European Review for Medical and Pharmacological Sciences 2010; 14: 427-434

Nebivolol/Hydrochlorothiazide (HCTZ) combination in patients with essential hypertension: a pooled analysis from five non-interventional studies with a focus on diabetic and elderly patients

E. MALACCO

III Division of Internal Medicine, "L. Sacco" Hospital, Milan (Italy)

Abstract. – *Background and Objectives:* **Nebivolol is a third-generation beta-blocker, characterized by unique pharmacological properties. The combination of nebivolol and hydrochlorothiazide (HCTZ) has been evaluated in large-scale clinical trials. This post-marketing surveillance analysis evaluated the effectiveness of the nebivolol/HCTZ combination in a "real-life" setting that included diabetic and elderly patients.**

Patients and Methods: **The analysis was based on data from five non-interventional studies conducted in Germany, which lasted up to 12 weeks. Data from patients treated with nebivolol/HCTZ 5/12.5 mg/day in combination were pooled. The following parameters were calculated at the final visit, in the whole population and in elderly (>70 years) and diabetic subgroups: (1) difference from baseline in diastolic blood pressure (DBP) and in systolic blood pressure (SBP); (2) percentage of responder patients (reduction in DBP or SBP of 10 or 20 mmHg, respectively). Alterations in laboratory parameters were also monitored.**

Results: **In total, 86 patients (mean age 58.9±10.8 years) were included in the analysis. Nebivolol/HCTZ significantly reduced both DBP (–11.8±7.9 mmHg; $p<0.0001$ vs baseline) and SBP (–22.5±13.5 mmHg; $p<0.0001$ vs baseline). In total, 81.4% of patients were responders (75% and 83.3% in elderly and diabetic patients, respectively). No clinically significant alterations in laboratory parameters were observed.**

Discussion: **This study confirms that nebivolol/HCTZ is an effective and well tolerated therapeutic strategy in a real-life setting as well as in clinical trials. Therefore, this combination may represent a first-choice therapy in the management of hypertension.**

Key Words:

Hypertension, Nebivolol, Hydrochlorothiazide, Combination therapy.

Introduction

Hypertension, defined as blood pressure (BP) ≥140/90 mmHg, is widely accepted as a major and independent risk factor for cardiovascular morbidity and mortality[1]. The results of a meta-analysis of many observational studies have shown a positive correlation between hypertension and the incidence of cerebro- and cardiovascular disease[2]. Therefore, reducing BP is a major goal in the prevention of these events as it has been demonstrated that even a small decrease in BP is associated with a lower incidence of cardiovascular disease[2].

Antihypertensive therapies provide substantial benefits in controlling hypertension[1]. Patients treated with an antihypertensive therapy achieve up to a 30-40% reduction in the rate of fatal and non-fatal strokes, and a 20% reduction in the rate of coronary events, when compared to untreated subjects with hypertension[1]. On this basis, the current guidelines of the European Society of Hypertension/European Society of Cardiology (ESH/ESC) have stressed the importance of an early initiation of the antihypertensive treatment, in order to reach a target BP value of ≤140/90 mmHg[1]. The target is lower in high-risk patients, such as those with diabetes and the elderly, as a lower BP is associated with further benefits in the reduction of cardiovascular mortality and morbidity in these higher risk populations[1].

Despite the availability of several different classes of antihypertensive agents, the proportion of patients achieving adequate BP control following monotherapy is not ideal. It has been calculated that less than 50% of patients achieve a reduction in diastolic BP (DBP) ≥10 mmHg, and

Corresponding Author: Ettore Malacco, MD; e-mail: ettore.malacco@tiscali.it.

only 20-30% of subjects achieve optimal BP control[1,3]. Therefore, in many patients a combination therapy is required to reach target BP values[1]. Current ESH/ESC guidelines have suggested that a combination of two antihypertensive drugs may be an effective approach not only in patients not responding to monotherapy, but also in subjects with multiple risk factors[1].

In particular, the combination of a beta-blocker and hydrochlorothiazide (HCTZ) is widely used in clinical practice and is associated with a large reduction in the incidence of cardiovascular events, as demonstrated in placebo-controlled trials and meta-analyses[4-6]. The combination of third generation beta-blockers with HCTZ is considered by ESH/ESC to have less or no dysmetabolic action compared with classical beta-blockers, so they can be considered a valid option for initial and subsequent antihypertensive treatment strategies[1].

