Research Article

A specific training on hypertension guidelines improves blood pressure control by more than 10% in hypertensive patients: the VALNORM study

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Abstract

VALNORM was designed to assess the impact on blood pressure (BP) control of a specific training in new European Society of Hypertension-International Society of Hypertension (ESH-ISH) guidelines for hypertension management. It was an 8-week prospective, randomized, open, blinded end points design study. General practitioners (GPs) located in France were randomized in two groups: group 1 (G1) without training to the guidelines and free attitude for the prescription whereas group 2 (G2) received a specific training in ESH guidelines. The primary efficacy criteria was strict BP control at week 8 (systolic BP/diastolic BP [SBP/DBP] <140/90 mm Hg and/or SBP/DBP <130/80 mm Hg if diabetes or renal insufficiency). All physicians used the same treatment (valsartan 80 or 160 mg once daily alone or in fixed combination with hydrochlorothiazide 12.5 or 25 mg once daily). BP was measured in the GPs' office with an electronic device. The groups GPs included 4,436 patients with essential uncontrolled hypertension (G1: 595 physicians, 2,308 patients; G2: 502 physicians, 2,128 patients). Patients' main characteristics were: age = 61 ± 13 years, 52% female, BP = 160 ± 13/92 ± 9 mm Hg. No difference was observed between the two groups. The primary efficacy criteria showed in G2: 47.8% of BP control vs. G1: 44.7%, P = .005. Subgroup analysis according to age, body mass index (BMI), previous diabetes, and antihypertensive treatment showed that higher efficacy in G2 was more significant in these high-risk subgroups: age >60 years (G1: n = 1,150, G2: n = 1,035), BMI ≥25 kg/m^2 (G1: n = 1540, G2: n = 1430), diabetes (G1: n = 267, G2: n = 290), no previous antihypertensive treatment (G1: n = 1,111, G2: n = 1,005). The percentage of patients with controlled BP in each subgroup was: diabetes: G1 11.2% vs. G2 17.9% (P = .001), age >60 years: G1 40.3% vs. G2 43.7% (P = .022), BMI ≥25 kg/m^2: G1 43.2% vs. G2 45% (P = .165), untreated: G1 48.2% vs. G2 52.4% (P = .005). Specific training on the guidelines showed a positive impact on BP control, highly significant in patients at high cardiovascular risk such as diabetic hypertensive patients. © 2007 American Society of Hypertension. All rights reserved.

Keywords: Continuous medical education; guidelines; hypertension; antihypertensive.

Introduction

Modern medicine is characterized by the rapid development of new data applications and techniques that constantly modify the strategies of patient management.[1] As a consequence, professional guidelines providing a synthesis of evidence concerning current scientific data and expert opinion are considered to be tools that facilitate decision making by defining the most appropriate strategy for a given clinical situation.[1]

Guidelines on hypertension management[2-4] have established the therapeutic goal for the treated hypertensive patient. However, most evaluation studies have observed high percentages of uncontrolled hypertensive patients.[5,6] Similar observations have been reported regarding the low impact of guidelines on the management of associated risk factors.[7,8]
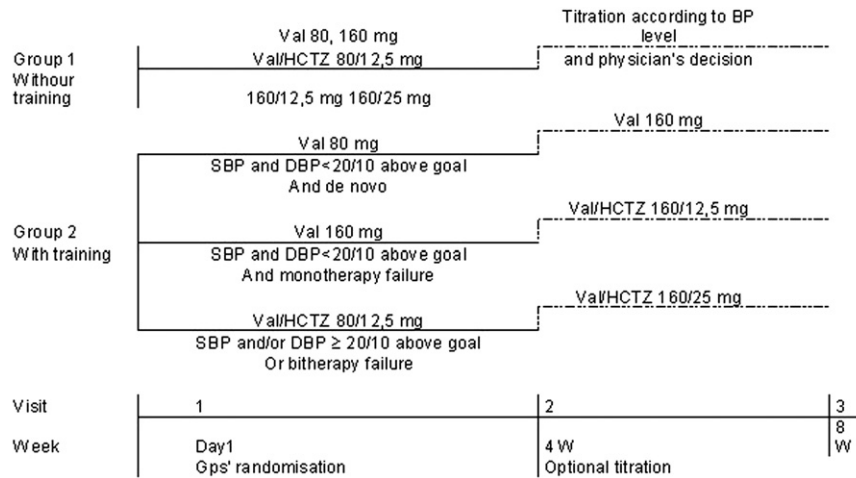
Figure 1. Treatments: Study outline.

