

ORIGINAL ARTICLE

Risk factors for uncontrolled hypertension in Italy

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To identify factors related to poor control of blood pressure in primary care, we designed a retrospective case-control analysis of clinical and demographic data recorded in the General Practitioners (GP) database. Study data were provided on a voluntary basis by 21 GPs from a practice-based network in primary care. The study included 2519 hypertensive patients enrolled between January 1 and December 31, 2000. The interventions were antihypertensive medication, and the main outcome measures were control of systolic and diastolic blood pressure (BP). The independent variables considered were: age of patient and GP; patient gender, body mass index, history of smoking, diabetes mellitus, or cholesterol tests; family history of hypertension; previous visits for cardiologic, nephrologic, or vascular surgery evaluation; prior hospitalizations for myocardial infarction or heart failure, and number of admissions for surgery; length of patient follow-up, type of antihypertensive medication, mean daily dosage,

adherence to the drug regimen, and number of other medications currently being taken by the patient. Blood pressure was uncontrolled ($>140/90$ mmHg) in 1525 (60%) of the 2519 hypertensive patients enrolled. The presence of diabetes mellitus, increasing patient age, and increasing GP age significantly increased the risk of uncontrolled BP. Factors significantly associated with a reduced risk of uncontrolled BP were the number of other medications currently being taken by the patient and a prior history of MI. We conclude that the failure of antihypertensive medication to adequately control BP is determined by both the patient's characteristics and factors related to the patient-doctor relationship. Successful treatment of hypertension requires patient adherence to the regimen that has been agreed on by the patient and the physician.

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Introduction

In Italy, hypertension is a common medical disorder affecting more than 8 million people.¹ In the Ravenna (Italy) area, antihypertensive drugs are prescribed for an estimated 19% of the population of 355 000.² Despite significant efforts to diagnose and treat hypertension, approximately two out of three people with hypertension have not achieved the generally recommended target blood pressure (BP) of less than 140/90 mmHg,^{3,4} thus remaining at a higher risk for heart attack, stroke, heart failure, and kidney disease. Failure to achieve the targeted BP control is a global problem. In the United States, fewer than 30% of hypertensive patients have BP values lower than 140/90 mmHg,⁵ while, in the United Kingdom, only 6% of hypertensive patients

have attained these target BP levels.⁶ Even with less stringent levels of BP control of 160/95 mmHg, data from Australia, Canada, Finland, India, Scotland, and Spain suggest that no more than 20% of the population would achieve this goal.⁷

The identification of factors related to poor control of BP can help to target populations in need of medical attention, and to aid in the development of effective treatment strategies for specific subpopulations.⁷ The objective of the present case-control study was to identify risk factors for uncontrolled BP among those patients enrolled in the Pandora project, a prospective ongoing global outcomes study begun in 1996 to organize a database for epidemiological assessments and to improve the management of hypertension in primary care.

Methods

Data collection and patients

Of 330 general practitioners (GPs) in the Ravenna, Italy area, 21 voluntarily participated in the PAN-DORA project. In Italy, the GP is the doctor working

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outside the hospital, who is delegated by the National Health System to provide care for a known number of subjects. Each GP was asked to enrol two hypertensive patients per week in the study, starting on 01/01/1996. When this study was carried out, the GPs participating in the Pandora project had a cohort of about 33 000 beneficiary subjects representing 9.3% of persons living in the Ravenna area. The Pandora project was approved by the Local Ethics Committee, and informed consent was obtained from each patient enrolled.