Nebivolol is a third-generation beta-blocker with unique characteristics that is clinically administered as a racemic mixture of *d*- and *l*-enantiomers that have different pharmacological activities[7-11]. Nebivolol is a new lipophilic, selective $beta_1$-adrenoceptor antagonist that also has endothelial nitric-oxide (NO) mediated vasodilatory activity, and has been approved for the treatment of hypertension in the US[12] and for hypertension and chronic heart failure in Europe.[13] Nebivolol exerts its vasodilatory effects via the activation of the L-arginine/NO pathway[8,10,14]. Endothelial-derived NO acts through the enhancement of cyclic guanosine monophosphate and thereby influences cardiac contractility[15]. Nebivolol has proven BP-lowering capability and results of dose-finding studies have shown that nebivolol 5 mg/day is optimal for the antihypertensive treatment[7,16,17].

Nebivolol, as monotherapy or in combination with other antihypertensive medications, produces significant BP reductions in patients with hypertension[18,19]. In clinical studies, performed in the US, different dosages were used, depending on BMI and ethnicity. In one large, multicenter placebo-controlled study (n>600)[18] the addition of nebivolol 5-20 mg/day to existing antihypertensive therapy resulted in significant reductions in baseline BP following 12 weeks' treatment ($p \leq 0.015$ versus baseline)[18]. A significantly greater proportion of patients achieving treatment response was observed with nebivolol than placebo (53.0-65.1% vs 41.3%; $p \leq 0.028$) and nebivolol was associated with significantly better BP control rates (41.3-52.7% vs 29.3%; $p \leq 0.029$)[18].

The efficacy and safety of a combination of nebivolol and HCTZ were assessed in several interventional studies[16,17,20]. These trials have shown the marked BP-lowering effect of this combination, but were conducted in an experimental setting. Therefore, a further evaluation of the effectiveness of the nebivolol/HCTZ combination in a real-life scenario may be of particular interest.

On this basis, this study evaluates the antihypertensive efficacy of nebivolol/HCTZ 5/12.5 mg/day combination therapy, via a pooled analysis of several non-interventional post-marketing studies conducted in a real-life setting, in a high risk population that included diabetic and elderly patients.

Patients and Methods

Analysis Design and Population

This pooled analysis is based on the results of a series of non-interventional post-marketing studies conducted in Germany between 2002 and 2007. The studies were selected according to the following criteria: (1) outpatients with essential hypertension treated with nebivolol, at various dosages, and followed by a general practitioner; (2) patient surveillance between 6 and 12 weeks; (3) analysis and report provided by GKM Gesellschaft für Therapieforschung mbH, a midsize, independent, full-service contract research organization for the pharmaceutical industry and for manufacturers of medical devices and food supplements (see http://www.gkm-therapieforschung.de/enUK/home/index.htm). According to these criteria, five studies were selected. In total, 262 patients were being treated with nebivolol/HCTZ combination therapy. Among these patients, data regarding diabetic and elderly patients treated with the combination of nebivolol/HCTZ 5/12.5 mg/day were pooled and analyzed in the present analysis. Patients with missing data were excluded.

Evaluation Parameters

Patients were visited by their own general practitioner at baseline and at the end of the study period (6 or 12 weeks, according to the specific design of each study). At each visit, BP was measured with a standard sphygmomanometer.

The following parameters were evaluated: (1) difference in diastolic blood pressure (DBP) and in systolic blood pressure (SBP) from baseline to the final visit; (2) percentage of responder patients (defined as experiencing a reduction in DBP or SBP of 10 or 20 mmHg, respectively) at the final visit.

The safety of the combination was assessed by monitoring the alterations in glycaemia and in lipid profile from baseline to the final visit using standard laboratory measurements.

Data Analysis

Data were analyzed with descriptive statistics. The comparison between baseline and final data, and between patients receiving nebivolol/HCTZ for 6 and for 12 weeks, was conducted by the analysis of covariance. Statistical analysis was conducted with SAS® software, version 9.1 [SAS Institute Inc., Cary, NC, USA]).