Discrepancy between guideline application and current medical practice has become a major concern today, and much has been written on how to improve this situation.[9] It appears that practice guidelines may be insufficiently understood, disseminated, and even insufficiently accessible to the practitioner.[10-15]

Such observations should result in concrete measures aimed at improving the quality of care in the management of hypertension.[16-19] This necessary improvement should first concern the instruction and training of the practitioners who need to be regularly informed of updated therapeutic guidelines, and who should all be provided with didactic and practical tools for their implementation.[20,21]

In an attempt to identify the factors that are likely to facilitate rapid guideline implementation within medical practice, several studies underline the importance of continuous medical education (CME) performed in compliance with a defined methodology. Guidelines summarized in a report of the French health authority, Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES), recommend the following actions: interventions of opinion leaders; outreach visits; CME by interactive training sessions; use of written or electronic reminders (study summaries, therapeutic objectives, schedule of the therapeutic decisions); and, lastly, evaluation by audit-feedback.[1] Such actions have to be evaluated in randomized studies specifically aimed at verifying their efficacy.

The aim of the present study was to evaluate the impact of a specific CME program on hypertension management in terms of blood pressure (BP) control by assessing whether a measurable difference exists in terms of BP control and management of cardiovascular risk factors between a group of hypertensive patients treated by general practitioners (GPs) properly trained in hypertension management guidelines and a similar group of hypertensive patients treated by GPs with no specific guideline training.

Methods

Study Design

This was an 8-week multicenter, prospective, randomized, open, blinded end points study carried out between June 2004 and May 2005.

Therapeutic Design

GPs from France were randomized into two equal groups and asked to include in the study the first four consecutive eligible patients agreeing to participate. For randomization, we preselected from a national database 1000 GPs to participate in each group. Contact had been established with them in order to obtain their approval. The preselection was performed in order to respect the national geographic distribution of GPs. One group (group 1) did not receive the specific training while the second (group 2) was specifically trained in the European Society of Hypertension (ESH) guidelines for hypertension management. Both groups were provided with the same medications but the therapeutic design differed; medications were given as follows (Figure 1):

In group 1 (without guidelines training) GPs could "freely prescribe" valsartan 80 mg (VAL80), valsartan 160 mg (VAL160), or the fixed combinations VAL80/HCTZ12.5, VAL160/HCTZ12.5, or VAL160/HCTZ 25 as starting dose.

In group 2 (with guidelines training), the starting dose depended, as recommended by the guidelines, on initial BP and risk stratification levels at randomization, prior to antihypertensive treatment. After 4 weeks of treatment, in case of uncontrolled BP, the investigator was provided with a fixed titration design in compliance with the guidelines: depending on the BP value, uncontrolled patients on VAL160 monotherapy switched to VAL160/HCTZ12.5 while uncontrolled patients on the bitherapy VAL80/HCTZ12.5 switched to VAL160/HCTZ25.

Investigator's Training and Guidelines Implementation

A nationwide network of principal investigators was responsible for the regional coordination of the training sessions and study implementation. The training in ESH guidelines of group 2 study investigators was performed by 30 local experts recognized as national opinion leaders.

The specific methodology for the investigators' training consisted of interactive training sessions organized for small groups of participants (<25) to maximize the training impact. Each session was organized as workshops, including two sessions; the first one being principally a presentation of guidelines and the second one being interactive questions/answers and presentation of clinical cases. In addition, principal investigators were required to visit the local investigators of group 2 at their offices, and the study investigators were provided with specific tools such as a CD-ROM summarizing both the protocol and the guidelines, and an electronic (or printed when requested) reminder of the guidelines. Regarding the immediate, short-term, and long-term evaluation of the training, the investigators were presented with three questionnaires, the first of which was to be completed immediately after the training, the second at the end of the study, and the third about one year later.

