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An Open Label, Multi-Center, Non-Interventional Study of the Safety of Nebivolol (Nebilet) In the Treatment of Hypertension in Filipino Adult Patients: A Post Marketing Surveillance Study

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Abstract

Background: Nebivolol is a potent third generation beta-blocking agent indicated for the treatment of hypertension, and is distinguished from other beta blockers by its dual mechanism of action involving high β-1 cardioselectivity and unique nitric-oxide (NO) induced vasodilation. This study aims evaluate the safety and efficacy of Nebivolol (Nebilet) 5mg in the treatment of hypertension among Filipino adult patients.

Methods: This is a prospective, open-label, non-interventional study which evaluated the safety of Nebivolol (Nebilet) 5mg in Filipino adult subjects with hypertension, aged 21 to 80 years, in an out-patient setting.

Results: A total of 1,154 patients were recruited into the study, 36 (3%) of which had reported adverse events (AEs). Majority of the AEs were due to headaches (18%) and other non-specified events (32%). Most of the adverse events reported were mild to moderate and some were known effects of β- blockers. There were no serious or unsuspected adverse events described during the study. In terms of efficacy, nebivolol reduced blood pressure to less than 140/90 mmHg or a decrease of >10 mm Hg diastolic blood pressure (DBP) in 82% of subjects in the first follow-up visit. At the end of the treatment period, 97% had achieved target blood pressure levels.

Conclusions: The study has shown that nebivolol is a safe and effective medication in hypertensive Filipino adult patients.

Keywords: Nebivolol; Nebilet; Hypertension; vasodilator; Beta-Blocker, Beta-Blocking, Beta-antagonist; D-nebivolol; L-nebivolol; Nitric oxide; PMS; Post Marketing Surveillance; Phase iv

Introduction

Beta-blocking agents often differ with regards to their selectivity for receptors, lipophilicity, duration of action and intrinsic sympathomimetic activity. Presently, newer beta-blockers were deveNebivolol is a potent cardio-selective beta-blocking agent indicated for the treatment of hypertension, which is distinguished from other selective beta-1-adrenergic antagonists by its peculiar hemodynamic profile. It promotes arterial and venous vasodilation that is not related to its action as a beta 1-adrenoceptor blocker. Nebivolol is indicated for the treatment of essential hypertension and of stable mild and moderate chronic heart failure in addition to standard therapies in elderly patients >70 years.

The pharmacology of Nebivolol has been summarized in several publications and reviews. The peculiar combination of the cardioselective (ß1-selective) ß-blocking properties with the restoration of NO activity and consequent reversal of endothelial dysfunction has been also demonstrated in most recently published clinical studies in hypertensive patients. In particular, Nebivolol was shown to induce a systematic hemodynamic response, consisting in preservation of cardiac output, reduction of peripheral resistance, and improved diastolic dysfunction. This pattern has favorable implications not only in the treatment of hypertension, but may also be clinically relevant in the treatment of heart failure, one of the major complications of hypertension.

Nebivolol is a third-generation β-blocker, combining selective β1-adrenergic receptor blockade with a vasodilatory property, mediated by the L-arginine/ NO pathway. Nebivolol hydrochloride is the racemate of two enantiomers: d-nebivolol (SRRR-nebivolol) and l-nebivolol (RSSS-nebivolol). The mixture (1:1) of the two enantiomers is named dl-nebivolol. The two enantiomers have different pharmacological activities: d-nebivolol is responsible for the selective β1-antagonism, while l-nebivolol is involved in the endothelial/NO-dependent vasodilation. Chemically nebivolol is (RSSS+SRRR)-[iminobis (methylene)] bis [6-fluoro-3,4-2H-1-benzopyran-2-methanol] hydrochloride. 1-3 Nebivolol is a lipophilic drug, with an ionisation constant (pKa) of 8.2 and a partition co-efficient octanol/water of 1.4. Nebivolol is structurally different from conventional β-blocking drugs, which are usually modelled on naturally β-adrenergic agonists such as adrenaline and noradrenaline.

Nebivolol has a dual mechanism of action. It has β-receptor activity, which means that it is a highly selective β1-receptor antagonist and a β3-receptor agonist. It also stimulates nitric oxide release; this property is responsible for the vasodilatory, antioxidant, antiproliferative and antiplatelet actions of the drug.

The haemodynamic profiles of nebivolol and atenolol appear to be completely different. The response to atenolol is typical of β1-blockers, with evidence of reduce cardiac output and increased peripheral vascular

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resistance, whereas that of nebivolol is characterized by a decrease in systemic vascular resistance and an improvement in left ventricular performance, partly secondary to an improvement in diastolic function [1]. These observations were confirmed in two studies comparing the hemodynamic effects of nebivolol and atenolol in healthy subjects [2,3]. In both these studies nebivolol significantly increased left ventricular ejection fraction (LVEF), stroke volume, cardiac output and end-diastolic volume, while end-systolic volume remained unchanged. Atenolol, on the other hand, significantly decreased LVEF and cardiac output; stroke volume and end-diastolic volume remained unchanged, while the end-systolic volume increased significantly. Peripheral vascular resistance was significantly reduced by nebivolol and increased by atenolol. The analysis of diastolic function showed that the peak filling rate was improved by nebivolol and decreased by atenolol.

Nebivolol has also been found to have favourable haemodynamic characteristics in hypertensive patients in studies using systolic time intervals1 or radionuclide ventriculography [4]. The results of these studies showed that nebivolol improves left ventricular function by increasing stroke volume, LVEF and diastolic compliance and reducing systemic vascular resistance. Nebivolol seems to maintain a better haemodynamic profile in hypertensive patients when compared to other beta-blockers. In a double-blind crossover trial, the systemic vascular resistance index fell during nebivolol treatment (7.5%) but did not change during bisoprolol treatment [5] while the cardiac index decreased significantly during bisoprolol treatment (10%) but did not change in the period of nebivolol administration.

In a double-blind parallel group study, nebivolol increased stroke volume, cardiac output and ejection fraction and decreased peripheral vascular resistance, whereas atenolol exerted opposite effects on these haemodynamic parameters [6]. Morever, only nebivolol improved diastolic function by increasing left ventricular compliance. In recent years, understanding of the role of the coronary microcirculation in human arterial hypertension has improved substantially because coronary flow reserve of the left anterior descending artery can now be assessed by trans-oesophageal or transthoracic Doppler echocardiography [7-15].

Coronary flow reserve (CFR) is the difference between coronary blood flow at rest and after maximal vasodilatation induced by the administration of a vasodilator (for example, adenosine or dipyridamole). It is usually expressed as the ratio of maximal (hyperaemic) to resting coronary blood flow. CFR is impaired in hypertensive patients as a consequence of increased afterload, left ventricular hypertrophy, vascular hypertrophy, endothelial dysfunction and extravascular compression related to diastolic dysfunction. In a study performed in newly diagnosed grade I-II hypertensive patients, nebivolol induced an absolute increase of 8% or more in coronary flow reserve in nine of the 14 patients investigated (64.3%). This study showed that nebivolol preserves coronary flow at rest and increased hyperaemic flow velocities despite the reduction of metabolic (O2 consumption) and haemodynamic (diastolic blood pressure) determinants. The increase of hyperaemic coronary flow velocities appeared to be due to the reduction of coronary resistance [16].