Results

Analyzed Population

In total, 86 patients (39 males; mean age 58.9±10.8 years), taking nebivolol/HCTZ 5/12.5 mg/day, were included in this analysis. Baseline characteristics of the entire population are reported in Table I. Most patients (n=63; 73.3% of the entire population) had initiated nebivolol as a first therapy. Only six patients were being treated with concomitant medications (digitalis glycoside, bile acid sequestrant, inhibitor of production of uric acid, bisphosphonate, platelet aggregation inhibitor, and opioid, respectively). Seventy-three subjects (84.9% of the entire population) were included in studies that were 6 weeks in duration. Among the evaluated patients, 20 subjects were aged >65 years, and 24 were diabetics. Baseline characteristics of these subgroups are summarized in Table I.

Effect on BP

BP lowering in patients treated with nebivolol/HCTZ for 6 weeks (n=73) was similar to that observed in subjects treated for 12 weeks (n=13) [6 weeks: –11.7 mmHg and –23.0 mmHg for DBP and SBP, respectively; 12 weeks: –12.4 mmHg and –19.7 mmHg for DBP and SBP, respectively; p=0.1 between the groups]. This may allow pooling of data in patients taking nebivolol for different durations of the therapy.

Therefore, the analysis of the *whole population* (n=86) revealed that the combination of nebivolol/HCTZ 5/12.5 mg/day produced a significant reduction in both DBP (–11.8±7.9 mmHg; p<0.0001 vs baseline) and SBP (–22.5±13.5 mmHg; p<0.0001 vs baseline) when compared with baseline (Figure 1). If expressed as percentages, the reductions from baseline were 12.4% (DBP) and 14.1% (SBP) [Figure 2].

In *elderly patients* (n=20), nebivolol/HCTZ 5/12.5 mg/day combination therapy produced significant reductions versus baseline values in both DBP (–11.0±8.4 mmHg; p<0.0001) and SBP (–22.5±13.6 mmHg; p<0.0001) [Figure 1].

Table I. Baseline characteristics of the study population and of elderly and diabetic patient subgroups. Data are expressed as mean ± SD and in percentage.

	Whole population (n = 86)	Elderly patients (n = 20)	Diabetic patients (n =24)
Age, years	58.9 ± 10.8	73.2 ±7.2	58.0 ±9.9
Male, number (%)	39 (45.3)	6 (30.0)	39 (37.5)
Height, cm	169.7 ± 9.4	167.6 ± 7.8	168.6 ± 9.4
Weight, kg	81.4 ± 15.0	76.3 ± 11.3	81.5 ± 11.5
Heart rate, bpm	79.7 ± 9.9	79.8 ± 10.2	79.7 ± 11.3
DBP, mmHg	95.2 ± 9.1	93.3 ± 8.5	97.9 ± 8.7
SBP, mmHg	159.4 ± 16.3	161.9 ± 20.8	156.6 ± 10.1
Diabetic subjects, number (%)	24 (27.9)	6 (30.0)	24 (100)
Nebivolol/HCTZ as a first therapy, number (%)	63 (73.3)	16 (80.0)	12 (50.0)
Observation period of 6 weeks, number (%)	73 (84.9)	18 (90)	11 (45.8)