Study Population

The study population consisted of a representative group of 4,436 male and female hypertensive outpatients with 2,308 recruited by group 1 and 2,128 by group 2.

The main inclusion criteria were an age ≥18 years; hypertension defined by a diastolic blood pressure (DBP) ≥90 and/or a systolic blood pressure (SBP) ≥140 mm Hg, or, in patients with diabetes or chronic renal impairment, a DBP ≥80 mm Hg and/or an SBP ≥130 mm Hg; patients untreated or on diet and exercise; patients uncontrolled despite current antihypertensive monotherapy or bitherapy; or patients experiencing unacceptable side-effects before switching to the study treatment.

Exclusion criteria were severe or secondary hypertension as defined in the guidelines, type 1 diabetes, known or suspected allergy or hypersensitivity to valsartan or to HCTZ, severe hepatic or renal or any life-threatening disease, current treatment with potassium-sparing diuretics, pregnancy, breast feeding, absence of efficient contraception, drug and/or alcohol abuse, known non-compliance to medical regimens. Written informed consent to participate in the study was obtained prior to any study procedures.

Evaluation Criteria and Measurement Methods

The primary end point (impact of a specific training in hypertension management on strict BP control after 8 weeks of therapy) was evaluated as the percentage of patients strictly controlled according to the target level indicated in the 2003 ESH guidelines, ie, SBP <140 mm Hg and DBP <90 mm Hg in patients with uncomplicated hypertension, and SBP <130 mm Hg and DBP <80 mm Hg in patients with hypertension and type 2 diabetes and patients with hypertension and chronic renal insufficiency.

BP was assessed according to the guidelines,[2-4] in the sitting position and after a 5-minute rest, and using a validated automated oscillometric electronic device fitted with a cuff adapted to the arm circumference, and a printer (705CP, Omron Healthcare, Inc., Bannockburn, IL). The average of 3 measurements obtained at 1- to 2-minute intervals was calculated, and 1 measurement was performed in the standing position after 2 minute orthostatism.

The secondary end points also comparatively assessed at the discharge visit were the absolute lowering of SBP and DBP value at the 8th week and the rate of responders defined as a DBP <90 mm Hg or a drop in DBP >10 mm Hg and a SBP <140 mm Hg or a drop in SBP >15 mm Hg. Safety was assessed primarily in terms of the frequency of side-effects per body system and in terms of serious adverse events (AEs) the GP suspected to be related to the study medication. Vital signs were recorded as appropriate, and biochemical assessments were performed before initiation of the fixed combination therapy according to French regulatory requirements.

Statistical Methods

The sample size was determined based on the primary criteria, percentage of patients controlled for both systolic and diastolic BP. With a power of 90%, an alpha level of 5%, and 55% expected controlled patients, a minimum of 2,095 patients per arm (total 4,190) was needed to demonstrate a 5% difference, considered as clinically significant. A total of 4,436 patients were therefore enrolled assuming that 5% of patients would not be able to be evaluated (premature discontinuation, missing data). Efficacy parameters were analyzed by subgroups of patients distributed by age, gender, weight, hypertension characteristics, and prognostic factors (cardiovascular risk factors, target organ damage, associate disease). Safety data were analyzed in terms of frequency of side-effects, biological values beyond the normal limits or higher, and description of other parameters such as abnormal electrocardiogram data and vital signs.

Results

Investigator's Specific Instruction

In both groups of study investigators (n = 1,097), the investigators' characteristics were representative of the national GP population in terms of gender, year of doctorate thesis, and practice location. Fifty-two ESH guideline training sessions were organized throughout France for the 502 investigators belonging to group 2.

Table 1
Patients'clinical characteristics at study initiation*

	Group 1 (n = 2,289)	Group 2 (n = 2,105)	Total (n = 4,394)
Evaluated n	2,288	2,104	4,392
Gender (%)			
Men	48.1%	48.0%	48.0%
Women	51.9%	52.0%	52.0%
Age (years)			
Mean ± SD	61.4 ± 12.6	60.8 ± 12.6	61.1 ± 12.6
BMI (kg/m^2)			
Mean ± SD	27.7 ± 4.8	27.9 ± 5.0	27.8 ± 4.9
Diabetes (%)	12.1	14.6	13.3
Dyslipidemia (%)	36.8%	38.7%	37.7%
Tobacco consumption (%)	15.9%	19.0%	17.4%
Familial cardiovascular history (%)	19.8%	22.3%	21.0%
Previous treatment (%)			
Untreated	50.6%	50.0%	50.3%
Monotherapy	35.6%	36.2%	35.8%
Bitherapy	12.6%	12.6%	12.6%
Tritherapy or more	1.3%	1.3%	1.3%

BMI, body mass index; SD, standard deviation.