The favourable haemodynamic profile of nebivolol is of potential advantage for hypertensive patients, whose left ventricular compliance is often impaired, even before overt evidence of left ventricular hypertrophy (LVH). Nebivolol has been studied in both animals and patients with LVH. Nebivolol reduces diastolic and systolic blood pressures and LVH in hypertensive patients [17]. This is an important aspect since the reduction of LVH improves the prognosis of hypertensive patients and reduces the incidence of cardiovascular events. In a recent experimental study it was shown, in spontaneously hypertensive rats, that the antihypertensive effect of nebivolol was accompanied by important reductions of LVH and collagen deposition in both vascular and left ventricle tissue, and these changes were maintained for a long period after therapy withdrawal [18]. Enhancement of arterial relaxation, reduction of LVH and prevention of collagen accumulation could reduce ventricular and vascular stiffness and improve cardiovascular function. These experimental results support the clinical usefulness of nebivolol in hypertension.

Dose-finding studies established that 5 mg of nebivolol is the most appropriate dose for antihypertensive treatment [19-21] The trough-to-peak ratio of nebivolol is 0.90, [21] demonstrating that most of the hypotensive effect is still present 24 hours after a dose. The value of the trough-to-peak ratio for an antihypertensive drug should be >0.50 to justify once-a-day administration. The peak-to-trough ratio of nebivolol was recently compared directly with that of bisoprolol and carvedilol in a randomised, double-blind, placebo controlled, cross-over trial in 16 healthy males. Subjects received 10 mg bisoprolol or 50 mg carvedilol or 10 mg nebivolol or placebo on the first morning of each experimental period, followed by 5 mg bisoprolol once daily or 25 mg carvedilol twice daily or 5 mg nebivolol once daily or placebo for 1 week. The heart rate trough-to-peak ratios (expressed as percentages) in the long-term were as follows: bisoprolol 58%; carvedilol 85%; nebivolol 91% [22]. The blood pressure lowering effect of nebivolol follows the circadian rhythm of blood pressure as monitored by ambulatory blood pressure measurements [23,24].

Randomised, double-blind, placebo-controlled trials have established the efficacy and tolerability of nebivolol in patients with mild to moderate essential hypertension [20,21,25-27] In these evaluations, Nebivolol was administered in single daily doses of 1 to 10 mg/day for 4 to 12 weeks. These studies included a variable number of patients aged 18 to 71 years.

Doses of nebivolol >5 mg reduced systolic and diastolic blood pressures to a greater extent than placebo. These placebo-controlled studies showed that the percentage of responders (defined as patients achieving a diastolic blood pressure <90 mmHg or a decrease of >10 mmHg) ranged from approximately 50 to 80%, depending on the treatment duration. In an open observational study [28] the antihypertensive activity of nebivolol was assessed in 3,741 patients who had been previously treated (group A=1,656) or untreated (group B=2,085). After 2 weeks the percentage of responders was 52% in group A and 61% in group B. These figures rose to 74% and 86%, respectively, by 6 months. Similar results were found in another more recent and larger observational study (5,740 patients) [29]. Again, it was found that the response rate to nebivolol rose over time. This study demonstrated the efficacy and safety of nebivolol for the treatment of mild hypertension in normal clinical practice. Blood pressure reductions with nebivolol as monotherapy or add-on therapy were very similar [29]. The conclusions of both these studies were that the antihypertensive efficacy of nebivolol continues to increase during treatment [28,29].

Nebivolol has been compared with several standard antihypertensive therapies, including other beta-blockers (atenolol, metoprolol, bisoprolol), [27-33] calcium-channel blockers (amlodipine, nifedipine), [34,35] ACE-inhibitors (enalapril, lisinopril), [24,36,37] angiotensin II receptor antagonists [38] and a thiazide diuretic (hydrochlorothiazide) [25].

In the studies comparing nebivolol with other beta-blockers, both

nebivolol and the comparator agent produced significant reductions in blood pressure and these reductions were similar for nebivolol and either atenolol, metoprolol or bisoprolol. [27-33] In the atenolol studies, nebivolol 5 mg once daily produced a similar reduction in blood pressure as 50 and 100 mg of atenolol [27,31,39].

Therefore, the antihypertensive efficacy of nebivolol was similar to that of other beta-blocking drugs.

Nebivolol 5 mg once daily was similar in efficacy to amlodipine 5 or 10 mg once daily and nifedipine 20 mg twice a day but the percentage of patients with fully normalized blood pressure (diastolic blood pressure <90 mmHg) was significantly higher with nebivolol than with nifedipine or amlodipine [24,34,35,40] In addition, nebivolol tended to prevent increases in early morning blood pressure better than nifedipine, as assessed by 24-hour ambulatory blood pressure measurements [41]. Furthermore, in the studies comparing nebivolol with nifedipine or amlodipine, heart rate was decreased by nebivolol and slightly increased with the two dihydropyridines: the lower heart rate is a potential advantage of nebivolol, due to the epidemiologically determined relation between heart rate and cardiovascular morbidity [37,40].

The antihypertensive effect of nebivolol 5 mg once daily was similar to that of lisinopril 20 mg once daily, although nebivolol appeared to achieve maximal blood pressure reduction earlier in therapy [36]. In contrast, reduction of diastolic blood pressure with nebivolol 5 mg/daily was greater than that achieved with enalapril 10 mg/daily [37,42].

The antihypertensive efficacy of nebivolol 5 mg once a day and losartan 50 mg once a day was investigated in a multicenter double-blind trial in 314 patients with essential hypertension [38] The difference between nebivolol and losartan was not statistically significant as far as the systolic blood pressure reduction was concerned, whereas nebivolol achieved a statistically significant, greater reduction of diastolic blood pressure after 3, 6 and 12 weeks of treatment, in spite of the fact that addition of hydrochlorothiazide was required in a significantly smaller proportion of subjects treated with nebivolol. The prevalence of patients with normalised blood pressure (diastolic blood pressure <90 mmHg) was also significantly higher with nebivolol than with losartan after 6 weeks whereas after 12 weeks it was similar with both drugs. The conclusion of this study was that nebivolol has a greater effect on diastolic blood pressure than losartan.

In a recent meta-analysis 43 of 13 randomised controlled trials in which nebivolol was compared in nine studies with a variety of other antihypertensive drugs (ACE-inhibitors, other beta-blockers, angiotensin II receptor blockers, calcium-channel blockers) and in other studies with placebo, antihypertensive response rates were statistically significantly higher with nebivolol than with ACE-inhibitors and all antihypertensive drugs combined. Moreover, a higher proportion of patients receiving nebivolol had normalised blood pressure levels compared with patients receiving angiotensin II receptor blockers, calcium channel blockers and all of the antihypertensive drugs combined [43].