All GPs were supplied with a personal computer that was connected to a remote server via a modem, a printer, an automatic BP device (Dinamap 1846SX, Critikon, Tampa, FL, USA), and a dedicated software package dubbed So.Ge.Pa.[®] The remote server is also linked to the Local Health Unit database (patient, GP, prescription, hospital, and death records) and to the hypertension unit. At the remote station, a team of different specialists (computer scientist, economist, statist, epidemiologist, pharmacologist) produces a variety of reports which are regularly returned to the various operators. The So.Ge.Pa.[®] software controlled the operation of the BP device, which was connected to the computer. The BP value recorded and entered into the database at each visit represented the average of three consecutive readings obtained at 1-min intervals after the patient had remained seated for 5 min. BP was measured in the dominant upper arm during the daytime, morning or afternoon, in accordance with conventional clinical practice. A tube 3.6 m in length and a cuff of 23–33 cm for normal subjects or 31–40 cm for obese subjects were used. Clinical and laboratory data were gathered and stored either by the GPs themselves or through links with Health Service databases, as already documented.⁸

At the enrolment visit, the GP recorded the patient's currently prescribed antihypertensive regimen, defining the drug(s), active ingredient(s), and the number of tablets the patient was instructed to take daily. At the end of each visit, the antihypertensive treatment was again prescribed by the GP, who had complete discretion to decide the type of drug and the dosage for an individual patient, and the frequency with which BP would be measured. The antihypertensive drugs purchased by each patient were identified from the pharmaceutical database kept by the Local Health Unit of Ravenna, which logs each prescription, records the code number of the prescribing physician, the national health number of the patient, the date dispensed, the Anatomical–Therapeutic–Chemical classification (ATC), the number of packs, and the number of tablets per pack.

All drug prescriptions considered in this study are fully reimbursed by the National Health System.

The completeness and coherence of the information recorded for each patient were periodically checked at the remote station and only those patients whose recorded data which satisfied the

inclusion criteria of the study were considered in the analysis.

Patient characteristics and outcome measures

The main outcome measure for this case–control study was BP control (yes/no). Adequate control was defined as a representative SBP of less than 140 mmHg and a DBP of less than 90 mmHg; for patients with diabetes, BP control was defined as a representative SBP of <130 mmHg and a DBP of <85 mmHg.⁴

Eligible patients were at least 18 years of age, and had been enrolled in the Pandora project for at least 1 year prior to the BP measurement period from 1 January to 31 December 2000. Patients were excluded if they had end-stage renal disease or malignant systemic disease (ie lupus erythematosus). The representative BP was the BP reading from the most recent visit during the measurement period. Only those patients whose records included at least one BP value measured at least 365 days before the representative value were included in the study. The control group consisted of those patients with diagnosed hypertension whose BP was adequately controlled at the end of the measurement period. Cases were those patients with diagnosed hypertension whose BP was not adequately controlled at the end of the follow-up measurement period. A patient follow-up period was defined retrospectively as the interval, in days, between the representative BP and the earliest BP value present in the patient's record.

The independent variables considered in this study included the age of the patient and GP; patient gender, body mass index (BMI); history of smoking, diabetes mellitus, or cholesterol tests; family history of hypertension; previous visits for cardiologic, nephrologic, or vascular surgery evaluation; prior hospitalizations for myocardial infarction (MI) or heart failure; number of admissions for surgery; and length of patient follow-up, type of antihypertensive medication, mean daily dosage (MDD), utilization of antihypertensive drugs and number of other medications currently being taken by the patient (antiaggregants, anti-inflammatories, antihypolipemia drugs, antiasthmatics, and drugs for the treatment of heart diseases).

Utilization of antihypertensive drugs

Utilization of antihypertensive agents was defined for the purpose of this study as the MDD of the drugs purchased during the follow-up period, expressed as the number of tablets per day. The formula utilized was: number of tablets prescribed from the first to the penultimate prescription, divided by the number of days from the first to the last prescription. The duration (expressed in days) of the antihypertensive treatment (DT) was then calculated as the

number of days from the first to the last prescription plus the number obtained by dividing the number of tablets indicated in the final prescription by the MDD.