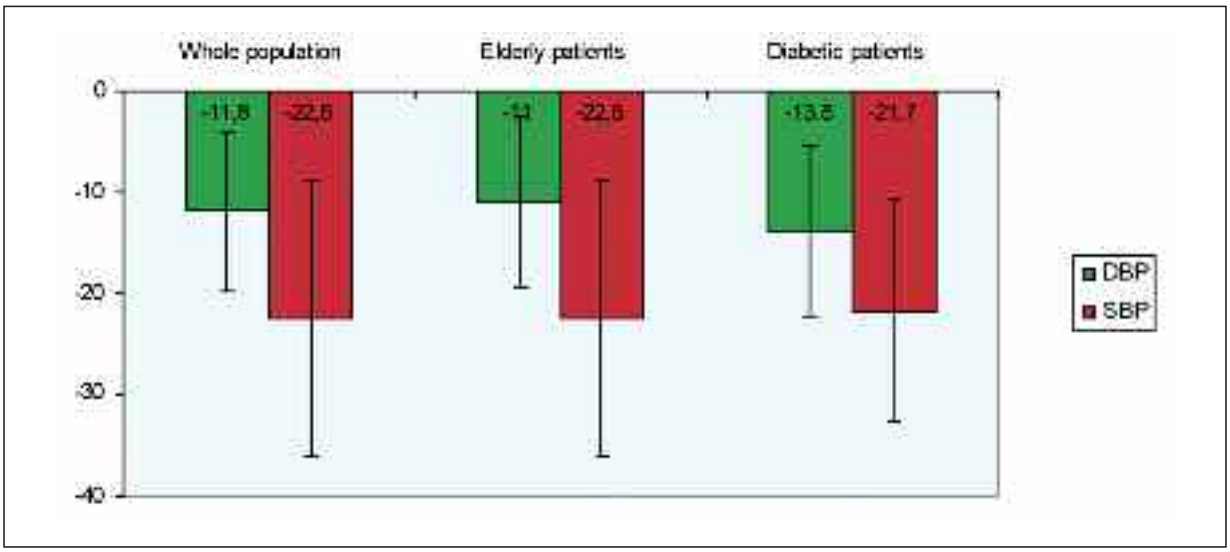

Figure 1. Variation in diastolic blood pressure (DBP) and systolic blood pressure (SBP) at the final visit versus baseline values, in the whole population (n=86), elderly patients (n=20) and diabetic patients (n=24). $p<0.0001$ vs baseline for all comparisons.

The percentage reductions were 11.8% in DBP and 13.9% in SBP (Figure 2).

When considering *diabetic patients* (n=24), the reductions in DBP and SBP were –13.8±8.4 mmHg and –21.7±10.9 mmHg, respectively ($p<0.0001$ vs baseline for both comparisons [Figure 1]. The percentage reductions were 14.1% (DBP) and 13.9% (SBP) [Figure 2].

The percentage of responders after nebivolol/HCTZ administration in the *whole population* (n=86) is 81.4% (Figure 3). Responders comprised 75% of the *elderly* group and 83.3% of the *diabetic* population (Figure 3).

Safety Evaluation

No clinically significant differences in glycaemia and lipid profiles were seen with nebivolol/HCTZ 5/12.5 mg/day combination therapy. Baseline and final values for all parameters evaluated are shown in Figure 4. Overall,

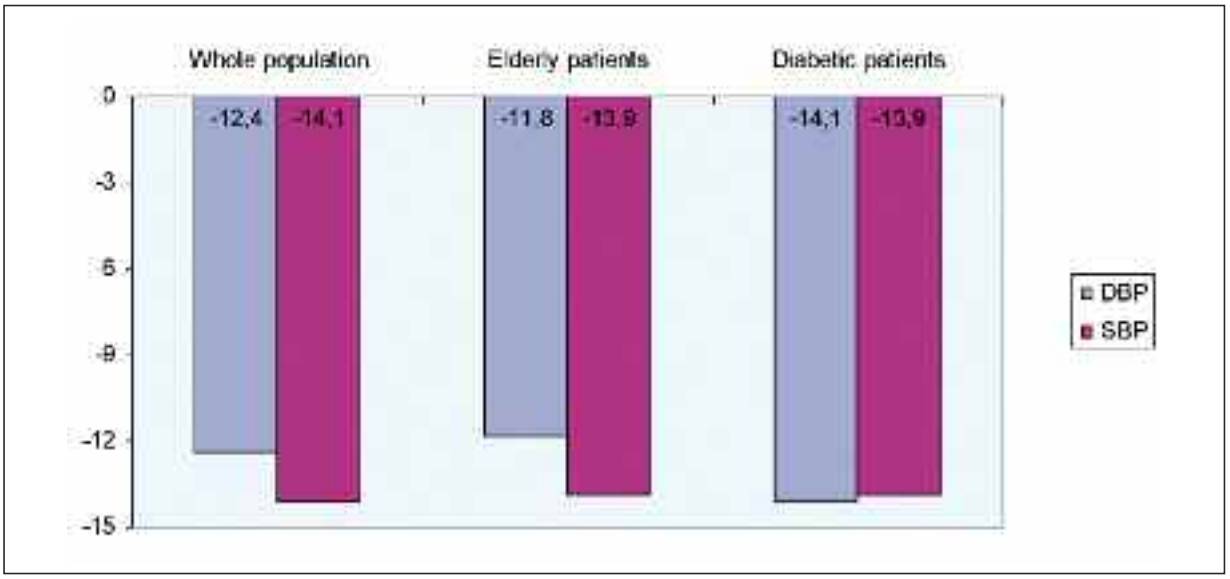

Figure 2. Percentage variation in diastolic blood pressure (DBP) and systolic blood pressure (SBP) at the final visit versus baseline values, in the whole population (n=86), elderly patients (n=20) and diabetic patients (n=24).

