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How Can Hypertensive Patients Be Better Treated? The Contribution of Combination Therapy

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Summary: Recent studies demonstrated that target blood pressure (BP) in treated hypertensive patients should be below 140 mmHg for systolic blood pressure (SBP) and below 90 mmHg for diastolic blood pressure (DBP). However, population studies from several countries have demonstrated that in clinical practice the proportion of controlled hypertensive patients is less than 30%. In order to elucidate these questions in France we analysed a large population of 145 000 subjects examined at the Centre d'Investigations Préventives et Cliniques in Paris (IPC). Among those with high BP at the time of their IPC visit, only 20% received an antihypertensive treatment. Among those receiving an antihypertensive treatment, less than 27% (24% in men and 30% in women) presented with BP values less than 140 mmHg for SBP and less than 90 mmHg for DBP. This analysis also showed that 72% of hypertensive patients presented with at least one modifiable associated cardiovascular risk factor and that more than 30% of hypertensive men and more than 25% of hypertensive women presented with at least two associated risk factors. The use of combination therapies could help to increase the percentage of well-controlled hypertensive subjects. It has been shown that in order to reach this BP level, combination therapy should be used in more than two-thirds of the treated subjects. The trandolapril–verapamil combination is the first fixed combination of an angiotensin-converting enzyme inhibitor and a non-dihydropyridine calcium-channel blocker. Administered once daily, this combination reduces BP more than a classic monotherapy. The effects of the trandolapril–verapamil combination on risk factors are either neutral (metabolic parameters), or even beneficial (reduction in heart rate). **Key Words:** Hypertension—Antihypertensive treatment—Risk factors—Blood pressure control—Combination therapy.

INTRODUCTION

Data from well-conducted controlled clinical trials show that hypertension-related risk for cardiovascular complications is significantly reduced, although not abolished, by antihypertensive treatment (1). In fact, it has been shown that a decrease in blood pressure (BP) only partially reversed the risk of cardiovascular complications, especially coronary complications in hypertensive individuals. These results can be explained by the fact that coronary heart disease is determined by a large number of risk factors, especially metabolic determinants, that are very often altered in both treated and untreated hypertensive patients. As shown in several recent clinical trials, the benefits of antihypertensive treatment are proportional to the degree of BP reduction obtained by the treatment (2,3). These studies demonstrated that target BP in treated hypertensive patients should be below 140 mmHg for systolic blood pressure (SBP) and below 90 mmHg for diastolic blood pressure (DBP) (2). In some cases, such as in diabetic patients, target BP should be less than 130/85 mmHg (3). It has also been shown that, in order to reach this BP level, combination therapy should be used in more than two-thirds of the treated subjects (2). In fact, in the Hypertension Optimal Treatment (HOT) Study, less than 30% of the treated patients reached target BP with a single drug.

However, information from controlled clinical trials is only a partial reflection of the situation in clinical practice. Population studies from several countries have demonstrated that the proportion of controlled hypertensive patients is less than 30% (4,5), whereas a recent sur-

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vey in the U.K. indicated that only 6% of hypertensive subjects presented with BP levels below the limit of 140/90 mmHg (6).

In order to clarify the situation in France, we analysed a large proportion of 145 000 subjects living in the Paris area. Some preliminary results of this analysis concerning BP control and associated risk factors in hypertensive patients are presented in this paper.

THE IPC POPULATION

The French national health care system (Securité Sociale-CNAM) provides all working and retired persons and their families with a free medical examination every 5 years. The Centre d'Investigations Préventives et Cliniques (IPC) is one of the biggest medical centres of this kind in France. Since 1970, approximately 25 000 examinations per year have been performed for persons living in the Paris area (7,8). In this paper, we present data which describe a population of 145 332 individuals aged between 18 and 80, composed of all those who had a free health check at the IPC Centre between January 1992 and December 1997 (92 641 men and 52 691 women). The IPC centre received the approval of the national authorities, Comité National d'Informatique et des Libertés (CNIL), for these analyses. Everyone included in this analysis gave their informed consent at the time of the examination. Among the volunteers, 75% were white-collar workers. Based on the national statistics on mortality, our cohort presented a 30% lower mortality rate than the general population of France. This can be explained by the fact that people who came for the health check were apparently healthy and motivated to be followed up. Interestingly, compared with the national data, the distribution of the different causes of mortality in our cohort was identical to that of the general population.