The primary objective of this study was to evaluate the safety of Nebivolol (Nebilet) 5 mg in usual clinic practice when used in the treatment of hypertension in adult patients by assessing the incidence of adverse events at 2 follow-up visits (Day 14 to Day 60 after baseline visit).

The global/ overall efficacy of Nebivolol (Nebilet) 5 mg was assessed by doctors at 2 follow-up visits based on the following parameters:

a. Blood pressure <140/90 mmHg or diastolic blood pressure reduction >10 mmHg compared to baseline

b. % of patients with diastolic blood pressure <90 mmHg at follow-up visits

c. % of patients with systolic blood pressure <140 mmHg at follow-up visits

Methods

Ethical conduct

The trial was conducted following the principles set forth by the National Guidelines for Biomedical/Behavioral Research of the National Ethics Committee (NEC) of the Philippines; The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research; World Medical Association Declaration of Helsinki regarding protection of the rights and welfare of human subjects participating in this study; applicable government regulations and institutional research policies and procedures.

Study population

The Philippine Food and Drug Administration have approved a study population of 3000 patients to be enrolled in the study within 3 years. The decision to use Nebivolol (Nebilet) 5mg was a joint decision made by the subject and the Investigator. The Investigator discussed product information with the subject as per usual practice.

Inclusion criteria: Filipino patients, male or female, age 21 to 80 with arterial hypertension that were treatment-naïve to Nebivolol.

Exclusion criteria: Subjects with conditions contraindicated with the use of Nebivolol (Nebilet) 5 mg based on the approved local product label in the Philippines were excluded in this study. These conditions included:

1. Hypersensitivity to Nebivolol (Nebilet) or to any excipients in the formulation

2. Liver insufficiency or liver function impairment.

3. Acute heart failure, cardiogenic shock or episodes of heart failure decompensation requiring intravenous inotropic therapy.

Study design

This is a prospective observational, non-interventional study which evaluated Nebivolol (Nebilet) 5 mg in Filipino adult subjects with hypertension, 21 to 80 years of age.

The data collected was under routine clinical conditions, therefore, subjects who had any of the contraindications specified in the product package insert were excluded. Nebivolol (Nebilet) 5 mg was prescribed and administered according to the approved product information of the drug in the Philippines. A. Menarini Philippines, Inc. did not provide the drug for this study.

Endpoints

Parameters on safety

Safety of Nebivolol (Nebilet) 5mg was evaluated by assessing the incidence of adverse events at follow-up visits. All adverse events, whether detected by the Investigator or reported by the subject, were recorded on the case report form (CRF), with the date of occurrence, time of onset, duration, likely relationship to study medication, action taken, patient outcome and whether the event met the criteria for serious adverse event [44-47].

Parameters on efficacy

Efficacy of Nebivolol (Nebilet) 5 mg was evaluated using the following parameters: sitting blood pressure <140/90 mmHg or diastolic blood pressure reduction >10 mmHg compared to baseline, % of patients with sitting diastolic blood pressure <90 mmHg, and % of patients with sitting systolic blood pressure <140 mmHg at follow-up visits.

Efficacy and safety assessments

The use and dosage recommendations for Nebivolol (Nebilet) 5 mg were based on the approved local product label and were adjusted solely according to medical and therapeutic necessity. The recommended dose of Nebivolol (Nebilet) is one tablet (5 mg) daily, given preferably at the same time of day. Tablets were to be taken with meals or upon Investigator's judgment.

The individual assessment of treatment in terms of safety and efficacy lasted up to 60 days.

Baseline visit

At baseline visit, the following information were obtained and recorded: demographic profile (name of physician, name of institution, date of visit, date of birth and sex), medical history, complete physical examination, and concomitant medications. The prescription of Nebivolol (Nebilet) was documented and the schedule for the next visit was explained.

Follow-up visits (day 14 up to day 60)

During the follow-up visits, the following information were obtained and recorded: date of visit, study drug medication and frequency, changes in concomitant medications if any, adverse event/s, efficacy parameters and patient status at the end of the study.

Safety analysis

The safety population was defined as all patients who received at least one dose of study medication during the observation period. Safety data (Adverse Events, SAEs, premature discontinuations from the study, and concomitant medications) were summarized within the safety population in accordance with A. Menarini Philippines, Inc. SOP for safety reporting.

Baseline characteristics (demographics and medical history) were also summarized within the safety populations.

Statistical Analysis

All retrieved CRFs were encoded and were included in the efficacy and safety analysis.

For continuous demographic and efficacy variables, the mean ± standard deviation, median, minimum and maximum values were presented. For all qualitative and discrete parameters, frequencies and percentages in each class were presented. Descriptive statistics were presented at each scheduled assessment on these parameters.

To test for significance of difference of Visit 2 and Visit 3 parameters compared to baseline, 90% confidence intervals were computed and p-values using paired t-test were presented.

Sample Size Determination

The Philippine Food and Drug Administration (FDA) requires that a Post Marketing Surveillance study be conducted nationwide and has approved a sample size of 3000 patients in 3 years duration for this study.

Results

Study conduct, patient disposition and baseline characteristics

A total of 1,140 CRFs were retrieved, with 18% of them less than 40 years old, 50% were between 40 and 60 years old and 3% were older than 60. Slightly more females were enrolled at 54% and men accounting for about 45% (Table 1).

About 70% had family history of hypertension and approximately the same percentage was taking concomitant medications. A small percentage, 3% had history of allergy (Table 2).

About one fourth of the patients were smoking or had diabetes. Slightly more than half had hyperlipidemia. Approximately 17% were newly diagnosed hypertensives (Table 3).

Efficacy

	N (%)
Age (years)	
N with age data	1,140
Mean + SD	52.41+13.29
Median	52.00
Minimum	18
Maximum	93
Gender	
Male	518 (44.88)
Female	618 (53.55)
Missing data	18 (1.56)
Weight (kg)	
N with weight data	923
Mean+SD	65.91+12.91
Median	65.00
Minimum	35.00
Maximum	132.90

Table 1: Characteristics of study participants.

	N (%)	
With allergies		
Yes	40	(3.47)
No	611	(52.95)
Missing answer	503	(43.59)
With family history of hypertension		
Yes	787	(68.20)
No	105 (9.10)	
Missing answer	262	(22.71)
With concomitant drugs		
Yes	822	(71.23)
No	332	(28.77)

Table 2: Other relevant history and concomitant drugs.

At baseline, the average systolic blood pressure was 152 mmHg with a maximum of 240 mmHg while the average diastolic blood pressure was 93 mmHg with a maximum of 139 mmHg (Table 4). The average heart rate was 85 beats/min with a maximum of 140 beats/min (Table 5).

At Visit 2, 82% had blood pressures below 140/90 mmHg or had a reduction of more than 10 mmHg in diastolic blood pressure. About 95% had diastolic blood pressure below 90 mmHg and 84% had systolic blood pressure less than 140 mmHg (Table 6).