* The two groups were comparable at baseline. No significant statistical difference was observed between the two groups for any parameters.

Patients at Study Initiation

The 4,436 patients were included in the two groups of study investigators as follows:

Group 1 (managed by 595 investigators without guidelines training): 2,308 patients, and group 2 (managed by 502 investigators with guidelines training): 2,128 patients.

Of these, 4,348 completed the study (group 1: 2,262 patients and group 2: 2,086 patients). Premature study discontinuations were mostly due to undesirable side-effects (2.3% in group 1 and 3.1% in group 2), and treatment inefficacy (.3% group 1 vs. .1% in group 2). One death was reported in group 1. The patients' characteristics were comparable (Table 1). About 28% of the study population was shown to be obese (≥25 kg/m^2), with a similar distribution in the two study groups, and abdominal obesity was observed in 42% of the study population. Half of the study population was not receiving antihypertensive treatment prior to the study. The two groups were also comparable at inclusion in terms of BP values and severity, previous therapy, and prognostic factors (Table 2).

Efficacy Results

At week 4, 95% of group 2 patients who were untreated before the study were receiving VAL80, in compliance with the study protocol; 67.5% of uncontrolled patients of the same group previously treated by a monotherapy received VAL160, and 45.5% of those previously under bitherapy or with a systolic/diastolic BP level >20/10 mm Hg higher than the target level received VAL80/HCTZ12.5. Overall, in group 2, the prescribed treatment was in accordance with the protocol in 60% of the patients at week 4 and in 77.6% at week 8. At week 8, the drug use was comparable in the two groups; the duration of drug exposure was 55.7 ± 10.7 days in group 1 and 55.1 ± 11.3 days in group 2.

Table 2
Baseline blood pressure values of the study patients distributed according to the presence of associated risk factors*

	Group 1			Group 2		
	Total (n = 2,289)	HTN + diabetes or RI (n = 325)	HTN only (n = 1,964)	Total (n = 2,105)	HTN + diabetes or RI (n = 364)	HTN only (n = 1,741)
Diastolic BP (mm Hg)						
Mean ± SD	92 ± 9	90 ± 10	93 ± 9	92 ± 9	89 ± 9	93 ± 9
Systolic BP (mm Hg)						
Mean ± SD	160 ± 12	161 ± 14	160 ± 12	160 ± 13	159 ± 13	160 ± 13

BP, blood pressure; HTN, hypertension; SD, standard deviation; RI, renal impairment.

* The two groups were comparable at baseline.

Table 3

Comparative results of the two groups at the W4 and W8 evaluations of the primary efficacy parameter (achievement of BP control)*

| | | Percentage (%) of Controlled Patients | | | | | | |
| | | Week 4 | | | | Week 8 | | |
	n	SBP	DBP	SBP and DBP	n	SBP	DBP	SBP and DBP
Group 1 (no training)	2,262	36.5	67.0	33.2	2,211	48.0	74.8	44.7
Group 2 (training)	2,086	38.0	66.0	35.8	2,023	51.0	76.1	47.8
P group 1 vs group 2				.009				.005

BP, blood pressure.

* P values represent difference for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) control.

The analysis of the primary objective (percentage of patients strictly controlled for both SBP and DBP according to the target) in the total population of hypertensive patients showed, after 8 weeks of treatment, a significantly better BP control in group 2 in which patients were treated according to the guidelines and to the protocol therapeutic design: 47.8% vs. 44.7% (Δ = 3.1%, P = .005). Table 3 displays the comparative results of the two groups regarding the primary objective of the study (achievement of BP control) at both evaluations of week 4 and week 8.