The calculations were based on the total number of tablets purchased by each patient, regardless of the active principle that each contained. Three categories for use of antihypertensive medication were defined, regardless of the type and number of active ingredients taken: patients were defined as (1) *occasional users* if they received only one prescription of antihypertensive medication during the study period; (2) *interrupted users* if, during the study period, they interrupted the use of any antihypertensive drug; (3) *continuous users* if, during the study period, they continuously took antihypertensive drugs (by maintaining, combining or switching the active ingredient) without interrupting the pharmacological therapy. In the case of nonoccasional users, four types of antihypertensive treatment were identified on the basis of MDD: patients with MDD <0.5 tablets/day; patients with MDD ≥0.5 tablets/day and <1 tablet/day; patients with MDD ≥1 tablet/day and <2 tablets/day; patients with MDD ≥2 tablets/day.

Statistical analysis

Continuous variables are presented as mean values plus or minus the standard deviation. Statistical significance between means was calculated by independent-samples *t*-test or, alternatively, by paired-samples *t*-test. Association between categorical variables and BP control was tested using the Pearson's χ^2 test.⁹ For all analyses, *P*-values of less than 0.05 were considered significant.

Unadjusted odds ratios were obtained to identify factors predictive of not achieving adequate control of BP, the outcome variable. A multivariable logistic regression model¹⁰ was then developed, identifying factors predictive of not achieving adequate BP control while simultaneously adjusting for potential confounders. A forward stepwise approach was undertaken setting entry/removal criteria for

each independent variable at (P -value_(in) = 0.05, P -value_(out) = 0.10) using the Wald test statistic. The fit of the model was assessed with the Hosmer–Lemeshow goodness-of-fit test statistic,¹⁰ with P <0.05 taken to be evidence of a statistically significant difference between observed and predicted values. All statistical analysis were performed with the SPSS statistical package.¹¹

Results

Patient characteristics

There were 6392 hypertensive patients in the Pandora project population from 1 January to 31 December 2000, representing 19.4% of the total beneficiaries in the care of the 21 GPs. Of these, 2519 met the inclusion criteria for the present study, including 1525 cases (60.5%) and 994 controls (39.5%). All the subjects included in the study were white. The characteristics of the patients enrolled are shown in Table 1. Compared with controls, cases were significantly older and less likely to smoke. The percentage of patients who had diabetes mellitus was significantly greater among cases than controls. The percentage of patients with previous hospital admissions for cardiovascular reasons and the percentage of patients taking two or more co-medications were higher in the controls than in the cases. Compared with controls, cases also had a slightly higher BMI, which was statistically significant, and a significantly shorter duration of follow-up.

Utilization of antihypertensive drugs

Cases and controls differed significantly in their use of antihypertensive medications (Table 2). Adherence to the antihypertensive regimen was significantly higher among cases compared with controls (83.4 vs 77.7%, P <0.001). Although by definition, cases were those patients with uncontrolled BP, the MDD and number of classes of antihypertensive agents purchased in the pharmacy were

Table 1 Characteristics of case and control patients at enrolment

Characteristics	Control patients no. 994	s.d.	Case patients no. 1535	s.d.	P-value
Age (years)	63.1	12.3	66.3	11.3	<0.001
Gender (male)	44.3		42.2		NS
Body mass index (kg/m ²)	27.4	4.8	27.8	4.9	0.041
% family history of hypertension	31.0		32.5		NS
% smoking habit	12.5		9.6		0.025
% regular physical activity	8.7		6.8		NS
% diabetes mellitus	2.9		13.9		<0.001
% previous hospital admissions for cardiovascular reasons	7.9		5.6		0.022
% of patients taking one co-medication	33.8		35.0		NS
% of patients taking two or more co-medications	28.1		23.8		0.016
Days of follow-up	950	291	919	314	0.013
No. of surgery admittances	31.7	18.9	31.1	19.8	NS

significantly greater than those of the control group. With regard to the type of antihypertensive drugs used, approximately 50% of cases and controls received angiotensin-converting-enzyme (ACE) inhibitors. The use of diuretics and β -blockers was greater among controls, whereas the use of calcium channel blockers was greater among cases.

The MDD value increased significantly ($P < 0.001$) when passing from patients currently taking no other medications to patients taking one co-medication and to patients taking two or more co-medications (0.84, 0.98, and 1.27 tablets/day, respectively).

