Baseline Characteristics and Early Blood Pressure Control in the CONVINCE Trial

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Abstract—Blood pressure (BP) control rates around the world are suboptimal. Part 2 of the National Health and Nutrition Educational Survey (NHANES) III indicates that only 27.4% of hypertensive Americans aged 18 to 74 years have a BP of <140/90 mm Hg. We wanted to assess BP control during the first 2 years and to describe the baseline characteristics of patients enrolled in the Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Study, an international clinical trial that compares outcomes in hypertensive patients randomized to initial treatment with either controlled-onset extended-release verapamil or the investigator's choice of atenolol or hydrochlorothiazide. At randomization, BP was <140/90 mm Hg in only 20.3% of the 16 602 subjects (average±SD age 65.6±7.4 years; 56% women, 84% white/7% black/7% Hispanic). The average BP at enrollment was 148/85 mm Hg for patients taking BP medications (n=13 879) and 161/94 mm Hg for previously untreated patients (n=2723). After medication titration, with a transtelephonic computer that recommended an increase in the dose or number of antihypertensive agents whenever the BP was 140/90 mm Hg, 84.8% of the subjects attained the goal BP. During 2 years of treatment, BP control was maintained in 67% to 69% of the subjects (69% to 71% for systolic BP of <140 mm Hg and 90% for diastolic BP of <90 mm Hg). These data suggest that the control of systolic BP is more difficult than the control of diastolic BP. The US national goal of having 50% of hypertensives with a BP of <140/90 mm Hg may be achievable if a forced titration strategy is used. Interested investigators, free care and medications, and well-educated subjects may make the attainment of such a goal easier in the CONVINCE study than in the general population. **(*Hypertension*. 2001;37:12-18.)**

Key Words: clinical trials ■ verapamil ■ atenolol ■ hydrochlorothiazide

Recent data from several countries indicate that hypertension is not being well controlled.[1–4] In the United States, Healthy People 2000 set a goal of having 50% of hypertensives with a blood pressure (BP) of <140/90 mm Hg, but recent data from many sources indicate this target is not being met.[3] Part 2 of the National Health and Nutrition Educational Survey (NHANES) III indicates that only 27.4% of US hypertensives (aged 18 to 74 years) have a BP of <140/90 mm Hg, even when measured in the subject's home by specially trained visiting nurses.[5] Data from several surveys (often based on the Health Plan Employer Data Information Set [HEDIS]) indicate that few organized medical care delivery systems attain the recommended level of BP control.[6–9] Many reasons for the lack of hypertension control have been suggested, including nonadherence to medications, limited availability of medications, and unwillingness to intensify treatment (by either patient or physician).[10–12]

The Controlled ONset Verapamil INvestigation of Cardiovascular Endpoints (CONVINCE) Study is a double-blind, randomized, international clinical trial that compares 2 initial treatments for hypertension. One treatment begins with a physician-directed choice of hydrochlorothiazide (HCTZ) or atenolol, and the other treatment begins with controlled-onset extended-release (COER) verapamil (Covera-HS; Searle Pharmaceuticals). The protocol for this study includes an increase in antihypertensive medication (in either dose or

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number of agents) whenever the BP is not at goal (<140/90 mm Hg).[13]

The CONVINCE Study therefore provides an excellent opportunity to examine the extent of BP control in a clinical trial in which forced titration of antihypertensive medication is recommended whenever the BP is ≥140/90 mm Hg.

Subjects and Methods

Enrollment

Because of the large number of sites, which span half of the world, a simple automated transtelephonic system (interactive voice response system [IVRS]) was used for randomization, assignment, and tracking of subjects and blinded medication. A 1-page case report form that summarizes data for each subject at randomization (and every 6 months thereafter) was faxed to a central location (PAREXEL International, Waltham, Mass).

