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Proton-Pump Inhibitors Therapy and Blood Pressure Control

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Abstract
Objective: To evaluate the potential impact of inhibitors of proton-pump in blood-pressure. .
Methods: In a 24-hour-ambulatory-blood-pressure-monitoring (AMBP)-database we analyzed records of 462-hypertensive-patients according Proton-Pump Inhibitors (PPI). 150(33%)-patients were regularly users of PPI, and 312(67%) nonusers of PPI. Ambulatory-blood-pressure was measured non-invasively for 24--hours by the Spacelab-devices programmed-to-measure every 20-minutes during-daytime and every 60-minutes during-nighttime.
Results: Systolic-blood-pressure (SBP) was lower in the Proton-Pump Inhibitors (PPI)-group (135±20.vs.139±16mmHg, p=0, 02) as well as diastolic-blood-pressure (DBP) (76±10.vs.83±10mmHg, p<0.001). Multivariate-analysis showed that use of beta-blocker (OR, 2.60) and PPI (OR, 2.70), were independently associated with blood-pressure-control.
Conclusions: This study shows that concomitant PPI therapy in hypertensive-patients was associated with a small but statistically significant-reduction in 24-hours-BP, even after multivariate-adjustment. However, this statistical difference seems to lack clinical relevance.
Keywords: Proton-Pump-Inhibitors, Blood-Pressure-Reduction, 24-hours Ambulatory-Blood-Pressure

1. Introduction
Blood Pressure (BP) is an important biologic parameter that is predictive of cardiovascular outcome[1]. Evidences from randomized trials have shown that effective antihypertensive treatments reduce cardiovascular morbidity and mortality[2]. However, community-based studies show that blood pressure goals are achieved in only 25 to 40% of the patients who take antihypertensive drug treatment[2,3]. It is estimated that roughly half of deaths due to coronary heart disease can be attributed to sub-optimal BP control[1]. The investigation of factors which have an influence on BP control has a relevant interest.

A variety of therapeutic agents or chemical substances can induce a transient or persistent change in blood pressure, or they can interfere with the blood pressure-lowering effects of antihypertensive drugs[3]. Some experimental studies have suggested that Proton-pump inhibitors (PPI) could play a role in blood-pressure (BP) reduction[3,4,5]. Moreover, since PPI are used for long periods on prevention of digestive hemorrhage in cardiovascular patients who use the antithrombotic therapy[6,7] PPI must be taken into account for potential drug-drug interactions.

The potential role they may have PPI in patients at high cardiovascular risk in whom an adequate BP control is even more important is unknown. Often patient's polymedicated by the complexity of diseases intercurrents, that could also interferes or dilute with the potential pleiotropic effects. We study hypertensive patients according IBP therapy, and investigate the effect of PPI on BP using ABPM 24 hours in all cases.

2. Patients and Methods
In this transversal study, we analyze clinical data – which were stored in a database – of patients over 18 years old with diagnosis of essential hypertension and therapy of antihypertensive drugs. These data were analyzed by ABPM. Patients were divided in two groups: those who use PPI and those who do not use it. All patients provided written consent to the participation in the record according to the requirements of the ethics committee within each hospital. All ethics committees from all hospitals approved the study. Inclusion criteria were: Medical suspicion of white-coat hypertension or drug resistant hypertension, and exclusion criteria: pregnant women or patients who do not follow the treatment. The study included 462 patients from 492 patients recruited. Mean age was 59±12 years, 259 were men (56%). A prospective surveillance of BP was performed.

Participants underwent 24-h ABPM during the working day before the clinic visit. At ~08.00 hours, participants were attached with an ambulatory BP monitor (90207 ABP monitor. Spacelabs Healthcare, Washington, USA) on the non-dominant arm. The apparatus was programmed to measure BP at twenty min intervals during daytime (08.00–22.00 hours) and at sixty minutes intervals during nighttime (22.00–08.00 hours). On average, the cuff successfully inflated 76% of the time across all participants. Participants were asked to carry on with their daily activities but they have to stop moving and have to be quiet during measurements. Also, during measurements, patients were asked to write down any abnormalities, such as: headache, nausea, or feeling stressed – on their ambulatory diary cards. Only patients with 20 or more successful daytime readings were included. Patient instructions and monitors' applications were performed by an experienced researcher, who was trained in the procedures of blood pressure measurement. The researcher used a standardized protocol based on the European Society of Hypertension guidelines (www.eshonline.org).