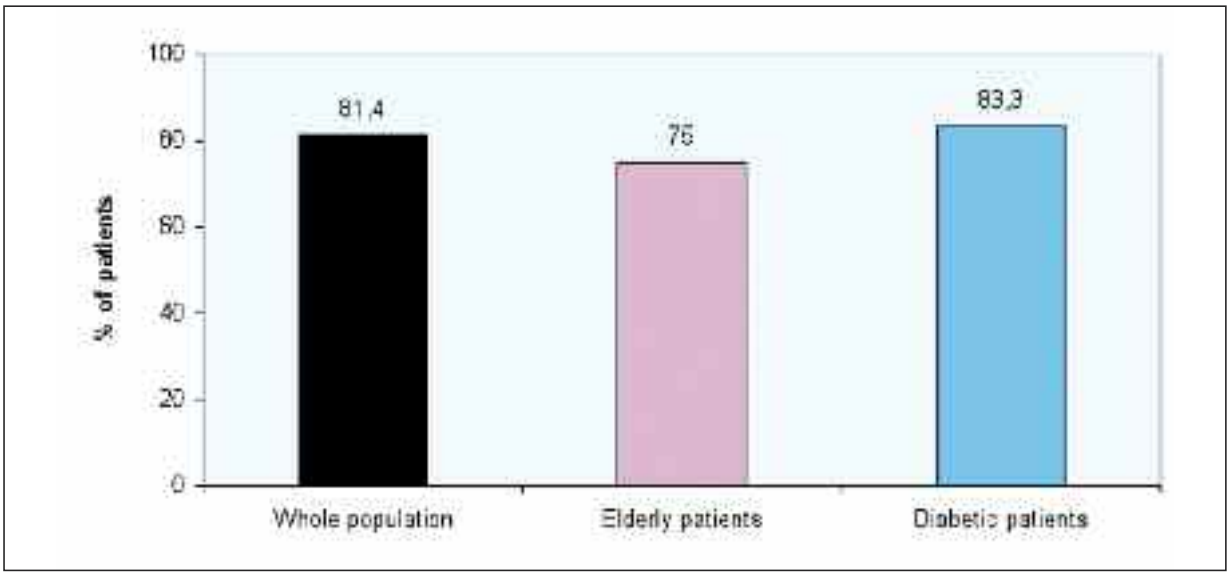

Figure 3. Proportion of responder patients (reduction from baseline in DBP pressure or SBP equal to 10 and 20 mmHg, respectively) at the final visit, in the whole population (n=86), elderly patients (n=20) and diabetic patients (n=24).

these results were similar to those observed in the elderly and diabetic patient subgroups (data not shown).

Discussion

The results of this pooled analysis of post-marketing studies, conducted in a real-life setting, indicate that the administration of the combination nebivolol/HCTZ 5/12.5 mg/day produces a significant reduction (between 10% and 15%) in BP in hypertensive patients. Moreover, the effect of the nebivolol/HCTZ combination was observed after 6 weeks of treatment and was maintained for up to 12 weeks. Such BP lowering is likely to be associated with a clinically important reduction in the incidence of cardiovascu-