Once an eligible subject provided signed informed consent, site personnel called the IVRS using a toll-free number. With a touch-tone keypad, the caller entered the subject's birthdate, gender, verification of inclusion and exclusion criteria, and confirmation of signed informed consent. The IVRS then generated the blinded treatment assignment, maintaining a continuously updated registry of enrolled subjects and their characteristics. On the completion of enrollment, the data were transferred electronically to the Data Coordinating Center (Coordinating Centers for Biometric Research at the University of Minnesota), which prepared summaries and tables that described the enrolled subjects. Blood pressure data were gathered with the same system during office visits at least every 6 months. Most subjects visited a clinical site at monthly intervals for titration of drug therapy until the BP was <140/90 mm Hg ("End of Titration (EOT)").

Revision of Sample Size

The formal results of the power calculation and related assumptions have been published.[13] The sample size was increased from 15 000 to 16 600, because the rate of subjects who discontinued blinded study medication exceeded expectations.

Statistics and Comparisons

The baseline characteristics are reported as mean±SD for continuous variables. We used χ^2 tests to compare the characteristics of participants taking a diuretic versus a β-blocker as the standard of care (SOC) choice.

Results

Recruitment

From September 30, 1996, through December 18, 1998, 16 602 subjects were randomized from 661 clinical sites in 15 countries. Approximately 70% of CONVINCE subjects were enrolled in the Americas (Table 1). The average number of participants per site was 25. The site with the highest enrollment randomized 195 subjects; 18 sites randomized >100 subjects. Sixty-six additional sites exceeded the initial recruitment goal of 50 subjects, and 43 additional sites enrolled 41 to 50 subjects. Bulgaria, the country with the third largest enrollment (7.6% of the total), had nearly 3 times the overall average number of subjects per clinical site. Spain and Israel (5.0% and 4.2% of total enrollment, respectively) had the highest rate of recruitment (number of subjects per clinical site per month of participation).

Demographics

The average CONVINCE participant was 65.6±7.4 (SD) years old at entry, with the women slightly older (66.0±7.6 years) than the men (65.0±7.1 years). Twenty-five percent of the CONVINCE participants were between 55 and 59 years old at randomization; 23.7% were between 60 and 64 years old and 22.1% were between 65 and 69 years old, with declining percentages of older individuals. Fifteen subjects (0.1%) were ≥90 years old, 1.0% were 85 to 89 years old, 3.2% were 80 to 84 years old, 9.1% were 75 to 79 years old, and 15.8% were 70 to 74 years old. The average age of CONVINCE subjects varied little among the participating countries: the lowest mean age was in Bulgaria (62.0 years old), and the highest mean age was in the United Kingdom (67.0 years old).

TABLE 1. CONVINCE Subjects and Drug Choice by Country

Country	Clinical Sites, n	Enrolled Subjects, n (% of total)	Percent With HCTZ as SOC Choice
United States	308	8201 (49.4)	45.1
Canada	109	3475 (20.9)	48.1
Bulgaria	14	1264 (7.6)	37.8
Spain	57	823 (5.0)	72.1
Israel	35	690 (4.2)	50.6
United Kingdom	21	509 (3.1)	56.8
Italy	33	385 (2.3)	47.3
Mexico	9	282 (1.7)	39.7
Sweden	23	262 (1.6)	35.1
Czech Republic	12	242 (1.5)	31.0
Hungary	16	184 (1.1)	42.9
Poland	10	130 (0.8)	29.2
Slovakia	6	71 (0.4)	23.9
Germany	5	69 (0.4)	52.2
Brazil	3	15 (0.1)	33.3
Total	661	16 602 (100)	46.5

More women than men were enrolled in CONVINCE: 9300 (56.0%) compared with 7302 (44.0%), respectively. The gender distribution between countries varied more than did the differences in average age. The greatest percentage of enrolled women was in Mexico (68.3%), and the lowest was in the Czech Republic (45.6%).

The race/ethnicity of CONVINCE participants (determined according to the self-report of each subject) was generally representative of the country of origin. Overall, 83.9% of the CONVINCE participants were white, 7.0% were black, 7.0% were Hispanic, 1.6% were Asian, and 0.5% were of "Other" race/ethnicity. These totals reflect the local custom in assignment of race/ethnicity: all participants from Spain except 1 were categorized as "Caucasian"; all 282 Mexican subjects were categorized as "Hispanic." In the United States, 74.2% of those recruited in CONVINCE were white, 13.9% were black, 10.9% were Hispanic, 0.6% were Asian, and 0.4% were of "Other" race/ethnicity; these percentages are very similar to those of the general US population.[14,15] Canadian CONVINCE participants also closely matched their national ethnic makeup: 91.8% were white, 6.0% were Asian, 0.8% were black, 0.3% were Hispanic, and 1.1% were "Other."