Prevalence of high blood pressure in the IPC 1992–1997 cohort

As shown in Table 1, high BP (defined as SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg or antihypertensive treatment) was observed in 27.4% of the females and 31.1% of the males. Among those with a high BP at the time of the IPC Centre visit, only 20% (16% among men and 29% among women) received an antihypertensive treatment. Among those receiving an antihypertensive treatment, less than 27% (24% in men and 30% in women) presented BP values less than 140 mmHg for SBP and less than 90 mmHg for DBP (Fig. 1). Thus, as shown in Fig. 2, among those classified as hypertensive patients, 94.6% (42 095 volunteers) were either untreated or insufficiently treated, whereas only 5.4% (2354 volunteers) presented with controlled BP levels.

Although these results have several limitations because they are based on a single BP evaluation, they demonstrate that even in a relatively highly motivated population (as was the case with the IPC cohort) the percentage of patients with elevated BP levels is very high.

The magnitude of this problem is also clearly demonstrated in Table 2, which shows mean BP values and other morphometric and biological parameters in normotensive and treated hypertensive male patients in three different age groups. In all age groups, treated hypertensive patients had higher levels of SBP (an increase of 20 mmHg) and of DBP (an increase of 10 mmHg). This

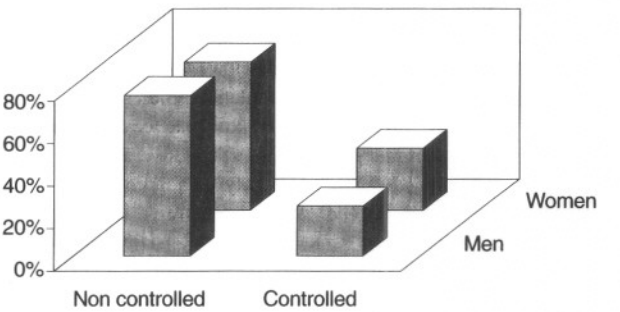

FIG. 1. Among treated hypertensive patients, 30% of women and 24% of men presented with blood pressure (BP) values less than 140/90 mmHg.

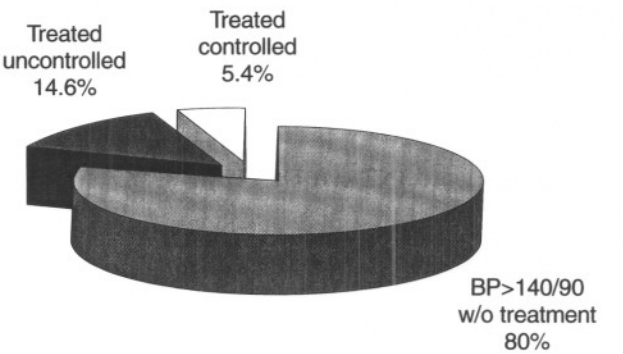

FIG. 2. Distribution of untreated and treated hypertensive patients. BP, blood pressure.