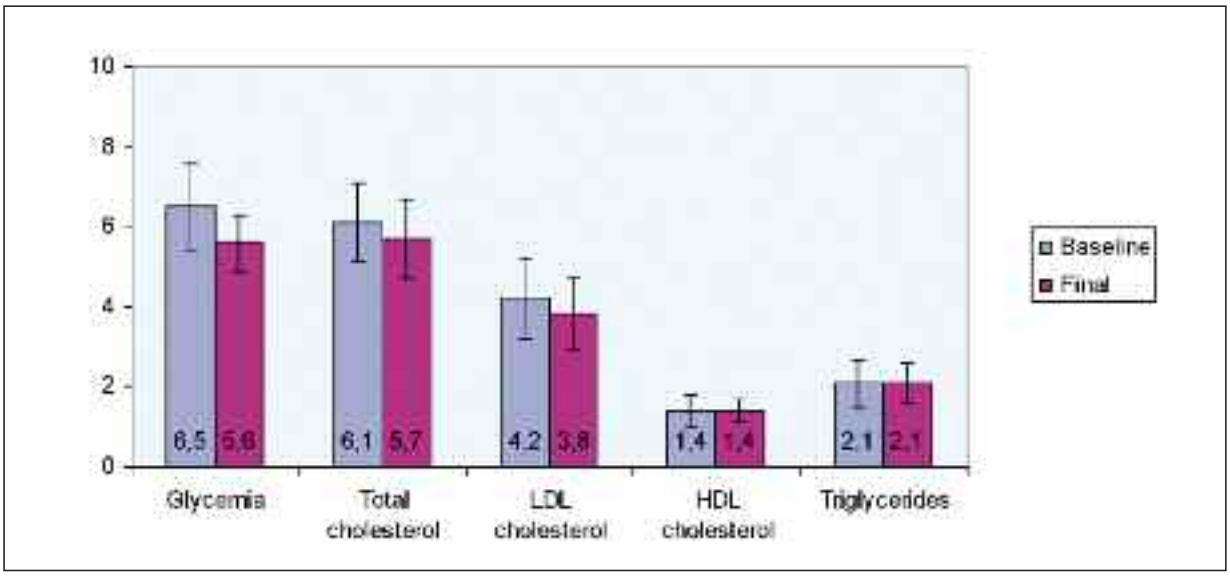

Figure 4. Baseline and final values for different parameters of the safety analysis, in the whole population evaluated (n=86). All data are expressed as mean±SD.

lar events, as elevated BP is considered the leading risk factor for the development of cardiovascular disease[2].

Previous studies have suggested that combining nebivolol with HCTZ or other antihypertensives results in an additive effect on BP lowering[7,16-19,21]. The benefits of nebivolol/HCTZ combination in terms of BP reduction were first indicated in a placebo-controlled multifactorial trial, conducted in 240 hypertensive patients[17]. After 12 weeks of treatment, a dose-related reduction for nebivolol and HCTZ was observed, both in clinical and ambulatory BP. Of note, this effect had a fast onset of action, since it was already evident after 2-4 weeks from the initiation of therapy. Similar findings were obtained in different prospective, double-blind trials comparing nebivolol with other antihypertensive drugs, like atenolol, lisinopril or amlodipine, in patients with hypertension[7,16,21]. In these trials, HCTZ addition was allowed in those patients who did not achieve BP control on monotherapy. Overall, all studies consistently showed that the administration of nebivolol/HCTZ had an additive effect in reducing BP. In a recent study[18], performed in the US (where different dosages of nebivolol are used, depending on BMI and ethnicity) the addition of nebivolol 5, 10 and 20 mg/day to existing antihypertensive therapy consisting of ACE inhibitors, angiotensin II receptor blockers or diuretics (or their combinations) for 12 weeks in patients with uncontrolled hypertension produced mean reductions of 3.3-4.6 mmHg in trough sitting DBP and 3.7-6.2 mmHg in trough sitting SBP compared with placebo. The additive clinical effect of nebivolol and HTCZ was also confirmed in a post-marketing analysis of data obtained in two multicenter trials, performed mostly in the US, with a parallel, double-blind design, conducted in patients with mild-to-moderate hypertension[19]. In these studies, the combination therapy with nebivolol/HCTZ in patients with poorly controlled hypertension (DBP ≥90 mmHg) produced significantly greater reductions in both SBP and DBP when compared to the nebivolol monotherapy. Of note, the reduction in BP and the subsequent improvement in the management of hypertension reported in the current study was also observed in two different subgroups of patients, namely elderly individuals and diabetic subjects, who are considered high-risk cardiovascular patients[1]. These findings are in line with other investigations showing the efficacy of the combination of nebivolol/HCTZ in elderly subjects[17] and in diabetic patients[22].