Treatment for Hypertension

Most participants (83.5%) were taking drug therapy for hypertension at the time of enrollment. There was, however, a very wide variation among countries: in Germany, only 33% of the 69 participants were taking antihypertensive drug therapy at enrollment compared with 97% of the 71 subjects enrolled in the Czech Republic. Because individuals already on treatment had only to switch from their previous antihypertensive drug regimen to blinded CONVINCE study medication at enrollment, it is not possible to determine what level (or stage) of untreated hypertension they would have had. Their average BP at enrollment was 148.0±15.7/85.4±9.5 mm Hg. The highest average on-treatment BPs were found in Germany (159.1/92.4 mm Hg, n=69) and Sweden (156.6/90.4 mm Hg, n=262); the lowest average systolic BP was found in the Czech Republic (144.1 mm Hg), and the lowest average diastolic BP was found in the United States (83.5 mm Hg).

The average BP of the 2701 subjects not taking antihypertensive medications at enrollment was higher (160.6±13.1/93.9±8.3 mm Hg) than that of the treated individuals, because the protocol required a BP of ≥140/90 mm Hg if a subject was not taking antihypertensive medication. This average BP is similar to that obtained during the placebo run-in phase in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[16] but lower than that in the Hypertension Optimal Treatment (HOT) Study.[17]

Choice of SOC Treatment

Table 1 shows the percentage of subjects for whom the investigator chose the diuretic (HCTZ) over the β-blocker (atenolol) as the SOC treatment. Despite the concerns of some regarding the efficacy of β-blocking agents in preventing cardiovascular complications in older hypertensive subjects,[18] 54% of the subjects in CONVINCE had atenolol chosen for them by their physician-investigator. The choice between the diuretic or the β-blocker showed considerable country-to-country variation, probably reflecting country-specific practice preferences. At the extremes, 72.5% of the 823 Spanish subjects had the diuretic chosen for them compared with only 22.7% of the 71 Slovakian subjects.

As seen in Table 2, the SOC choice varied by subgroup. Among men, 57.1% had atenolol chosen (over HCTZ) by their treating physician-investigator compared with 50.8% for women. The β-blocker was more commonly chosen than the diuretic in subjects who had previously had antihypertensive drug therapy (86.5% versus 80.4%). We do not know whether this represents more known coronary or other cardiovascular disease or its risk factors among the men, a reflection of previous adverse experiences with one or the other agent, or a greater propensity of diuretics to cause male sexual dysfunction.[19–21] The physician-investigators tended to prefer the β-blocker over the diuretic in younger subjects (55% of those <70 years old) and the diuretic over the β-blocker in older subjects (51% of those ≥70 years old). This may be in accordance with clinical trial data in older patients that suggests better outcomes when diuretics are used compared with β-blockers.[18] Blacks and Hispanics were the only racial/ethnic groups who showed a significant preference for a specific SOC choice. The physician-investigators chose HCTZ for 59% of blacks and atenolol for 72% of Hispanics.

TABLE 2. Selection of HCTZ (versus Atenolol) as SOC Choice for Randomized Patients by Subgroup

Subgroup	No. in Subgroup	HCTZ Chosen, n (%)
Age, y		
<60 years	4150	1796 (43.3)
60–69	7611	3453 (45.4)
70–79	4135	2102 (50.8)
≥80	706	361 (51.1)
Sex		
Men	7302	3132 (42.9)
Women	9300	4580 (49.2)
Treated with drugs at enrollment	13 723	6150 (44.8)
Previously untreated	2710	1496 (55.4)
SBP (on medication, mm Hg		
≤140	3770	1697 (45.0)
141–160	7023	3145 (44.8)
>160	2879	1284 (44.6)
Race/ethnicity*		
White	5998	2715 (45.3)
Black	1132	661 (58.4)
Asian	50	25 (50.0)
Hispanic	880	246 (28.0)
Other	34	11 (32.4)
History of myocardial infarction	1261	377 (29.9)
History of stroke	768	340 (44.3)
Cigarette use	3799	1746 (46.0)
Type II diabetes mellitus	3266	1622 (49.7)
Left ventricular hypertrophy	2007	851 (42.4)
Dyslipidemia	5152	2265 (44.0)
Obesity	8284	4118 (49.7)
Established vascular disease	2750	970 (35.3)
History of transient ischemic attack	349	128 (36.7)
Vascular bruit	814	355 (43.6)