Patients, who took their daily treatment during 20 or more days per month, were considered good users of the treatment. Variables were registered: sex, age, anthropometric measures, educational status, smoking history, alcohol intake, exercise, records of cardiovascular disease, diagnosis' date of hypertension, diabetes and time from diagnoses, Metabolic Syndrome (ATP criteria), sleep apnea syndrome (objective diagnosis with a sleep study). Some biochemical tests were performed: plasma lipids, Reactive C Protein and creatinine and urine albumin-to-creatinine ratio in the first morning urine sample.

All data were expressed as the mean± standard deviation for continuous variables and as proportions for categorical variables. The differences in the values of the variables between groups were tested with chi-square statistics or t-test when appropriate. Logistic regression was used to examine the associations with BP control. BP control was defined as 24-hour systolic <130 mm Hg and diastolic < 80 mm Hg. The models were adjusted for covariates, including age, sex, diabetes, albumin-to-creatinine ratio, history of ischemic cardiovascular disease and received treatment (diuretic agent, ACE inhibitor, ARB, or both, beta-blocker and three or more drugs for antihypertensive, antithrombotics drugs, statins, oral antidiabetic drug, and PPI). These covariates were selected from univariate analysis. P<0.05 was considered to be statistically significant. Data were analyzed using the SPSS, version 15.0 software package (SPSS Inc., Chicago, Illinois, USA).

3. Results

PPIs users were 150 (32%), and their distribution was: omeprazole 114 (76%); esomeprazole 16 (11%); lansoprazole 12 (8%); raveprazole 6 (4%), and pantoprazole 2 (1,3%) patients. Table 1 shows the baseline characteristics of patients included in the study. PPIs users were older (63±11 years vs 56±12, p <0.001), there were more women (57% vs 38%, p <0.001) and a lower proportion of patients with higher studies (12% vs 29%, p <0.001). No differences between groups were observed according to body weight and smoking status. Use of PPI also was associated with previous records of cardiovascular disease, 53 (35%) vs 36 (11%) of non PPIs users (p<0.001) (see table 1).

Also the number of treatments was different: 28 (36%) of PPIs users were taking 3 or more hypertension drugs vs. 29 (18%) of PPIs non users, p<0.01. The level of significance was maintained for the different class of antihypertensive family. Antithrombotic treatments (anticoagulants and antiagregants) were used by 40 (52%) of PPIs users vs. 48 (30%) of non users (p<0.01). Also statins use was more frequent among PPIs users, 55 (71%) vs. 83(51% p<0.01).

The table 2 shows mean BP in the ABPM study in the different groups. During 24h, SBP was lower in the PPIs users group 135±20 vs. 139±16 mmHg in the other group, p=0,003) as well as 24h DBP 76±10 vs. 83±10 mmHg (p<0.001). The average difference was 4 mmHg (SBP) and 7 mmHg (DBP), in the 24h lapse. Similar differences were found during daytime (6 and 7 mmHg respectively) and during nighttime (3 and 5 mmHg). Significances are shown in table 2. Adequate BP control (< 130/< 80 mmHg) was achieved in 63 (42%) for PPIs users vs. 67 (21%) for PPIs non users (p<0.001).

The table 3 shows univariate and multivariate analysis results from the clinical and therapeutic characteristics in relation to BP control achievement. Only two variables were independently associated with BP control in the ABPM (OR, 95%CI): use of beta-blocker 2.60 (1.23-5.45) and PPIs treatment, 2.70(1.50-4.82). On the other hand, albumin-to-creatinine ratio >30 mg/dL, 0.41 (0.17-0.99), and ischemic cardiovascular disease record, 0.37(0.17-0.80) were negatively associated with BP control.

