors, inhibition of basal and stimulated renin activity, and release of endothelium-derived nitric oxide release.[34] Conversely, the effectiveness of losartan in reducing BP is linked to inhibition of the cascade effects of angiotensin II by blockade of AT_1 receptors, and this has been widely demonstrated in clinical studies.[35] In our study, bisoprolol had a greater effect on DBP than losartan. We speculate that this beneficial effect is due to a reduction in central BP and arterial stiffening.

The favourable renal and cardiac effects that occurred during treatment with bisoprolol were similar to those observed with losartan, with no changes in laboratory and radionuclide parameters of renal function (GFR, ERBF, ERPF and RVR), or in cardiac performance, being observed. However, bisoprolol decreases systolic BP and HR, suggesting a reduction in double product. This would mean that cardiac haemodynamics change without significant decreases in CO and cardiac function. Indeed, because of the decrease in HR, left ventricular filling consequently increases, resulting in no significant changes in CO. For this reason, renal perfusion is preserved during long-term treatment with bisoprolol.

Our results agree with those of basic studies in rats and humans that have documented positive renal and central haemodynamic effects during short-term administration of bisoprolol resulting in a significant improvement in glomerulosclerosis and diminution of arterial damage.[36-38] However, these results do not agree with other findings of significant reductions in renal function (GFR, para-aminohippuric acid clearance, sodium clearance), urine volume and plasma renin activity in patients with hypertension treated with intravenous bisoprolol.[39]

In our current study, the renal changes observed were associated with a reduction in CO and HR and an improvement in systemic vascular resistance. However, renal mechanisms are probably involved in the effects of losartan as well as those of bisoprolol, modulating the glomerular filtration barrier and maintaining effective renal circulatory autoregulation. A particular ability of the kidney is to maintain constant renal blood flow (RBF), GFR and glomerular capillary pressure. The latter is a function of the balance between afferent and efferent vascular

resistance.[40] Prolonged reduction of glomerular capillary pressure and RVR by antihypertensive treatments has been demonstrated to attenuate glomerular degeneration, thereby preserving renal function.[41] However, these antihypertensive effects (decreases in RVR and glomerular capillary pressure and an increase in RBF) imply that, in order to maintain a stable GFR, the autoregulation set point will be reset toward lower BP.[42,43] Moreover, the non-significant decrease in RVR at the end of this study indicated that various pleiotropic mechanisms of these agents (such as an action on the bradykinin system by inhibiting renin release) might mitigate the fall in RVR over the long term. Furthermore, we observed a decreased FF in both treatment groups, and this was more significant in patients treated with losartan. FF is an indirect measure of glomerular capillary pressure and is attributable to the mild increase in ERBF and the small reduction in GFR with a concomitant decrease in efferent arteriolar resistance. Thus, high FF and glomerular capillary pressure are associated with the genesis of glomerulosclerosis, and this deleterious effect may in part be mediated through the synthesis of several growth factors, such as transforming growth factor-β_1, angiotensin II and endothelin-1.[44] The decline in FF and glomerular capillary pressure could be indicative of a positive prognosis for renal function. The significant, albeit modest, reduction in FF observed in this study is consistent with the finding in comparative studies that FF declines during treatment with other renin-angiotensin system (RAS) antagonists and could also explain the effects of bisoprolol on the RAS over the long term.[17,45] As hydrochlorothiazide was added to treatment in only a few patients during follow-up, we suggest this addition did not influence cardiac and renal haemodynamics.

Lastly, it is known that the early stage of renal disease is characterized by glomerular hypertrophy, focal segmental glomerulosclerosis, podocyte proliferation and altered glomerular haemodynamics, resulting in a decreased number of filtration slits.[46] Indeed, renoprotection provided by ARBs is not only related to lowered BP and inhibition of the RAS, but also to other mechanisms linked to ultrastructural remodelling of the kidney (decreased oxidative stress, correction of chronic hypoxia, inhibition of advanced glycation end-product formation, abnormal iron deposition in the interstitium, reduced proteinuria, and beneficial ultrastructural changes in the glomerulus).[46-48] However, previous studies have demonstrated that β-blockers seem to be at least as renoprotective as ARBs with regard to podocyte preservation, glomerular basement membrane ultrastructure and prevention of glomerular and tubulo-interstitial damage.[49] In addition, the renal haemodynamic effects and absence of adverse effects in hypertensive patients treated with bisoprolol may be linked to high β_1-adrenoceptor selectivity, since inhibition of the presynaptic β-adrenoceptor results in inhibition of the release of noradrenaline, renin, angiotensin II and aldosterone. This theory is supported by studies that have demonstrated a lack of occupancy of β_2-adrenoceptors by bisoprolol together with pleiotropic effects of the drug on the RAS and the glomerular membrane.[32,36] The magnitude of suppression of angiotensin II levels by β-blockers is comparable to that produced by ARBs.[49] However, by reducing the processing of pro-renin into renin, β-blockers (unlike ARBs) do not stimulate renin secretion. This unique action has important implications in the treatment of CV disease.[49]

A possible limitation of this research is the relatively small sample size of selected patients. However, our findings are particularly encouraging and should serve as a basis for future research, which should include larger samples, aimed at enhancing the safety of first-line management of hypertensive patients, particularly their renal and cardiac functions, with bisoprolol.

Conclusions

This study evaluated whether long-term treatment with bisoprolol or losartan may worsen kidney function in patients without renal injury and whether the effects of the two agents on the kidney may be comparable. Our results provide additional information regarding the utility of bisoprolol in preventing renal damage and

further decline, thereby preventing hypertensive nephropathy. Bisoprolol is more effective in BP control in that it achieves tighter control of DBP than losartan, and it can be a useful therapeutic option in the management of recently diagnosed hypertensive patients (ESH stage 1–2). Moreover, this study has confirmed that the effectiveness of the two drugs in maintaining renal function and haemodynamics is similar, with no significant influence on EF and CO over the long term. Providing further valuable data about the effects of selective β_1-blockers,[50] these results are indicative of the role of bisoprolol in the preservation of kidney function in patients with hypertension. While a possible limitation of this research is the relatively small sample size of selected patients, our findings are particularly encouraging and should serve as a basis for future research to confirm these data. Further prospective randomized and larger long-term studies of bisoprolol, aimed at improving the safety of first-line management of hypertensive patients, particularly with respect to renal and cardiac function, are warranted.

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