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Hierarchical modeling of blood pressure determinants and outcomes following valsartan treatment in hypertensive patients with known comorbidities: pooled analysis of six prospective real-world studies including 11,999 patients

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Note: Stefaan Vancayzeele passed away on 27 August 2020. This article is dedicated to him in recognition of his leadership in real-world evidence studies, including the six studies included in the pooled analysis reported here.

TRANSPARENCY

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D. Hamarneh is now at Ro'ya Tholathiyat Al Aba'd (Amman, Jordan). D. Sun is now at Genentech (South San Francisco, CA, USA). Y. Van Camp is now in the House of Representatives of Belgium (Brussel, Belgium) and the Universiteit Antwerpen (Antwerpen, Belgium). Lorenzo Villa is now at the University of Colorado – Denver.

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ABSTRACT

Aims: Six prospective real-world studies of antihypertensive treatment with valsartan-centric regimens were pooled to (1) examine the effectiveness of ~90 days of second- or later-line valsartan treatment in hypertensive patients with known comorbidities; and (2) identify physician and patient-related determinants associated with systolic (SBP) and diastolic blood pressure (DBP) outcomes in these patients.

Methods and Materials: Pooled analysis of an evaluable sample of 11,999 hypertensive patients with known comorbidities treated ~90 days with valsartan-centric regimens. We applied hierarchical linear and logistic regression models to identify determinants of blood pressure (BP) outcomes and a potential physician class effect.

Results: Valsartan regimens resulted in mean(SD) systolic (SBP) and diastolic (DBP) reductions of 18.0(15.8)mmHg and 9.5(10.1)mmHg, respectively, at ~90 days; yielding SBP, DBP and combined SBP/DBP control rates of 44.0%, 67.2% and 39.3%, respectively. About a quarter of the variance in 90-day BP values was attributable to a physician class effect. BP outcomes declined with physicians' increasing years in practice and being male. At the patient-level, BP outcomes declined with SBP and DBP at diagnosis; diabetes; higher cholesterol and BMI; lower valsartan and HCTZ doses; and concomitant anti-hypertensives. Older age was associated with improved DBP. A proxy of physician vigilance, cardiovascular disease history was associated with improved BP outcomes; as were patient adherence and higher doses of valsartan in combination with HCTZ.

Conclusions: Valsartan-centric regimens have significant BP lowering benefits in this pooled sample of patients with known comorbidities. Many observed determinants of BP outcomes are modifiable or manageable.

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Keywords: angiotensin II receptor blockers; antihypertensive agents; blood pressure; epidemiologic studies; hypertension; logistic models; medication adherence; valsartan; determinant factors.

Running Title: Determinants of BP outcomes in patients with known comorbidities

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INTRODUCTION

Although guidelines for the treatment of hypertension have been widely available for decades and updated as recently as 2018[1,2], blood pressure (BP) control rates have historically been low and largely remain so. This is attributable, at least in part, to therapeutic inertia or not following practice guidelines on the part of physicians and poor adherence on the part of patients.[3,4] We showed in the prospective observational (real-world) PREVIEW study of 3,194 hypertensive patients seen by 504 general practitioners (GP) in Belgium[5], conducted under the then prevailing 2003 ESC/ESH guidelines[6], that 24% of the variance in SBP and 26% of the variance in DBP following approximately ~90 days of second-line treatment with valsartan regimens was attributable to a physician class effect.

The PREVIEW study[5] was followed by five similarly designed real-world studies (IMPROVE[7], INSIST[8], eNOVA[Novartis, data on file], BSCORE[9], EXCELLENT[10]) of various valsartan formulations (80mg, 160mg) and single-pill combinations (valsartan/HCTZ 80mg/12.5mg, 160mg/12.5mg, 160mg/25mg; valsartan/amlodipine 80mg/5mg, 160mg/5mg, 160mg/10mg) that followed a common data model, and evaluated BP values and BP control rates over a treatment period of ~90 days in daily clinical practice.[11] We report here on a pooled analysis of these six studies including 11,999 evaluable patients contributed by 2,349 Belgian GPs. Specifically, we evaluated (1) changes in SBP and DBP values, as well as SBP, DBP, and combined SBP/DBP BP control rates achieved from the start of valsartan treatment to ~90 days later; (2) the intraclass coefficients for a physician class effect as patients were "nested" under physicians; and (3) the patient-level and physician-level determinants of BP values and BP control rates as derived from hierarchical linear and logistic modeling.