Table 1: Characteristics of patients regarding Proton-Pump Inhibitors therapy

	No Proton-pump inhibitors treatment N=312	Proton-pump inhibitors treatment N=150	P value
Variable			
Demographic characteristic			
Male sex-no.(%)	194(62%)	65(43%)	<0.001
Age-yr	56±12	63±11	<0.001
University education	92(29%)	18(12%)	<0.001
Clinical characteristic			
Smoking history-no/total no.(%)			
Never	64/324(20%)	22/154(14%)	NS
Former	94/324(29%)	38/154(25%)	NS
Current	166/324(51%)	94/154(61%)	NS
Alcohol ingestion			
Nothing	226(72%)	114(76%)	NS
Daily intake-gr/24 h	27±19	37±19	NS
Moderate or vigorous exercise#	200(60%)	82(52%)	NS
History of ischemic cardiovascular disease	36(11%)	53(35%)	<0.001
History of cerebrovascular disease	18(5.6%)	32(35%)	<0.01
History of coronary artery disease	15(4.8%)	20(13%)	<0.01
History of peripheral vascular disease	15(4.8%)	19(13%)	<0.01
Time from hypertension diagnosis-yr	9.1±8.9	9.4±8.4	NS
History of Diabetes Mellitus	53(17%)	45(30%)	<0.01
Time from diabetes diagnosis-yr	8.9±7.7	7.2±7.1	NS
Glycated hemoglobin-%	6.1±1.0	6.1±0.9	NS
Body-mass index	30±5.1	30±5.8	NS
Waist circumference: (men >102 cm, women > 88 cm)	144(53%)	75(54%)	NS
Diagnosis of Metabolic Syndrome	98(31%)	43(29%)	NS
Atrial Fibrillation	12(3.8%)	22(15%)	<0.001
Sleep Apnea Syndrome	33(11%)	17(11%)	NS
Laboratory results			
Cholesterol-mg/dL			
Total	192±39	195±38	NS
LDL	115±36	115±37	NS
HDL	52±14	53±13	NS
Triglycerides-mg/dL	132±90	131±71	NS
Reactive C Protein-mg/dL	3.2±6	3.0±2.8	NS
Creatinine- mg/dL	0.91±0.2	0.95±0.4	NS
Albumin-to-creatinine[§] ratio. Level >30 mg/dL-no. (%)	32(13%)	23(24%)	<0.05
Medications-no. (%)			
Diuretic agent	89(28%)	68(45%)	<0.001
ACE inhibitor, ARB, or both	172(55%)	106(71%)	<0.01
Calcium-channel blocker	75(24%)	61(41%)	<0.001
Beta-blocker	40(13%)	39 (26%)	<0.01
3 or more drugs for hypertension	56(18%)	56(37%)	<0.001
Antithrombotics drugs*	90(29%)	79(53%)	<0.001
Statin	156(50%)	107(71%)	<0.001
Antidiabetic drug[&]	74(24%)	46(31%)	NS

Plus-minus values are means±SD. Percentages may not total 100 because of rounding.
Defined as a score on the Physician-based Assessment and Counseling for Exercise (PACE) evaluation of 4 to 8, indicating moderate exercise at least five time s per week to vigorous exercise at least 3 days at week for a least the previous 6 months.
ACE denotes angiotensin-converting enzyme. ARB angiotensin-receptor blocker.
The body-mass index is the weight in kilograms divided by the square of the height in meters.
[§]The ratio is based on measurement of albumin in milligrams and creatinine in grams.
*Aspirin, clopidogrel or vitamin K antagonists. [&]: Oral Antidiabetic drugs or insulin

Table 2: Ambulatory Blood-Pressure Monitoring regarding Proton-Pump Inhibitors therapy

Blood-pressure- mm Hg	NoProton-pump inhibitors treatment (N=312)	Proton-pump inhibitors treatment (N=150)	p value
24-hour systolic	139±16	135±20	0.02
24-hour diastolic	83±10	76±10	<0.001
Daytime systolic	142±16	136±20	0.005
Daytime diastolic	86±11	79±10	<0.001
Nighttime systolic	131±18	128±21	0.05
Nighttime diastolic	75±10	70±10	<0.001
24-hour control-n(%)*	67(21%)	63(42%)	<0.001