At Visit 3, 97% had blood pressures below 140/90 mmHg or had a reduction of more than 10 mmHg in diastolic blood pressure. About 99% had diastolic blood pressure below 90 mmHg and 97% had systolic blood pressure less than 140 mmHg.

The reduction in systolic and diastolic blood pressures and heart rate

	N (%)	
Smoker		
Yes	336	(29.12)
No	783	(67.85)
Missing answer	35	(3.03)
Prior history of coronary artery disease		
Yes	148	(12.82)
No	950	(82.32)
Missing answer	56	(4.85)
Prior myocardial infarction		
Yes	62	(5.37)
No	1043 (90.38)	
Missing answer	49	(4.25)
Prior percutaneous coronary intervention		
Yes	5 (0.43)	
No	1096 (94.97)	
Missing answer	53	(4.59)
Prior coronary artery bypass surgery		
Yes	8 (0.69)	
No	1094 (94.80)	
Missing answer	52	(4.51)
Cerebrovascular accident in the previous months		
Yes	34	(2.95)
No	1067 (92.46)	
Missing answer	53	(4.59)
Hypertension		
Yes	939	(81.37)
No	196	(16.98)
Missing answer	19	(1.65)
Hyperlipidaemia		
Yes	583	(50.52)
No	523	(45.32)
Missing answer	48	(4.16)
Atrial fibrillation		
Yes	36	(3.12)
No	1020 (88.39)	
Missing answer	98	(8.49)
Diabetes		
Yes	233	(20.19)
No	849	(73.57)
Missing answer	72	(6.24)

Table 3: Medical history.

Baseline Visit				
	N	**Mean+SD**	**Min**	**Max**
SBP	1154	152.75 ± 15.93	90.00	240.00
DBP	1154	93.30 ± 10.05	20.00	139.00
Heart rate	1111	85.86 ± 11.62	54.00	140.00
Visit 2				
	N	**Mean ± SD**	**Min**	**Max**
SBP	1125	134.29 ± 12.91	90.00	185.00
DBP	1125	83.36 ± 8.64	30.00	181.00
Heart rate	1092	77.00 ± 9.04	50.00	121.00
Visit 3				
	N	**Mean ± SD**	**Min**	**Max**
SBP	1080	125.05 ± 10.57	90.00	160.00
DBP	1080	78.06 ± 7.06	40.00	100.00
Heart rate	1061	73.16 ± 8.10	48.00	112.00

Table 4: Descriptive statistics, blood pressure and heart rate, Visits 1 to 3.

	Visit 2	**Visit 3**
	N (%)	**N (%)**
BP ≤ 140/90 or diastolic blood pressure reduction >10 mmHg from baseline	921 (81.87)	1049 (97.13)
% of patients w/ diastolic bp ≤ 90 mmHg	1063 (94.49)	1078 (99.81)
% of patients w/ systolic bp ≤ 140 mmHg	944 (83.91)	1050 (97.22)

Table 5: Efficacy results.

	Baseline to Visit 2			
	N	**Mean ± SD**	**90% Confidence Limits for Mean**	**p-value***
SBP	1125	18.79 ± 13.20	(18.14, 19.44)	<0.0001
DBP	1125	10.05 ± 10.41	(9.54, 10.56)	<0.0001
HR	1092	9.01 ± 8.61	(8.58, 9.44)	<0.0001
	Baseline to Visit 3			
	N	**Mean ± SD**	**90% Confidence Limits for Mean**	**p-value***
SBP	1080	28.25 ± 14.90	(27.50, 28.99)	<0.0001
DBP	1080	15.45 ± 10.45	(14.92, 15.97)	<0.0001
HR	1061	12.88 ± 10.56	(12.35, 13.41)	<0.0001
*Used paired t-test				

Table 6: Mean Reduction in Blood Pressure (mmHg) and Heart Rate (/min).

were significant with p-values less than 0.0001 and there were further reductions in all three parameters in Visit 3 (Table 7).

Safety

Only 36 patients (3%) developed adverse events during the treatment period. This is consistent with data in the approved product label (Table 8).

Most of the adverse events reported were mild to moderate and some were known effects of therapy (Table 9).

Out of the 44 reported adverse events, only 4 led to treatment discontinuation (bradycardia, dizziness, palpitations and 1 unspecified reason) (Table 10). In 9 patients, dose was reduced while in majority of patients, treatment was continued with no changes (Table 11).

About 80% of the adverse events resolved or improved with time, about 6% was unchanged during the treatment period while outcome in 14% was not reported (Table 12). It should be noted that only 7% and 16% were classified as definite and probable consequences of nebivolol therapy (Table 13).

Listed (Table 14) are the adverse events reported during the treatment period involving 1,154 patients.

Discussion

Beta- blockers are one of the oldest classes of anti-hypertensive drugs in the market. In recent years, newer, safer and more effective β- blockers have emerged. Nebivolol, a 3rd generation β-receptor antagonist, is the most recent of its class and possesses a dual mechanism of action with the highest cardioselectivity as well as a NO induced-vasodilatory effect on the vascular endothelium. Safety and tolerability have always been a concern for traditional β-blockers with issues such as bradycardia, erectile dysfunction, impaired glucose tolerance as well as worsening of bronchospasm in predisposed patients.

This study focused on the safety and tolerability of nebivolol in hypertensive patients in a real world setting. The results showed that only 3% of patients experienced adverse events in the intention to treat population and in the per protocol population. All of the AEs were considered mild to moderate and the most commonly reported event was headache. These findings are consistent with the study of Lewin et

Baseline to Visit 2			
	N	**Mean ± SD**	**90% Confidence Limits for Mean**
SBP	1125	11.86 ± 7.86	(11.48, 12.25)
DBP	1125	10.04 ± 10.98	(9.50, 10.98)
HR	1092	9.83 ± 8.86	(9.39, 10.27)
Baseline to Visit 3			
	N	**Mean ± SD**	**90% Confidence Limits for Mean**
SBP	1080	17.86 ± 8.35	(17.44, 18.28)
DBP	1080	15.67 ± 10.97	(15.12, 16.22)
HR	1061	14.05 ± 10.51	(13.52, 14.58)

Table 7: Mean Percent Reduction (%) in Blood Pressure and Heart Rate.

	N (%)
With AE	36 (3.12)
Without AE	1,118 (96.88)
Total	**1,154 (100.00)**

Table 8: Number of participants with and without AEs.

Adverse event	**N (%)**
Bradycardia	2 (4.55)
Chest Pains	2 (4.55)
Dizziness	2 (4.55)
DOB	3 (6.82)
Dry mouth	3 (6.82)
Easy Fatigability	1 (2.27)
Erectile Dysfunction	1 (2.27)
Headache	8 (18.18)
Hyperacusis	1 (2.27)
Muscle pain	1 (2.27)
Nape Pains	1 (2.27)
Nausea	1 (2.27)
Palpitations	2 (4.55)
Temporal headache	1 (2.27)
Tingling sensation	1 (2.27)
Not specified	14 (31.82)
Total	44 (100.00)

Table 9: Number of AEs.