For the analysis of patients with an increased cardiovascular risk, subgroups were defined as follows: age >60 years (group 1: n = 1,150, group 2: n = 1,035), body mass index (BMI) $\geq$25 kg/m^2 (group 1: n = 1,540, group 2: n = 1,430), diabetes (group 1: 12.1%, n = 267, group 2: 14.3%, n = 290), absence

of antihypertensive treatment at randomization (group 1: n = 1,111, group 2: n = 1,005). As shown in Figure 2, the study population analyzed either in terms of BP level or distributed by subgroups of elevated cardiovascular risk showed better BP control in group 2 (trained investigators) as compared with group 1 (no training, free management) in hypertensive patients with diabetes (P = .001), elderly patients (P = .022), and in those untreated at randomization (P = .005). A multivariate analysis by logistic model of the factors likely to predict BP control showed the relationship between training and BP control achievement (P = .008).

Safety Results

AEs that occurred at a frequency $\geq$1% were mainly dizziness and headaches. Among the 121 AEs that were a
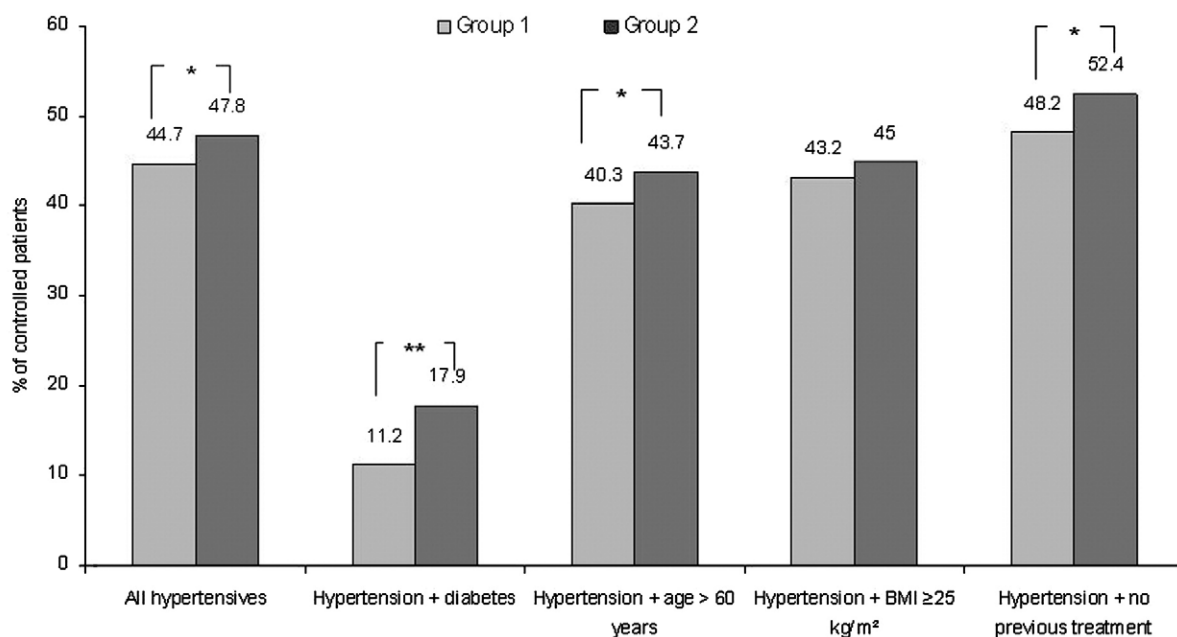

Figure 2. BP control (SBP + DBP) at week 8 in subgroups of patients from the two study groups. Significant differences in favor of group 2 are noted, except for the BMI.

cause for study cessation, 111 were not serious. One patient in group 1, having received VAL160/HCTZ12.5 for 2 months and with a medical history of newly diagnosed esophagitis, died from a myocardial infarction between visit 2 and visit 3; no relation with the study medication was suspected by the investigator.