*Race/ethnicity data are shown for participants from the United States (the country of greatest diversity).

Risk Factor Profile

The distribution of traditional cardiovascular risk factors observed on enrollment of the 16 602 subjects into CONVINCE is shown in Table 3. Although only 1 additional risk factor was required for eligibility, nearly half (49.4%) of the CONVINCE subjects had >1 additional traditional risk factor. Because individual risk factors increase the future risk of cardiovascular events more than additively, the 3.2 risk factors present in the CONVINCE study population (including age in 100% and male gender in 44%) suggest that this cohort is at an even greater risk for future cardiovascular events than was shown in other recent studies.[16,17,22–24] There was, again, a high between-country variation of the plurality of risk factors: the countries with the largest number of risk

TABLE 3. CONVINCE Subjects With Known Traditional Cardiovascular Risk Factors at Randomization

Traditional Risk Factor	Prevalence at Randomization, %	Countries With Highest Prevalence
Overweight (body mass index ≥28.5 kg/m^2 or by Metropolitan Life tables)	50.4	Spain, United Kingdom
Dyslipidemia	31.3	Poland,† Germany*
Cigarette use	22.6	Germany,* Bulgaria
Diabetes mellitus	19.8	Brazil,* Germany*
Known vascular disease	17.1	Slovakia,* Germany*
Left ventricular hypertrophy	11.7	Poland,† Brazil*
Previous myocardial infarction	7.8	Poland,† Czech Republic
Vascular bruit	4.9	Sweden, Canada
Previous stroke	4.7	Brazil,* Hungary†
Previous transient ischemic attack	2.1	Slovakia,* Germany,* Hungary†

*Fewer than 100 subjects were enrolled in this country.
†Between 100 and 200 subjects were enrolled in this country.

factors were Poland, Hungary, and Slovakia; the United Kingdom and Sweden enrolled patients with the fewest risk factors.

BP Control Rates

At randomization, only 20.3% of subjects had controlled hypertension (<140/90 mm Hg); this increased to ≈85% (at EOT) and remained relatively stable at ≈70% during the first 2 years of follow-up (Figure 1). At every time point, control of diastolic BP (to <90 mm Hg) was achieved in a higher proportion of subjects than was control of systolic BP (to <140 mm Hg). Because the CONVINCE study protocol recommended intensified therapy whenever BP was 140/90 mm Hg, many subjects were treated with >1 antihypertensive medication; this proportion also increased during the time of follow-up (Figure 2). Subjects not taking antihypertensive medication at enrollment achieved slightly better BP control, both at EOT (87.4% versus 84.3% for treated subjects) and subsequently (69% to 74% versus 64% to 69%). Even at 1 month after randomization, initially untreated

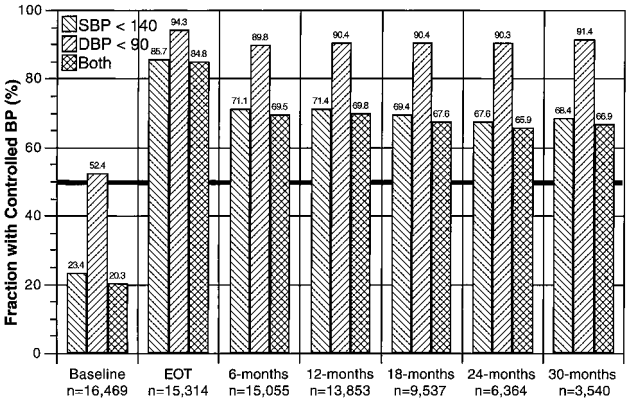

Figure 1. BP control (<140/90 mm Hg) in the CONVINCE Study. SBP indicates systolic BP; DBP, diastolic BP; Both, both systolic and diastolic BP.