TABLE 1. *Prevalence of high blood pressure (BP) in the IPC population*

	Men	Women	Total
SBP < 140 and DBP < 90 mmHg	60 694 (68.9%)	40 189 (72.6%)	100 883 (70.2%)
BP ≥ 140/90 or antihypertensive treatment	31 947 (31.1%)	12 502 (27.4%)	44 449 (29.8%)
Total	92 641 (100.0%)	52 691 (100.0%)	145 332

SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2. Mean value (± SD) of the main clinical and biological parameters in normotensive and treated hypertensive male volunteers of the IPC cohort 1992–1997

	< 45 years of age		45–54 years of age		≥ 55 years of age	
	Normotensive	Treated hypertensive	Normotensive	Treated hypertensive	Normotensive	Treated hypertensive
Age (years)	34.5 ± 6.7	39.3 ± 4.5	49.0 ± 2.8	50.0 ± 2.7	60.3 ± 4.7	63.2 ± 5.8
BMI (kg/m^2)[a]	23.9 ± 3.0	27.0 ± 4.2	25.1 ± 2.9	27.8 ± 4.0	25.2 ± 2.8	27.2 ± 3.4
Heart rate (bpm)[a]	64.0 ± 11.0	68.0 ± 12.0	64.0 ± 10.0	67.0 ± 11.0	64.0 ± 10.0	66.0 ± 11.0
SBP (mmHg)[a]	123.0 ± 7.0	142.0 ± 15.0	124.0 ± 7.0	143.0 ± 15.0	126.0 ± 7.0	146.0 ± 16.0
DBP (mmHg)[a]	75.0 ± 6.0	88.0 ± 11.0	77.0 ± 5.0	88.0 ± 10.0	77.0 ± 5.0	89.0 ± 10.0
PP (mmHg)[a]	48.0 ± 6.0	54.0 ± 9.0	48.0 ± 6.0	54.0 ± 10.0	49.0 ± 6.0	58.0 ± 11.0
Total cholesterol (g/l)	2.10 ± 0.42	2.29 ± 0.42	2.33 ± 0.40	2.37 ± 0.40	2.36 ± 0.39	2.33 ± 0.37
Triglycerides (g/l)[a]	0.97 ± 0.63	1.35 ± 0.94	1.12 ± 0.70	1.38 ± 0.81	1.10 ± 0.61	1.28 ± 0.71
Glycemia (g/l)[a]	1.00 ± 0.12	1.06 ± 0.15	1.05 ± 0.15	1.12 ± 0.24	1.06 ± 0.19	1.12 ± 0.24

[a]$p < 0.001$ normotensive versus treated hypertensive patients in all age groups. For total cholesterol, differences between normotensive and hypertensive subjects were observed only in the younger group.

BMI, body-mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure.

shows the very poor results in controlling BP, especially SBP, and demonstrates that despite the large number of guidelines and recommendations, the observed mean values of BP were close to what is theoretically the upper limit of accepted values (140/90 mmHg). Very similar differences were also observed between the normotensive and the treated hypertensive women of our cohort (results not shown).

There are many explanations for these observations. First, despite the large number of new, well-tolerated antihypertensive drugs, use of more drastic treatments can be responsible for several side-effects. Second, treatment compliance is insufficient and many patients do not follow the recommended treatments. Third, several coexisting factors, such as obesity, high salt diet and associated treatments such as anti-inflammatory drugs, contribute to the development of resistant hypertension. Fourth, systolic hypertension, especially in older subjects, is difficult to control. Finally, inadequate BP control may be attributed to the attitude of the majority of physicians who are not convinced there is a need to drastically reduce BP in treated hypertensive patients.

Prevalence of associated risk factors in hypertensive subjects

Another important conclusion from Table 2 is that treated hypertensive subjects have constantly higher levels of body-mass index (BMI), heart rate, glycemia and triglycerides, whereas total serum cholesterol was higher only in the group of younger subjects.

Table 3 shows that 72% of hypertensive men and women present with at least one modifiable associated cardiovascular risk factor. Interestingly, more than 30% of hypertensive men and more than 25% of hypertensive women present with at least two associated risk factors and this percentage goes up to about 40% for both genders if increased heart rate (> 75 bpm) is also taken into account.