Adverse event	**Severity**		**Total**
	Mild	**Moderate**	
Bradycardia	2	0	2
Chest Pains	0	2	2
Dizziness	0	2	2
DOB	2	1	3
Dry mouth	0	3	3
Easy Fatigability	0	1	1
Erectile Dysfunction	1	0	1
Headache	6	2	8
Hyperacusis	0	1	1
Muscle pain	0	1	1
Nape Pains	1	0	1
Nausea	1	0	1
Palpitations	1	1	2
Temporal headache	1	0	1
Tingling sensation	1	0	1
Not specified	9	5	14
Total	**25**	**19**	**44**

Table 10: Number of AEs by Severity.

Adverse event	Treatment				Total
	Continued	Reduced	Stopped	Missing Answer	
Bradycardia	1	0	1	0	2
Chest Pains	0	2	0	0	2
Dizziness	1	0	1	0	2
DOB	1	2	0	0	3
Dry mouth	3	0	0	0	3
Easy Fatigability	1	0	0	0	1
Erectile Dysfunction	1	0	0	0	1
Headache	5	3	0	0	8
Hyperacusis	0	1	0	0	1
Muscle pain	1	0	0	0	1
Nape Pains	1	0	0	0	1
Nausea	1	0	0	0	1
Palpitations	1	0	1	0	2
Temporal headache	1	0	0	0	1
Tingling sensation	1	0	0	0	1
Not specified	11	1	1	1	14
Total	**30**	**9**	**4**	**1**	**44**

Table11: Number of AEs by Treatment.

Adverse event	Outcome				Total
	Disappeared	Improved	Unchanged	Missing answer	
Bradycardia	1	0	0	1	2
Chest Pains	1	1	0	0	2
Dizziness	2	0	0	0	2
DOB	1	2	0	0	3
Dry mouth	2	0	1	0	3
Easy Fatigability	0	1	0	0	1
Erectile Dysfunction	0	0	1	0	1
Headache	2	6	0	0	8
Hyperacusis	1	0	0	0	1
Muscle pain	0	0	0	1	1
Nape Pains	1	0	0	0	1
Nausea	1	0	0	0	1
Palpitations	0	1	0	1	2
Temporal headache	0	1	0	0	1
Tingling sensation	0	1	0	0	1
Not specified	2	8	1	3	14
Total	**14**	**21**	**3**	**6**	**44**

Table12: Number of AEs by Outcome.

al. which described headache as the predominant AE reported, adding that the incidence of headache was similar when compared to placebo. The occurrence of headache may be due to vasodilatation which is related to the activation of the L-arginine-nitric oxide system which in turn, is mediated primarily through the l-isomer.

Other adverse events that were observed were difficulty of breathing, dry mouth, bradycardia, chest pains and dizziness, all of which were considered typical of β-blocker treatment and only had an incidence of about 0.2%. Compared with other β-blockers, the incidence of AEs observed during nebivolol treatment was still seen to be lower [45]. In addition, a trial on elderly heart failure patients showed that nebivolol had a similar adverse event profile compared to placebo except for an increased incidence of bradycardia [46].

Erectile dysfunction is also a common complaint in β-blocker users, but in this study, the incidence was only 0.09% with the use of nebivolol. In fact, Doumas et al. observed that nebivolol was found to have improved erectile function in patients who switched from conventional β-blockers which may be attributed to enhance no bioavailability [47].

With regards to its efficacy, nebivolol was found to be effective in lowering blood pressure significantly. After the first visit, 82% of patients had reportedly achieved target BPs less than 140/90 mmHg or >10 mmHg decrease in DBP. At the end of the treatment period, almost 97% of patients had a sustained reduction in both SBP and DBP. Bayar et al. has previously mentioned that in contrast with most β-adrenoreceptor blockers, nebivolol has vasodilatory properties that are dependent on the presence of the endothelium and are associated with activation of endothelial nitric oxide synthase. There is evidence that nebivolol, in addition to its β1-adrenoreceptor blocking effects, can stimulate endothelial NO production, which has been suggested to be mediated, at least in part, by a β3-agonistic effect. As a result, there is reduced peripheral resistance, increased stroke volume and preserved cardiac output leading to a decrease in blood pressure [6].

Conclusion

In conclusion, this post-marketing observational study demonstrates

Adverse event	Causal relation to drug						
	Definite	Probable	Possible	Unknown	Not related	Missing answer	Total
Bradycardia	0	0	2	0	0	0	2
Chest Pains	0	0	2	0	0	0	2
Dizziness	0	2	0	0	0	0	2
DOB	0	1	1	0	0	1	3
Dry mouth	0	0	2	1	0	0	3
Easy Fatigability	0	0	0	0	0	1	1
Erectile Dysfunction	0	0	1	0	0	0	1
Headache	3	1	2	1	1	0	8
Hyperacusis	0	0	0	1	0	0	1
Muscle pain	0	0	0	0	0	1	1
Nape Pains	0	0	0	0	1	0	1
Nausea	0	0	0	0	1	0	1
Palpitations	0	0	0	1	0	1	2
Temporal headache	0	0	0	0	1	0	1
Tingling sensation	0	1	0	0	0	0	1
Not specified	0	2	0	1	0	11	14
Total	**3**	**7**	**10**	**5**	**4**	**15**	**44**

Table 13: Number of AEs by Causal relation to drug.

that nebivolol is a safe and effective beta-blocker for the treatment of hypertension. The adverse events reported were consistent with the adverse event profile seen in previous clinical trials and had no significant effect on the outcome of treatment. Its cardioselective and unique vasodilating effects through nitric oxide stimulation makes it an ideal drug for the treatment of essential hypertension. In this real-world study, the use of nebivolol resulted in sustained decrease in both systolic and diastolic blood pressures, reinforcing its clinical usefulness in the maintenance of BP control.

Declarations

Ethical approval and consent to participate

Informed consent was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The terms of this arrangement have been reviewed and approved by the Institutional Ethics Review Committee of St. Luke's Medical Center, Research and Biotechnology Division, Quezon City, Philippines in accordance with its policy on objectivity in research.

Mental Sanity and the Italian Criminal Code

The Italian Criminal Code specifies different types of murder categorized in relation to the degree of responsibility, around the central concept that murder is the intentional or voluntary killing of a person committed with malice, according to Art. 575 of the Penal Code: "whoever causes the death of a human being is punishable by no less than 21 years in prison". Intentionality is the key element where degree of responsibility relies.

Jurisprudence, to attribute responsibility, when elements of doubt regarding incriminated suspect' mental state arise, relies on forensic psychiatrists that enter the criminal case to assess the mental state of the individual who committed the crime. Particularly, judges need to establish mental condition referred to the specific moment the crime has been committed. Psychiatric disorders as schizophrenia or psychotic disorders are recognized to diminish the capacity of appreciation of right and wrong and considered to be able to impair the decisional process of the subject, only in these rare cases, offence is causally determined by the mental disorder, indeed "no one may be punished for an act foreseen by the law as a crime, if at the time when it was committed the subject was not is imputable". Statistically, a small percentage of individuals suffering of mental disorders (MD) engage in criminal activities, between 5% and 16% of murderers are diagnosed with a major psychiatric disorder.