In the present study, the reduction in BP observed with nebivolol/HCTZ 5/12.5 mg/day in combination allowed the majority of patients to achieve a clinical response or normalization of BP at the end of the observation period, in accordance with current ESH/ESC guidelines[1].

This clinically-important finding confirms that the administration of a combination therapy may play a pivotal role in the achievement of optimal BP control. In fact, the combination of antihypertensive agents characterized by different and complementary mechanisms of action, like nebivolol (a third-generation beta-blocker) and HCTZ (a diuretic), may offer a greater efficacy than the respective monotherapies, and/or a more favourable tolerability profile[1,23-26]. This is particularly relevant for nebivolol, which has a dual mechanism of action; in addition to its selective $ß_1$-adrenoceptor antagonist activity, it also has a vasodilatory activity, mainly attributable to the *l*-enantiomer[8-10]. Previous researches have demonstrated that fixed-dose combinations provide several advantages over monotherapy and the co-administration of two separate agents in the treatment of hypertension. A recent meta-analysis that analysed data from 42 trials[24] stated that the additional reduction in BP through the combination of two drugs from different classes is approximately five times greater than dosage doubling of one drug. Current guidelines recommend the use of fixed-dose combinations over co-administration of agents if available, because of the improved compliance they can provide in the long-term clinical management of hypertension[1]. In particular, a fixed-dose combination of nebivolol and HCTZ may be particularly useful in elderly and diabetic patients, who are usually receiving treatment with a very high number of concomitant medications[1].

Since anti-hypertensive therapy often requires a long-term administration, tolerability is a particular concern. It has been suggested that traditional beta-blockers may be associated with negative effects on glucose and lipid metabolism[27,28]. On the contrary, the present study shows that the combination of nebivolol and HCTZ was well tolerated in a high-risk population; overall, no alterations of laboratory parameters were observed. These findings are in line with other previous investigations and further strengthen the recommendations of current ESH/ESC guidelines, which have highlighted that the third-generation beta-blockers, like nebivolol, don't have side effects on the metabolic profile[1]. It is likely that the

unique pharmacodynamic profile of nebivolol could play a role in avoiding the onset of these adverse events[7]. Nebivolol is a $beta_1$-adrenergic antagonist with NO-mediated vasoactivity that provides effective BP reduction without an influence on metabolic parameters and without an increased incidence of new-onset diabetes, unlike older beta-blockers[7, 29].

It must be acknowledged that this study presents several limitations. First, there is no direct comparison of nebivolol/HCTZ with any other antihypertensive treatment. However, comparisons are already available from previous studies[7,16,17,21]. Second, the observational nature of the present pooled analysis is *per se* associated with the presence of several confounding factors, thus limiting, at least in part, the ability to infer any direct cause-effect relationship. However, the real-life setting in which the study was conducted enhances the clinical significance by providing information that directly emerges from the clinical practice.

In conclusion, the results of this pooled analysis of post-marketing studies confirm the efficacy and the good safety profile of nebivolol/HCTZ combination therapy in a real-life scenario, including the elderly and the diabetic patients. This fixed-combination regimen may be particularly useful by improving the patient's compliance, especially in the elderly and the diabetic patients who are likely to be receiving multiple medications.

References

1) Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HA, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Erdine S, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Lindholm LH, Manolis A, Nilsson PM, Redon J, Struijker-Boudier HA, Viigimaa M, Adamopoulos S, Bertomeu V, Clement D, Farsang C, Gaita D, Lip G, Mallion JM, Manolis AJ, O'Brien E, Ponikowski P, Ruschitzka F, Tamargo J, van Zwieten P, Waeber B, Williams B. The task force for the management of arterial hypertension of the European Society of Hypertension, The task force for the management of arterial hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007; 28: 1462-1536.

2) Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet 2002; 360: 1903-1913.

3) Materson BJ, Reda DJ, Cushman WC, Department of Veterans Affairs single-drug therapy of hypertension study. Revised figures and new data. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. Am J Hypertens 1995; 8: 189-192.

4) Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. Br Med J 2009; 338: b1665.

5) MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990; 335: 765-774.

6) Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med 2005; 165: 1410-1419.

7) Agabiti Rosei E, Rizzoni D. Metabolic profile of nebivolol, a beta-adrenoceptor antagonist with unique characteristics. Drugs 2007; 67: 1097-1107.