Control of blood pressure

The percentage of normotensive patients increased from 32% at enrolment to 39.5% at the end of the follow-up period. At the end of the follow-up period, 22.3% (222 patients) of the control group had a representative BP of $<140/90$ mmHg even if they had suspended antihypertensive treatment. Antihypertensive treatment was suspended by 16.6% (253 patients) in the case group, even if their BP remained within the hypertensive range. Overall, 45.3% (1141 patients) of the cases had residual systolic hypertension, 2.4% (60 patients) had residual diastolic hypertension, and 12.8% (324 patients) had systolic–diastolic hypertension. The mean SBP of cases vs controls at enrolment (153 ± 20 vs 140 ± 21 mmHg, respectively) and at

the end of follow-up (153 ± 13 vs 126 ± 10 mmHg, respectively) was significantly higher ($P < 0.001$). Cases also had a higher mean DBP than controls at enrolment (82 ± 11 vs 80 ± 11 mmHg, respectively) and at the end of follow-up (81 ± 12 vs 74 ± 8 mmHg, respectively) (Figure 1). Among cases, there was a significant decrease in DBP from enrolment to the end of follow-up (82 ± 11 vs 81 ± 12 mmHg, respectively, $P < 0.005$) without any variation in SBP (153 ± 20 vs 153 ± 13 mmHg, respectively). By contrast, the controls showed a significant decrease from enrolment to the end of follow-up in both SBP (140 ± 21 vs 126 ± 10 mmHg, respectively) and DBP (80 ± 11 vs 74 ± 8 mmHg) ($P < 0.001$ for both comparisons). Using Joint National Committee VI guidelines,⁴ at the end of follow-up, 71.9% (1096 patients) cases had stage I hypertension, 23.1% (352 patients) had stage II hypertension, and 5.0% (77 patients) had stage III hypertension.

Risk factors

On enrolment in the study, there were significant differences in the risk factors present in cases and controls (Table 3). Several factors were significantly associated with the persistence of elevated BP, especially patient age of 50 years or more, the presence of diabetes mellitus, and the absence of a prior admission for MI. The risk of persistence of elevated BP, moreover, decreased with the increase in the number of other medications currently being taken by the patient. With regard to the characteristics of antihypertensive therapy, the risk of persistent elevated BP was higher in patients who used medication continuously, and in those receiving the highest MDD (Table 4).

The results of the multivariate logistic regression model (Table 5) indicate that the presence of diabetes mellitus, increasing patient age, and increasing age of the GP significantly increased the risk of uncontrolled BP. Hypertensive patients with diabetes were almost six times more likely to have uncontrolled BP compared to those without

Table 2 Utilization of antihypertensive drugs in the two groups of patients

Characteristics	Control patients	Case patients	P-value
Continuity of treatment^a			<0.001
% Continuous users	77.7	83.4	
% Interrupted users	15.7	13.1	
% Occasional users	6.6	3.5	
Mean daily dose^b			0.004
% <0.5 tablet/day	17.2	12.8	
% ≥ 0.5 – <1 tablet/day	39.9	37.6	
% ≥ 1 – <2 tablets/day	33.2	37.0	
% ≥ 2 tablets/day	9.7	12.6	
Number of antihypertensive drugs assumed^b			0.001
% 1 class	37.2	31.1	
% 2 classes	36.1	35.6	
% 3 or more classes	26.7	33.3	
Type of antihypertensive drug^a			0.010
% Diuretics	9.9	7.3	
% Beta blockers	17.9	14.4	
% Calcium channel blockers	18.0	23.1	
% Ace inhibitors	49.4	49.0	
% Angiotensin II antagonist	1.5	1.8	
% Other antihypertension drugs	3.3	4.4	

^aComputation carried out on treated patients (2403 subjects).

^bComputation carried out on not occasional treated subjects in the follow-up period (2192 subjects).