Personality Disorders (PD) are not automatically associated with a mental impairment, to evaluate their role in terms of mental sanity and mens-rea is necessary to prove that the influence of PD's has produced with consistency, intensity and seriousness, an effect on the ability to understand and to will of the subject consequently impeding an appreciation of the consequences of his/her conduct. Any definition of pathological personality must be clearly distinguished since personality disorders are not medical conditions, rather are extrinsic and lasting models covering the entire matrix of the person that functions in a non-functional adaptive way in response to environmental stimuli (Millon). In relation to SVPD issue around responsibility is still an open debate since internationally, Penal Laws, do not unanimously consider PD as a condition that can diminish the offender responsibility. Current research explores the existence of personality disorders in their most severe outcome as to understand relation between structured formations of the personality and violent offending.

Severe Personality Disorders

According to theory of personality developed by Millon, Borderline Personality Disorder, Paranoid Personality Disorder, Schizotypal Personality Disorder are defined as Severe Personality Disorders (SVPD) (Table 1).

Paranoid personality disorder

The influence of the disorder on interpersonal relations styles is evident, subjects diagnosed with PPD assume that others exploit them, harm them or deceive them, even when there is no evidence to support these expectations, such expectations make them anticipate behaviors that will not happen out of their minds and press them to react in an avoidant

manner, since they tend to think that others are plotting against them and may attack suddenly without any reason they can fantasize about eliminate the threat they perceive. The aggression could be triggered by the will to eliminate the fear of an expected event. Specific traits of PPD females in the study will be analyzed in the crime context by exploring the motivational sphere of the homicide.

Borderline personality disorder

BPD generates a significant level of emotional instability and is characterized by a distorted image of self, subjects experience feelings of worthlessness and the idea of being fundamentally defective. Pervasive emotional states are characterized by intense anger, rage, grief, shame, panic, terror and a chronic feeling of emptiness and loneliness. BPD distinctive behavioural pattern is impulsivity linked to a condition of intolerable pain and urgency. Another feature is mood instability; sudden changes occur moving from dysphoric states to depressive ones.

Impulsivity can be of two types: self-destructive-as suicide attempts, self- mutilation, suicide attempt and a more general form of impulsivity that expresses with substance abuse, eating disorders, verbal outbursts, reckless driving violent aggressions.

Schizotypal personality disorder

The subjects diagnosed of SPD are socially and emotionally detached, in the most severe form they may show oddities in thought, perception and communication like those detectable in schizophrenia. Although Schizotypal personality can sometimes precede the onset of schizophrenia, most adults with this personality disorder do not develop schizophrenia rather maintain a functional asset. Some people with SPD show signs of magical thinking that is the belief that one's thoughts or actions can control events and/or others without acting directly on them. People with a SPD may also have paranoid ideas. The essential feature of Schizotypal Personality Disorder (SPD) is the presence of a pervasive pattern of social and interpersonal deficits, exacerbated by an acute discomfort and a reduced ability to create and keep stable relationships as well as distortions and eccentricities of behavior.

Individuals with Schizotypal Personality Disorder often misinterpret both internal events and external events as if they have unusual meaning. These should be distinguished from delusion, in facts misinterpretation is more likely linked to the meaning associated to stimuli. Individuals with this personality model are often suspicious and may have paranoid-like ideation and interpret others' behaviors as malignant.

Functional subjects diagnosed with SPD show problems in dealing with others.

Inter-personal Experiences and Personality Correlates

Stern [20] considers contents of the mind as products of interpersonal experience, development of mental representations, possible pathways in which past interpersonal experience is internalized into mental structures. The process of structuring mental representations was approached by Benjamin who tried to explain how interpersonal experiences are internalized and how important is their role in defining the self as well as in guiding and managing future relationships. He proposed a copy processes model formed of three phases:

Identification: mirroring back others, by treating others as they treat us, reflects the basic of social learning and is often associated with the phase in which children identify with their caregivers;

Recapitulation: Maintaining a substantial stable style of relating to others based on the acquired model;

Introjection: Treating the self-copying the ways the self has been treated by others.

According to this theoretical approach failure to achieve to determined developmental goals may consistently influence the development of rigid relational style within the personality structure. Negative traumatic experience play a central role in the failure process, these may be experiences of physical abuse, sexual abuse, early loss of attachment figure, childhood injury or illness, consistently with numerous studies that confirm how traumatic childhood has characterizes the life of a high percentage of criminals.

Sample

Sample of current research N=30 incarcerated and convicted female murderers. The Italian penal system is composed of three degrees of judgement and all participants went through third degree condemnation. The age range was 21-52 years old. In Italy around 800 homicides are committed per year, crimes are solved by a rate of 60%. Most of these homicides are committed by men. Female prisoners' population corresponds to 4% of the general prisoner's population corresponding to 1% of murderers convicted and in detention. Women are responsible for the 2% of the killings of men on a year base rate.

Demographic Questions

Participants were asked to answer to a set of demographic questions that allowed the picking of relevant data regarding familiar background and level of education, it was also possible to appreciate previous criminal convictions of participants. All participants are female over the age of 18. All offenders are White Caucasian (N=30, 100%) and of European ethnicities. The range of education background varied from none to a high school diploma. None of participants had a college education (Figure 1).

Regarding childhood, offenders when children lived with: N=2 in adoptive families, N=2 with father or mother, N=4 with other relatives, N=3 in orphanage, N=19 with both parents (Figure 2).

Instrument

The MCMI-III is a clinically oriented tool used to assess personality models and personality pathologies, its theoretical framework originates from the evolutionary theory and describes personality as evolutionary constructs arising from the interaction between individual and environment, behavior derives from this specific interaction [19], MCMI inventory was used in over 600 researches.

Three dimensions of personality are measured to assess specific models of personality: assets / liabilities, guidance on self / on others, motivation, pleasure /pain to assess specific models of personality.

MCMM-III distinguishes between:

1. **Personality styles:** that comes predominantly from within the individual;
2. **symptomatic disorders:** 1) Characterized by the interaction between individual characteristics and environmental situations/external events. 2) Characterized by adjustment reactions: pathologic responses to environmental events.

Structure of MCMI-III corresponds to DSM V parameters; clinical scales are grouped into categories of personality and psychopathologies specifications reflect distinctions made by DSM that distributes disorders in Axis I and Axis II.