The presence of hypercholesterolemia or diabetes mellitus was significantly higher in hypertensive than in normotensive patients and these differences were significant even after adjustment for age (Fig. 3). Only tobacco consumption was lower in hypertensive subjects. It is now well established that among subjects with hyperten-

TABLE 3. Number of modifiable associated risk factors (ARF) among hypertensive men and women of the IPC cohort

	Hypertensive patients	
	Men	Women
0 ARF[a]	8955 (28%)	3551 (28%)
≥ 1 ARF	22992 (72%)	8951 (72%)
1 ARF	13005 (40.7%)	5713 (45.7%)
2 ARFs	7667 (24.0%)	2701 (21.6%)
3 ARFs	2112 (6.6%)	504 (4.0%)
4 ARFs	208 (0.7%)	33 (0.3%)

[a]ARF (associated risk factor): hypercholesterolemia, ≥ 2.5 g/l or treatment; hyperglycemia, ≥ 1.24 g/l or treatment; tobacco smoking, current smokers; obesity, body mass index > 27 in women or > 28 in men.

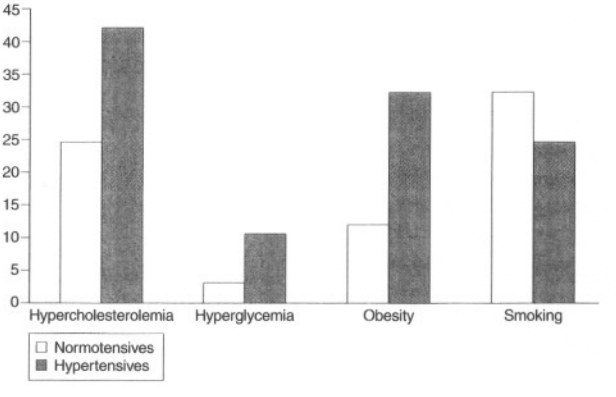

FIG. 3. Presence (%) of risk factors in normotensive and hypertensive patients.

sion, cardiovascular risk depends on both the BP levels and the presence of other risk factors and/or end-organ damage (9).

The results of the present analysis in a large French population demonstrate that hypertensive subjects present with a high cardiovascular risk profile as a result of insufficient BP control and of the very high frequency of associated risk factors.

Combination therapy as a more effective treatment of hypertension

The results from both clinical trials and clinical practice point out the necessity for more aggressive treatment of hypertensive patients in order to obtain BP levels below 140/90 mmHg. It is now also well established that when treatment is started with a monotherapy, less than 50% of subjects will achieve the target BP values. Three possible therapeutic approaches are possible when monotherapy fails to control BP:

(a) Increasing the dosage of the same drug is often ineffective (unless very low doses have been used initially), and can be associated with an increased incidence of the dose-related side-effects.

(b) Switching to another drug: the approach of single drug sequential therapy is the usual attitude of many physicians. However, it may lead to poor compliance with the treatment, especially if a second monotherapy fails to control BP levels.

(c) Combining two drugs as a combination therapy could help increase the percentage of well-controlled hypertensive subjects. The synergistic effects of the components of these combinations allow the possibility of obtaining major antihypertensive effects with relatively low doses of each active drug, reducing the presence of side-effects. In this approach physicians can use either free or fixed combinations. The use of a free combination has the advantage of greater flexibility in the dosage of each drug. However, the use of a fixed combination presents several advantages: in controlled clinical trials, the proposed doses of each drug were proven to have the best benefit–risk ratio for the patients; also, treatment simplification (i.e. 1 pill/day) can improve the patient's compliance with the treatment.

Over the last few years, several fixed combinations have been developed. Those among them combining low doses of diuretics with an angiotensin-converting enzyme (ACE)-inhibitor are the most commonly used. The trandolapril–verapamil combination is the first fixed combination of an ACE-inhibitor and a nondihydropyridine calcium-channel blocker. Administered once daily, this combination reduces BP more than a classic monotherapy (10,11). The effects of the trandolapril–verapamil combination on risk factors are either neutral (metabolic parameters), or even beneficial (reduction in heart rate). For these reasons the trandolapril–verapamil combination is of major interest for treating hypertensive patients, especially those presenting with associated risk factors.

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