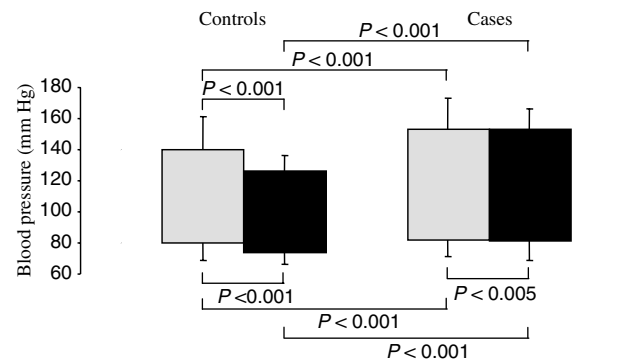


Figure 1 Blood pressure in control and case patients.

Table 3 Bivariate odds ratios about patients' characteristics

	% of study population that are cases	Odds ratio	95% confidence interval	P-value
<i>Patient's age</i>				<0.001
< 50 years (RC)	48.0	1.00		
≥ 50 years	61.9	1.76	(1.35–2.29)	
<i>MI previous admissions</i>				0.001
Absence (RC)	61.1	1.00		
Presence	42.9	0.48	(0.30–0.75)	
<i>Diabetes</i>				<0.001
Absence (RC)	57.6	1.00		
Presence	88.0	5.37	(3.61–7.99)	
<i>Cholesterol</i>				0.024
Surveying absence (RC)	64.5	1.00		
Surveying presence	59.3	0.80	(0.66–0.97)	
<i>Smoking habit</i>				0.025
No smoker (RC)	61.3	1.00		
Smoker	54.2	0.75	(0.58–0.96)	
<i>GP's age</i>				0.005
< 50 years (RC)	59.9	1.00		
≥ 50 years	72.3	1.75	(1.18–2.59)	
Number of comedications, (continuous)	—	0.89 ^a	(0.82–0.96)	0.004

RC: reference category of the risk factor.

^aRelated to one co-medication unit increment.

Table 4 Bivariate odds ratios about utilization of antihypertensive drugs

	% of study population that are cases	Odds ratio	95% confidence interval	P-value
<i>Continuity of treatment^a</i>				<0.001
Continuous (RC)	60.3	1.00		
Interrupted	54.1	0.77	(0.61–0.98)	
Occasionals	43.1	0.50	(0.34–0.73)	
<i>Mean daily dose^b</i>				0.004
≥ 2 (RC)	66.1	1.00		
[1–2[62.7	0.86	(0.64–1.16)	
[0.5–1[58.8	0.73	(0.54–0.98)	
< 0.5	53.0	0.58	(0.41–0.81)	

RC: reference category of the risk factor.

^aComputation carried out on treated patients (2403 subjects).

^bComputation carried out on not occasional treated subjects in the follow-up period (2192 subjects).

Table 5 Logistic regression model: predictors of not achieving adequate blood pressure control

	Odds ratio ^a	95% confidence interval	P-value
<i>Diabetes</i>			<0.001
Absence (RC)	1.00		
Presence	5.89	(3.86–8.99)	
<i>Patient's age (continuous)</i>	1.03 ^b	(1.02–1.04)	<0.001
<i>Number of co-medications (continuous)</i>	0.80 ^c	(0.73–0.88)	<0.001
<i>GP's age (continuous)</i>	1.06 ^b	(1.03–1.09)	<0.001
<i>MI previous admissions</i>			0.004
Absence (RC)	1.00		
Presence	0.47	(0.28–0.79)	

Variables are reported in order of entrance into the model. RC: reference category of the risk factor.

^aAdjusted for other variables in table.

^bRelated to 1 year age increment.

^cRelated to 1 comedication unit increment.

diabetes. Significant factors that reduced the risk of uncontrolled BP were an increasing number of other medications currently being taken by the patient and a prior MI. The Hosmer–Lemeshow goodness-of-fit test ($P=0.900$) indicated a good fit of the model.