Obs	Control Number	Adverse Event	Date of Onset	Date of Resolution	Severity	Treatment	Other	If yes, Other Treatment	Outcome	Causal Relation to Drug
1	0237	Bradycardia	14MAY2014	15MAY2014	Mild	Stopped	Yes	Alzor CCB 20/5mg/tablet OD Eltroxin 150 mg/tablet OD	Disappeared	Possible
2	0526	Palpitation	23APR2014	25APR2014	Moderate	Stopped			Improved	Unknown
3	0531	Dizziness	30JUN2014		Moderate	Stopped	Yes	LOSARTAN 50 mg OD	Disappeared	Probable
4	0701	Erectile Dysfunction	01JUL2014		Mild	Continued	No		Unchanged	Possible
5	0710	Bradycardia	17SEP2014		Mild	Continued	No			Possible
6	0901	Dizziness	01MAY2014	03MAY2014	Moderate	Continued	No		Disappeared	Probable
7	1292	Headache	06JUN2014	20JUN2014	Moderate	Continued	Yes		Improved	Definite
8	1298	Headache	19JUN2014	23JUN2014	Mild	Continued	No		Improved	Definite
9	1300	Headache	29JUN2014	13JUL2014	Mild	Reduced	No		Improved	Definite
10	1333		06JUN2014	07JUN2014	Mild		Yes	Omeprazole Maalox	Disappeared	Probable
11	1334	Hyperacusis			Moderate	Reduced	Yes		Disappeared	Unknown
12	1352		30MAY2014		Mild	Stopped	No		Disappeared	Unknown
13	1381		05DEC2014		Moderate	Continued	No		Improved	
14	1382		06DEC2014		Moderate	Continued	Yes	Pritor	Improved	Probable
15	1383		13NOV2014		Mild	Continued	Yes	Losartan	Improved	
16	1383		04DEC2014		Mild	Continued	Yes	Trivase	Unchanged	
17	1384		03DEC2014		Mild	Continued	Yes	Metoprolol	Improved	
18	1385		06SEP2014		Mild	Continued	Yes	Trivase Dologesic	Improved	
19	1386		05DEC2014		Moderate	Continued	Yes	Pritor, Trivase, Imdur, Zerodol		
20	1387		05DEC2014		Mild	Continued	Yes	Amlodipine		
21	1388		25JUN2014		Moderate	Reduced	Yes	Candez	Improved	
22	1388		15SEP2014		Moderate	Continued	Yes	Exforge	Improved	
23	1389		09DEC2014		Mild	Continued	Yes	Lanoxin Aldactone	Improved	
24	1390		09DEC2014		Mild	Continued	Yes	Relaxid		
25	2101	Dry mouth			Moderate	Continued	No		Unchanged	Possible
26	2102	DOB			Mild	Reduced	No		Improved	Probable
27	2102	Headache			Mild	Reduced	No		Improved	Probable
28	2103	Chest Pains			Moderate	Reduced	No		Improved	Possible
29	2103	DOB			Mild	Reduced	No		Improved	Possible
30	2104	Easy fatigability			Moderate	Continued	No		Improved	
31	2105	Headache			Mild	Continued	No		Disappeared	Not related
32	2106	Palpitations			Mild	Continued	No			
33	2107	Headache			Moderate	Reduced	No		Improved	Possible
34	2108	Chest Pains			Moderate	Reduced	No		Disappeared	Possible
35	2109	DOB			Moderate	Continued	Yes		Disappeared	
36	2109	Dry Mouth			Moderate	Continued	No		Disappeared	Unknown
37	2110	Dry Mouth			Moderate	Continued	No		Disappeared	Possible
38	2110	Headache			Mild	Continued	No		Disappeared	Unknown
39	2110	Nape Pains			Mild	Continued	No		Disappeared	Not related
40	2123	Temporal headache	15MAY2014		Mild	Continued			Improved	Not related
41	2126	Headache	12MAY2014		Mild	Continued	No		Improved	Possible
42	2126	Nausea	05MAY2014		Mild	Continued	No		Disappeared	Not related
43	2130	Muscle pain	10MAY2014		Moderate	Continued				
44	2264	Tingling sensation	06SEP2014		Mild	Continued	Yes	OLMESARTAN	Improved	Probable

Table 14: Line Listing Of Adverse Events.

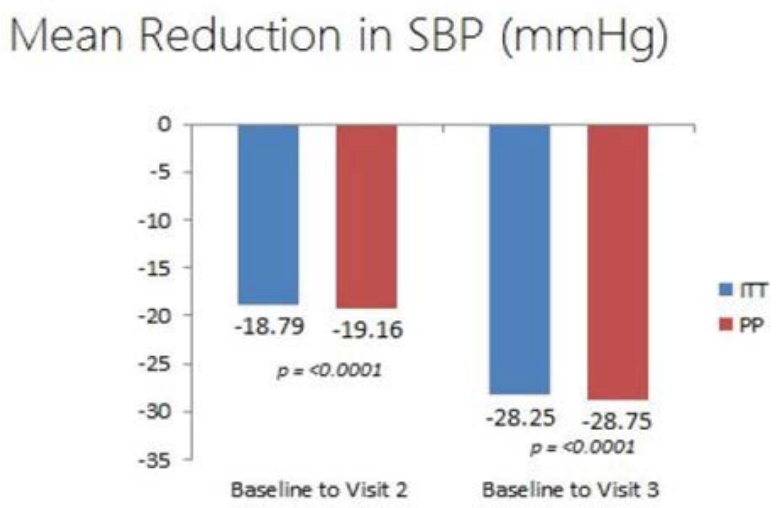

Figure 1: Mean reduction in systolic blood pressure SBP (mmHg) after treatment (ITT- Intention to treat, PP- Per population).

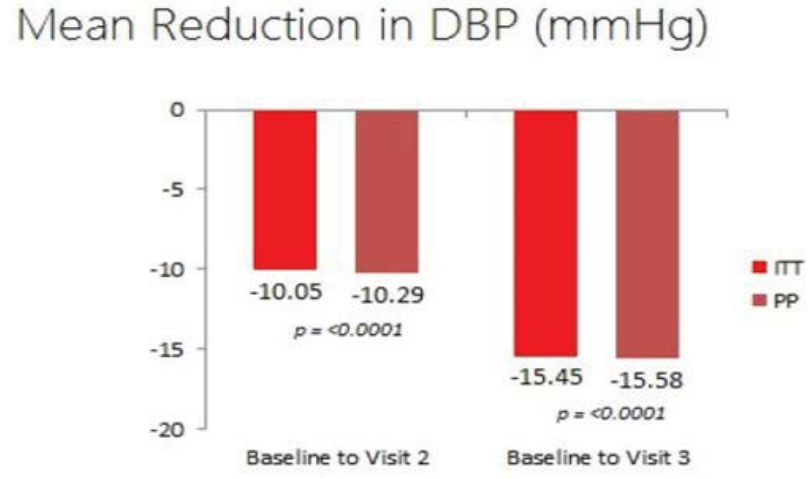

Figure 2: Mean reduction in diastolic blood pressure DBP (mmHg) after treatment (ITT- Intention to treat, PP- Per population).

The MCMI-III is a tool for self-assessment composed of 175 dichotomous response items: true/false.