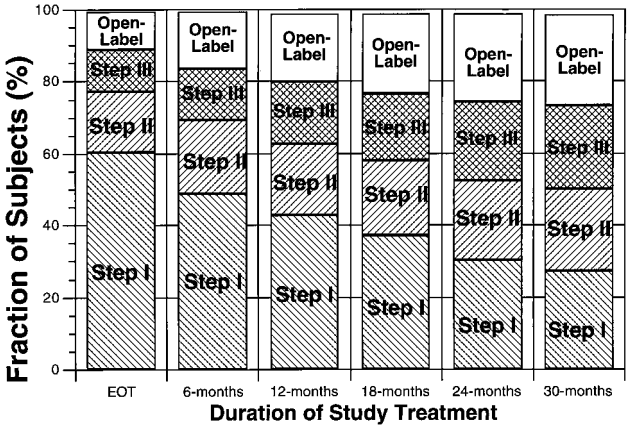

Figure 2. Distribution of treatment regimens in the CONVINCE Study. Step I indicates COER verapamil or HCTZ or atenolol; step II, COER verapamil plus HCTZ or atenolol plus HCTZ; step III, step II plus another antihypertensive drug (ACE inhibitor is recommended); and open-label, any regimen not including blinded COER verapamil, HCTZ, or atenolol.

subjects had slightly lower average BPs (144±16/84±9 mm Hg) than did previously treated subjects (148±19/85±10 mm Hg).

Discussion

These data indicate that at randomization in this clinical trial, only 20% of subjects had controlled hypertension, but the proportion increased substantially (to ≈85%) during forced titration of antihypertensive medications and then leveled off at ≈70% during 2.5 years of follow-up. Like many other recent clinical trials[16,17,25] and other studies,[26–28] the subjects in CONVINCE were more likely to achieve the diastolic BP target of <90 mm Hg than the systolic target of <140 mm Hg, as recommended by Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI)[29] and World Health Organization–International Society of Hypertension (WHO-ISH) guidelines.[30]

Compared with other recent hypertension trials, CONVINCE has the highest proportion of enrolled subjects with controlled BPs. At 12 months after randomization, the ALLHAT Research Group reported that 53% of their 14 722 subjects had a systolic BP of <140 mm Hg[31]; the corresponding value for CONVINCE is 71.4%. The Losartan Intervention For Endpoints (LIFE) Study reported that only 25.8% of their 9194 subjects had a systolic BP of <140 mm Hg at 12 months.[32]

These data have several potential limitations. Subjects who are lost to follow-up or who missed scheduled visits may have poorer control of BP. Also, the better BP control observed during follow-up may be due in part to regression to the mean if participants with poorer BP control on treatment at entry were more likely to be selected for enrollment. The risk assessment for CONVINCE subjects may underestimate the true risk of cardiovascular events because not each subject was systematically assessed for all risk factors. Eligible subjects for CONVINCE needed only to have documented presence of hypertension and 1 additional traditional cardiovascular risk factor. Some subjects are therefore likely to

have risk factors that were not identified at randomization, which put them at higher risk than the estimates given earlier. The CONVINCE Executive Committee consciously decided to document only the presence of known risk factors (over, for instance, making a distinction between a "present, absent, or unknown" risk factor), because of the desire to (1) mimic ordinary clinical practice, (2) maximize enrollment and generalizability of the conclusions, and (3) minimize data collection, and cost. Thus, CONVINCE conforms to the "large, simple trial" paradigm.[33]

These data indicate that a high prevalence of BP control (<140/90 mm Hg) can be achieved in a large hypertensive population if a forced titration strategy is used and medications are provided without charge to motivated subjects by well-trained healthcare providers. These features of CONVINCE may make it easier to achieve a higher level of BP control in this clinical trial than in the general population.

Appendix

List of CONVINCE Committees and Investigators

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