Mean ± Standart Deviation. * Systolic Blood-Pressure <130 and Diastolic <80 (mm Hg)

Table 3: Patient clinical and therapy characteristics, for 24 hour blood pressure control (univariate and multivariate analyses)

Characteristics	24 hour blood pressure			
	No 24 hour blood pressure control (N=332)	24 hour blood pressure control (N=130)	Univariate analysis control vs no control	Multivariate analysis control vs no control
	n (%)	n (%)	Odds ratio [95% CI]	Odds ratio [95% CI]
Men	207 (62)	52(40)	0.40(0.27-0.61)	0.63(0.35-1.15)
Age ≥ 60 years	134(41)	65(52)	1.58(1.04-2.39)	0.76(0.40-1.43)
University education	89(27)	21(16)	0.53(0.31-0.89)	-
Moderate or vigorous exercise	197(59)	74(57)	0.90(0.60-1.35)	-
Current smoking	64(19)	22(17)	0.94(0.63-1.42)	-
Metabolic syndrome	107(32)	34(26)	0.74(0.47-1.17)	-
Diabetes	71(21)	27(21)	0.97(0.58-1.59)	-
Obesity	151(45)	45(35)	0.63(0.42-0.97)	0.60(0.32-1.10)
Albumin-to-creatinine[§] ratio. Level >30 mg/dL-no.(%)	45(18)	10(11)	0.60(0.28-1.24)	0.41(0.17-0.99)
Atrial fibrillation	24(4.2)	10(7.7)	0.86(0.43-2.01)	-
Sleep Apnea Syndrome	39(12)	11(8.5)	1.44(0.71-2.91)	-
History of ischemic cardiovascular disease				
Cerebrovascular disease	47(14)	42(32)	0.35(0.21-0.56)	0.37(0.17-0.80)
Coronary artery disease	24(7.2)	26(20)		
Peripheral vascular disease	20(6)	15(11)		
	15(4.5)	16(15)		
Medication				
Diuretic agent				
ACE inhibitor, ARB, or both	100(30)	57(44)	1.81(1.19-2.75)	1.85(0.87-3.94)
Calcium-channel blocker	190(57)	88(68)	1.57(1.02-2.40)	1.19(0.62-2.32)
Beta-blocker	100(30)	36(28)	0.89(0.57-1.39)	-
3 or more drugs for hypertension	46(13)	36(28)	2.57(1.56-4.24)	2.60(1.23-5.45)
	70(21)	42(32)	1.79(1.14-2.81)	0.68(0.27-1.72)
Antithrombotics drugs*				
Statin	109(33)	60(46)	1.75(1.16-2.65)	0.66(0.31-1.41)
Antidiabetic drugs[&]	175(53)	88(68)	1.88(1.23-2.88)	1.27(0.66-2.43)
Proton-pump inhibitors treatment	86(26)	34(26)	1.01(0.64-1.61)	0.85(0.41-1.77)
	87(26)	63(48)	2.65(1.74-4.04)	2.70(1.50-4.82)

[§] The ratio is based on measurement of albumin in milligrams and creatinine in grams.* Aspirin, clopidogrel or vitamin K antagonists. [&]. Oral antidiabetic drugs or insulin

4. Discussion

The influence of drugs in BP is a well-known phenomenon. In general, drug-induced pressure increases are small and transient. However it can be more pronounced in patients with preexisting hypertension, in patients with renal failure, and in the elderly. On the other hand, some non-antihypertensive drugs like statins or rosiglitazone might lower systolic blood pressure particularly in patients with high blood pressure[3,4]. The potential mechanisms by which PPIs therapy may lower BP are unknown, and probably cannot be explained by a single simple mechanism. Like statins, PPI may exhibit a variety of pleiotropic effects. Currently available data suggest that PPI may be associated with immunoregulatory effects, osteoporosis-related fractures, *Clostridium difficile* associated diarrhea, community and hospital-acquired pneumonia and refractory hypomagnesemia[3,4]. Regarding to regulatory effect on BP, experimental studies have demonstrated that PPI may have a direct mechanism in the regulation of human vascular tone[3,4,5]. The vasorelaxant effects have been previously demonstrated in artery rings isolated from experimental animals[9-11]. Omeprazole and lansoprazole both induced