8) Baldwin CM, Keam SJ. Nebivolol: in the treatment of hypertension in the US. Am J Cardiovasc Drugs 2009; 9: 253-260.

9) Siebert CD, Hansicke A, Nagel T. Stereochemical comparison of nebivolol with other beta-blockers. Chirality 2008; 20: 103-109.

10) Kamp O, Metra M, Bugatti S, Bettari L, Dei Cas A, Petrini N, Dei Cas L. Nebivolol: haemodynamic effects and clinical significance of combined beta-blockade and nitric oxide release. Drugs. In press.

11) Ignarro LJ. Different pharmacological properties of two enantiomers in a unique beta-blocker, nebivolol. Cardiovasc Ther 2008; 26: 115-134.

12) Forest Pharmaceuticals. Bystolic (nebivolol) tablets. 2008 [cited 2009 29 October]; Available from: http://www.frx.com/pi/bystolic_pi.pdf.

13) Menarini Pharma. Nebilet 5 mg Tablets. 2007 [cited 2009 29 October]; Available from: http://emc.medicines.org.uk/medicine/9145/SPC/Nebilet+5 mg+Tablets/.

14) Cockcroft J. Nebivolol: a review. Expert Opin Pharmacother 2004; 5: 893-899.

15) Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med 1993; 329: 2002-2012.

16) Grassi G, Trevano FQ, Facchini A, Toutouzas T, Chanu B, Mancia G. Efficacy and tolerability profile of nebivolol vs atenolol in mild-to-moderate essential hypertension: results of a double-blind randomized multicentre trial. Blood Press Suppl 2003; 2: 35-40.

17) Lacourciere Y, Lefebvre J, Poirier L, Archambault F, Arnott W. Treatment of ambulatory hypertensives with nebivolol or hydrochlorothiazide alone and in combination. A randomized, double-blind, placebo-controlled, factorial-design trial. Am J Hypertens 1994; 7: 137-145.

18) Neutel JM, Smith DH, Gradman AH. Adding nebivolol to ongoing antihypertensive therapy improves blood pressure and response rates in patients with uncontrolled stage I-II hypertension. J Hum Hypertens 2009.

19) Papademetriou V. Comparison of nebivolol monotherapy versus nebivolol in combination with other antihypertensive therapies for the treatment of hypertension. Am J Cardiol 2009; 103: 273-278.

20) Agabiti Rosei A, Rizzoni D, Comini S, Boari G. Evaluation of the efficacy and tolerability of nebivolol versus lisinopril in the treatment of essential arterial hypertension: a randomized, multicentre, double-blind study. Blood Press Suppl 2003; 1: 30-35.

21) Mazza A, Gil-Extremera B, Maldonato A, Toutouzas T, Pessina AC. Nebivolol vs amlodipine as first-line treatment of essential arterial hypertension in the elderly. Blood Press 2002; 11: 182-188.

22) Schmidt AC, Graf C, Brixius K, Scholze J. Blood pressure-lowering effect of nebivolol in hypertensive patients with type 2 diabetes mellitus: the YESTONO study. Clin Drug Investig 2007; 27: 841-849.

23) Sica DA, Black HR. Pharmacologic considerations in the positioning of beta-blockers in antihypertensive therapy. Curr Hypertens Rep 2008; 10: 330-335.

24) Wald DS, Law M, Morris JK, Bestwick JP, Wald NJ. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. Am J Med 2009; 122: 290-300.

25) Whalen KL, Stewart RD. Pharmacologic management of hypertension in patients with diabetes. Am Fam Physician 2008; 78: 1277-1282.

26) Wojciechowski D, Papademetriou V. Beta-blockers in the management of hypertension: focus on nebivolol. Expert Rev Cardiovasc Ther 2008; 6: 471-479.

27) Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Bohm M, Anker SD, Thompson SG, Poole-Wilson PA. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J 2005; 26: 215-225.

28) Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. J Hypertens 2006; 24: 3-10.

29) Williams B, Poulter NR, Brown MJ, Davis M, McInnes GT, Potter JF, Sever PS, Thom SM. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. Br Med J 2004; 328: 634-640.

Acknowledgements

Editorial assistance was provided by inScience Communications Italy. This assistance was funded by Menarini, Firenze, Italy.