The instrument provides 8 basic patterns of personality: Schizoid, Avoidant, Dependent, Histrionic, Narcissistic, Antisocial, Compulsive and Passive-Aggressive; it defines three structures of pathological personality: Paranoid, Borderline and Schizotypal.

MCMI also generates nine clinical syndromes related to Axis I: Anxiety, Somatophorm disorder, Hypomania, Dysthymia, Alcohol Abuse, Drug Abuse, psychotic ideation, psychotic depression and psychotic delusions.

Ethics

Researcher personally assessed 30 female murderers. Access to group of offenders was authorized by the Penitentiary Administration and respected ethical guidelines of National Order of Psychologists Association. Participants were asked to consent on taking part in the research *via* a signature on the consent form. Participants were explained that they were free to withdraw from the interview at any time. Confidentiality was also explained before the collecting of data started. Participants were explained that all information release would be used in complete anonymity and for the sole and unique purpose of the study.

Results

Female offenders filled response sheets provided with the MCMI-III questionnaire and answered several biographical questions. Scores of 75-84 indicate a significant personality trait; scores 85 and higher indicate a personality disorder. The analysis and processing of the response resulted in a consistent frequency of diagnosis of SVPD: N=13 BDP, N=6 PPD, N=5 SPD, N=6 NO SVPD (20%) (Table 2 and Figure 3). For the N=6 participants who did not score above 85 the higher scoring

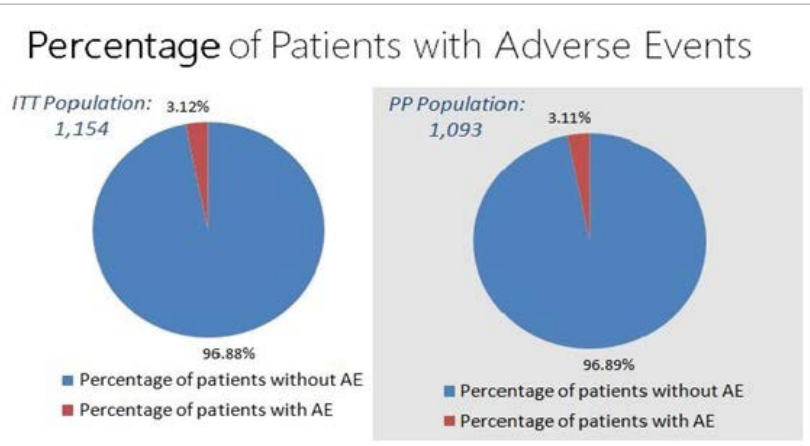

Figure 3: Percentage of patients with adverse events to nebivolol (Nebilet). Only 3% of patients had adverse events in the intention to treat (ITT) population and in the per protocol (PP) population.

resulted as follow N=2 Dependent, N=1 Avoidant, N=1 Negativistic, N=1 Antisocial, N=1 Narcissistic.

Personality disorders role in criminal behaviors

It was hypothesized that specific behavioral patterns of female murderers are consistent with the very violent nature of the criminal action it-self, research explored consistency and presence of personality models and interpersonal styles possibly to determine their role in violent behavior. N=24 female offenders were diagnosed with three major severe personality disorders.

Particularly, Borderline Personality' Model is characterized by impulsivity, affective instability and anger reactions, violent offenders may be more likely diagnosed with BPD compared to other personality disorders. Logan and Blackburn found that women condemned for violent crimes, with higher degree of violence involved, were more likely to be diagnosed with BDP, in a sample of 95 women incarcerated, those diagnosed with BPD were four times more likely to have been associated with violent offenses [22]. BDP appears to be a parameter for predicting violence [23], present study confirms that BDP is more represented in women of the sample.

Crime dynamics and characteristics

Weapons: Interesting element to be analyzed relate to instruments or methods used to kill: N=8 firearms, N=8 knives/scissors, N=3 strangulation/ suffocation, N=9 mixed methods, N=1 unusual object, N=1 sleeping pills. No weapon has been chosen relevantly in comparison to others. Location-Homicides perpetrated by women generally occur at home [24], present research confirms previous findings, N=26 committed murder at home.

Body disposal: Regarding victims' body disposal after murder, N=28 left the body at the location where murder occurred, N=2 with the help of co-offenders tried to hide the body to avoid investigations from law enforcement officers.

Planning: Considerations are done on the planning of killings, according to results no direct correlation can be done between the presence of a SVPD and level of planning, indeed both affected and not affected offenders display patterns of planning. In three (3) cases offense occurred in presence of co-offenders. A crime may be the result of a sudden impulse or rather be the result of a planning, the planning can be characterized by different levels of ideation, specific details may be previously conceptualized by the subject, in this second hypothesis is clear that preparation dimension cannot be associated with a mental state which inhibits control, crime planning is an element that reflects the degree of sophistication, which is non-consistent when subject suffers from serious mental disorders that inhibit a concrete and balanced evaluation of the circumstances. N=29 murders show a level of planning only N=1 case is a result of an impulse; this specific case relates to a BPD diagnosis.

Victims: Victims' relationship to the offender was obtained during the assessment. Victims of female offenders are more likely persons belonging to their interpersonal sphere. Emotions' role and internal processes linked to it play a central role in this group of criminals. Only in N=2 cases victim was a stranger, N=28 were intimate partners, victims were husbands, lovers, relatives. No young children were between the victims.

Discussion and Conclusion

High prevalence of diagnosis of Severe Personality Disorders is significant to the purpose of the study especially in relation to NON-SVDP. Murder has not a direct link with a Severe Personality Disorder except for the internal emotional dynamics involved. Murder is more closely linked to the way relationships are experienced than to the personality pathology that instead represents the layout and the frame in which they have evolved and structured over time. The percentage of women who have killed and who do not show signs of pervasive personality disorders demonstrate that personality disorder holds a secondary role and not a causative direct role in the will to kill. The inter-relational dimension is the intimate space where murder is built long before being materially committed. Present research confirms that female violent offenders offend more than men in the sphere of intimate relationships, elements linked to the way these offenders relate to their victims as well as the cognitive processes involved give insight to their motivational drive to kill. SVPD are characterized by pervasive patterns of imbalanced interpersonal functioning which express in a general inability in managing relations in a functional and stable way but the same emotional cognitive complexity is found in NON-SVPD offenders represented in the 20% of sample. Findings draw a line between pathological and functional. Murders are committed in N=29 cases show degree of planning and sophistication. Forensic implications can be drawn both on a psychiatric dimension and on a judicial dimension.

Murderous behavior arises from a continuous modelling and re-

modelling of interpersonal experiences that derive from experiences of satisfaction, safety and respect, projecting into patterns of personality. Transactions between persons and environment constitute specific patterns that unveil inner cognitive processes and working models offering an insight of personality and its expression in violent offending behavior.

Limitation of the Study

Limitation is represented by the small sample N=30, in this perspective is important to highlight that in Italy female offenders represent less than 5% of total criminal offenders and less than 2% of murderers. 30 respondents represent 25% of 120 homicidal women incarcerated in the national territory.

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