concentration-dependent, reversible and reproducible relaxations of human artery internal mammary. The mechanism of this effect on arterial tree can be explained by the regulation of intracellular Ca2+.[3,4] Other potential pathway involves PPI interactions with cardiovascular drugs[3,4]. PPI are CYP2C9 and CYP2C19 moderate inhibitors which may reduce the metabolism of the substrates of this pathways (i.e. losartan, torasemide or some beta-blockers) and serum concentrations could increase[3]. In another side, other data do not support the fact that PPI use may have a significant and inmediate impact on hemodynamic parameters in a high-risk intensive care setting[17]. However this has not been studied in patients who were clinically stable in the daily practice.

The ABPM shows that patients who take PPI had a lower SBP and DBP than those who do not take PPI drugs. The reduction of BP was similar in day and night values. These findings suggest that PPI therapy in hypertensive patients may be associated with a small – but significant – reduction of the average blood pressure in 24 hours. However, this reduction of less than 5 mmHg systolic BP not seems to be important enough to provide cardiovascular protection in the subgroup of patients with advanced cardiovascular disease[3]. Whatever we do not know whether this effect could be maintained steadily over time.

PPI users had ischemic cardiovascular disease, diabetes, atrial fibrillation or microalbuminuria more often than nonusers. These patients are considered to be high risk patients, and current guidelines establish more aggressive therapeutic objectives and the use of antithrombotic therapy which advise for the treatment with PPIs for preventing digestive disease. This might suggest that PPI therapy is a bias result to an aggressive treatment in a highly motivated group of patients, mostly after myocardial infarction. Although all patients have been recommended with a reduction of salt intake in their diets, the monitoring of this recommendation should have been contrasted. Beside the previous stated, a higher use of diuretics in the PPI group can make a significant difference in BP control.

The main limitation of this observational study is that it is based on a database of ABPM. We are aware that this study does not provide the guarantees of a controlled prospective study and that this type of disease is an extremely complex disease and there are many factors that can influence and beyond those provided in the analysis should be thought. And what could be considered a bias is rather strength of the study. Because patients with major cardiovascular damage are undoubtedly aware, are often better treatment compliers; promoting better control of blood pressure. It could not to tip the balance towards a potential protective effect for the use of PPIs. And although, it seems undeniable hypotensive effect of PPIs at least in the short term. Our study was unable to demonstrate that the differences could have a beneficial clinical impact, as would have been desirable to find.

To date, know the publications of other studies that are intended to look at the impact of PPIs in controlling BP in clinical practice are lacking. But perhaps the mayor interest of this trial is that we could assess the extent to which the use of IBP through its hypotensive effect could have a clinically relevant protective effect of cardiovascular standpoint. When, we were able to compare hypertensive patients with different degrees of cardiovascular damage. Moreover there are a lot questions unanswered that remain. We do not know with certainty which could be the threshold needed in reducing SBP and / or BDP and this value remains unchanged regardless of cardiovascular risk. If indication of IBP is common and observations tend to emerge about unexpected benefits of the drug, and if a reasonable biologic rationale can be profferes, trialists take the next logical step and devise a randomized, controlles trial to determine whether a causal relationship clinical outcome can be shown.

This study offers insights into factors associated with better BP control with an unselected patient population, in contrast to the rigorously controlled conditions of randomized clinical studies. It provides feedback from real-world clinical situations. Probably our main issue is that our experience endorses the fact that PPIs could contribute to a better control of BP in patients with cardiovascular risk. Encouraging conducting controlled studies that can respond to the many questions raised.

In conclusion, this study raises the possibility that PPI therapy reduces the BP among patients with hypertension. However, our findings do not support the hypothesis of this effect may provide cardiovascular protection. Possibly in part to a diminished response of impaired vascular tree, by interaction with a greater number of drugs and certainly by factors that we still are unknown.

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