Discussion

Poor control of BP appears to be determined by both the patient's characteristics and factors related to the patient–doctor relationship. Randomized controlled trials (RCT) generally conducted at tertiary-care centres in highly selected patient populations have demonstrated that any reduction of elevated BP either to levels within the normal range^{12,13} or to those above 140/90 mmHg lowers the likelihood of morbidity and mortality due to cardiovascular or renal events, as well as premature death.^{14–17} However, the lack of applicability of these findings to the community-based practice setting is demonstrated by the finding that normal BP levels are achieved in more than 50% of patients treated in RCTs^{13–16} and only in less than 30% of those treated in actual clinical practice.^{4–7}

In this observational, practice-based study, the majority (60%) of hypertensive patients failed to reach the targeted goal BP. A possible bias could have been introduced by the patient selection process, because the GPs might have selected those patients who were generally more compliant than the general patient population. If true, such a bias could contribute to further support present findings since the general population of hypertensive patients in Ravenna could be expected to have even poorer BP control. The use of clinic BP measurements might have substantially overestimated the proportion of patients with uncontrolled hypertension as a result of the ‘white coat’ component.^{18,19} However, most of the patients had been treated with antihypertensive drugs for an average of 2.5 years prior to study enrolment, suggesting that the BP values recorded were representative. Lastly, pre-treatment BPs could not be reliably ascertained for most of the patients, and they were included because they had established hypertension and were taking antihypertensive drugs.

The purpose of this study was to identify factors contributing to poor control of BP in patients receiving long-term antihypertensive therapy. Other studies have evaluated barriers and facilitators to the management of hypertension in primary care, including physician-related factors, ethnicity of the patients, co-morbidity, and continuity of care.^{20–24} In this study, several factors appear to affect the risk of uncontrolled BP in the primary care setting: the patient's age, the presence of comorbidities such as diabetes mellitus and/or target organ damage (ie previous MI), the number of other medications currently being taken by the patient, and the GP's

age. How these factors affect BP control is not known. However, the medical status of the patient is known to be an important determinant. In the present study, confirming the results of other papers,^{22,23} a prior MI enhanced the probability of achieving goal BP, possibly because GPs and patients may be more motivated to treat a symptomatic disease than asymptomatic conditions, or because patients with a prior MI were seen by hospital physicians and had their treatment regimen prescribed by specialists rather than by their primary-care physician. Moreover, our physicians have little training and experience in treating to target, as we have observed in patients with diabetes.

According to the results of this study, an increase in the number of other medications currently being taken by the patient decreases the probability of poor control of BP. A possible explanation for this phenomenon is that, although the patients taking other medications present a more complex clinical situation, they are more accustomed to and careful about their treatment, they take higher doses of the drugs and thus control their BP in a better way.

An unexpected finding was that the dosing regimen of antihypertensive drugs and utilization of antihypertensive drugs did not influence BP. A study at a hypertension hospital clinic found that the intensity of antihypertensive therapy was not associated with the degree of BP control, and that older patients needed more than one drug to reduce their BP.²⁵ Others have found that the BP in adult hypertensive patients gradually increases over time,²⁶ which may have contributed to the findings in the present study. An additional factor may have been the fact that fewer than 10% of cases received diuretics, the use of which often results in BP control in patients with resistant hypertension.²⁷

The recent findings of Berlowitz *et al*²⁸ strongly support a substantial physician component to poor BP control, for reasons that are not entirely clear. Other studies have indicated the doctor–patient relationship as an important factor affecting the control of hypertension.^{20,21} In the present study, the likelihood of poor BP control was increased when the GP was aged 50 years and older. Moreover, in a previous study, we found that adherence to antihypertensive treatment was lower in newly treated patients who were followed by older physicians.²⁹ This study provides a framework for identifying hypertensive patients who are at a high risk of poor control, and many of the factors identified may be amenable to improvement. Older patients and diabetics can be targeted for greater attention to BP control, particularly in view of the evidence for improvement in clinical outcomes with hypertension therapy in these populations.^{17,16} In conclusion, the failure of antihypertensive medication to adequately control BP is determined by both the patient's characteristics and factors related to the patient–doctor relationship. Successful treatment of

hypertension, also in asymptomatic conditions, requires patient adherence to the regimen that has been agreed on with the physician.

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