Investigator's Evaluation Regarding the Specific Training

The immediate training assessment by the participating investigators shows that 90% of them were satisfied, showing good adhesion to the study-specific training. The short-term evaluation of the training by the participating GPs (sent to the investigators at the end of the study) shows 95% satisfaction with the pedagogic competence of the expert instructors, 94% satisfaction with the training contents, 94% satisfaction with relevant answers to trainee's questions, 91% satisfaction with the interactivity character of the sessions, and 85% were satisfied with the small number of trainees per training session. The long-term evaluation (1 year after the end of study) is ongoing.

Discussion

This study consisted of randomizing two groups of investigators to be trained or not in hypertension management guidelines and both provided with the same antihypertensive treatments (based on valsartan ± HCTZ) though with different therapeutic designs, and set out to demonstrate the efficacy of this training on BP control. The percentage of patients at BP goal (44% to 48%) was above the average (<25%) reported in most epidemiologic trials.[5-7,22,23] This encouraging overall result is likely to be due in part to the use of the valsartan combination therapy; indeed we observed a reduction in BP from baseline and satisfactory rates of responder patients independently from the presence of other cardiovascular risk factors. At the end of the study, the treatment exposure of the patients was similar in the two groups. However, the results obtained in group 2 indicate that the specific training of half of the investigators and the compulsory respect of the recommended lifestyle measures may have enhanced the positive outcome of the study's antihypertensive treatment.

Despite similar results in terms of absolute BP lowering after 8 weeks of treatment, a significant difference was observed between the two groups regarding the primary efficacy criterion. This difference can be reasonably attributable to the fact that the management of the patients was different. It is noticeable that therapeutic efficacy was significantly enhanced in group 2 by the initial GPs' training in the management of hypertension as widely recommended,[3,4,21–23] ie, the respect of lifestyle measures, the adaptation of the initial dosing, or the adjunction of another antihypertensive agent such as a diuretic according to sys-

tolic and diastolic BP levels at initiation of treatment, prior antihypertensive treatment, and BP control. The protocol provided group 2 (trained group) with an optional titration schema to be used according to the new guidelines, at week 4. This result, especially marked in the diabetic population, confirms the necessity of combining training to guidelines (including lifestyle measures) with the application of a therapeutic titration design as recommended by these guidelines.

Other studies on guideline implementation have also shown the benefit of training and intensive support on hypertension control,[24] with an additional benefit related to individualized tools.[25]

It is noticeable, however, that although satisfactory BP control was obtained by the group of GPs having undergone special training in hypertension guidelines and treating patients according to the protocol-specific titration design, still 42% to 46% of the study population was not at goal after 8 weeks. This remains an elevated percentage of uncontrolled patients. Another noticeable observation is that, despite training, group 2 GPs underestimated the calculated cardiovascular risk (figures not presented in the results) as recommended by the ESH,[3,4] which confirms the overall insufficient awareness of the importance of additional cardiovascular risk factors in hypertension management in general practice.

Similar findings were observed by Roumie et al[26] using the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure seven guidelines in the U.S. Veterans Administration system. In their study, authors reported that simply referring the physicians to the guidelines had relatively little impact and using reminders had only a small incremental effect. The major impact was observed using a multifactorial intervention.

A multifactorial intervention including patient education improved BP control compared with provider education alone.

Some limitations are to be taken into account in this study. First of all, care should be taken when extrapolating the encouraging data from this 8-week trial to longer term. It should also be remembered that the investigators voluntarily accepted to participate in the specific training, indicating possibly a greater motivation than that of the overall medical population of GPs given the number of practitioners who avoid any change in their medical practice, except in case of clinical complications.[27]

Moreover, further studies are needed to determine whether the efficacy of the method selected for this study may be enhanced by using more sophisticated techniques and materials such as an electronic reminder to be systematically used at each visit, a computerized patient file, etc.

Conclusion

The better BP control obtained after 8 weeks in the group managed by the trained investigators, especially with the diabetic hypertensive population, confirms the efficacy of combining a specific training in the new recommendations on the management of high BP to a therapeutic titration design that takes into account not only initial systolic and diastolic BP levels but also the existence of prior antihypertensive therapy and the level of BP control. Nevertheless, much remains to be done regarding the calculation of the cardiovascular risk, which is a considerably important parameter when treating a hypertensive patient. In this study, valsartan was observed to be effective and safe whatever the patient's profile in terms of cardiovascular risk.

Acknowledgments

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