All studies were conducted under the 2003 ESC/ESH guidelines that defined hypertension as SBP≥140 mmHg and/or DBP≥90 mmHg, but SBP≥130 mmHg and/or DBP≥80 mmHg for diabetic patients.[6] We acknowledge that European and North-American guidelines have evolved since, however because GPs' knowledge and practice patterns was assessed

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under the prevailing 2003 ESC/ESH guidelines, we report results here using the then prevailing BP cut-off values.

METHODS

The methodology of the studies has been described in detail elsewhere. Summarized below are the essentials of design, patients, data collected, and statistical analysis in function of the pooled analysis reported herein.[11]

Design

Data from six similarly designed, prospective, multicenter, pharmaco-epidemiologic studies were pooled [16-21] (**Table 1**). Each study included a baseline assessment and a follow-up assessment approximately 90 days ("~90 days") later as accommodated in routine clinical practice and at the treating GP's clinical discretion. The decision to treat with valsartan was made by the prescribing physician per his/her best clinical judgment. There were no required assessments and tests, and only data available from routine clinical practice were collected. Approvals for each study were obtained from ethical committees in Belgium. Excluded from the pooled analyses were a similarly designed study with patients with undetected impaired fasting glucose, type 2 diabetes, and/or metabolic syndrome as we aimed to limit the present analyses to patients with known comorbidities and thus greater certainty on the part of the treating GP.

Patients

Eligible subjects were male and female patients with hypertension (SBP≥140 mmHg and/or DBP≥90 mmHg; SBP≥130 mmHg and/or DBP≥80 mmHg for diabetic patients) treated with valsartan as second-line mono- or combination therapy in whom first-line treatment failed or was not tolerated; with known comorbidities and hence no undetected conditions at the time of initiation of valsartan therapy. Excluded were patients sensitive to any angiotensin receptor blockers (ARBs), thiazides, or calcium channel blockers; on any investigational drug in the past 30 days; or prescribed other ARBs during the study period.

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Variables and Measurements

Physicians

Variables included demographics, practice type, practice location/setting, patient mix, sources of information and knowledge related to hypertension, self-reported hypertension management practices, prescription patterns, management of side effects, SBP/DBP thresholds for treatment initiation and intensification, perceptions of patient adherence, and knowledge of practice guidelines.

Patients

Patient data at baseline included demographics, anthropometrics, hypertension and cardiovascular history, comorbidities, lifestyle, prior antihypertensive medications, SBP and DBP, clinical status, starting doses, concomitant anti-hypertensive and other relevant medications, and adherence within the past 4 weeks. Patient data at ~90-day follow-up included SBP and DBP, clinical status, changes in dosing since previous visit, concomitant medication(s) taken or changed since previous visit, and within the past 4 weeks.

Blood Pressure

BP was measured three times at 1- to 2-minute intervals in a sitting position after 5 minutes of rest. The mean was recorded as the mean sitting SBP (hereafter SBP) and mean sitting DBP (hereafter DBP).

Statistical Analysis

Descriptive statistics were used to describe the study patients, including proportions and appropriate measures of central tendency and dispersion. Because each physician recruited several patients, patients could not be considered independent but instead “nested” under their treating physician. We applied two-level hierarchical linear and logistic modeling with backward elimination ($p \geq 0.10$). Adjusted slope coefficients or odds ratios and 95% confidence intervals (CIs) were calculated to estimate the direction and strength of the relationship between individual variables and BP values and control. As the studies from which data were pooled

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differed in terms of valsartan formulations, we also assessed whether a particular study was associated with improved outcomes. Such study effect was interpreted as a proxy variable for the strength of the valsartan formulation and classified as a patient-related determinant. Statistical significance was set at $p<0.05$ and all tests were two-tailed. Sample size calculations were performed when each of the six studies in this pooled analysis were being designed; all studies met their respective minimum sample size. Hence this pooled analysis should be adequately powered.

RESULTS

Patient Characteristics

Of the 11,999 patients with evaluable data, mean age was 64.0 years (standard deviation [SD] 11.7), 52.0% were male, and 24.2% had diabetes (**Table 2**). Further, 17.5% of patients had a history of myocardial infarction and/or coronary artery disease, and 4.4% had experienced heart failure. Cerebrovascular conditions were present in 9.3% of the patients, peripheral arterial disease in 6.2%, and renal impairment in 3.8%. About one-quarter (24.2%) of patients were smokers. The majority (74.0%) of patients were above normal weight (BMI>25kg/m^2), and more than half (55.5%) had received cholesterol-lowering treatment. Mean (SD) total cholesterol level was 212.7 (40.0)mg/dL.

Patients had received on average 2.6(1.1) antihypertensive drugs as first-line treatment. Most of the patients were prescribed valsartan 160mg (39.1%), followed by valsartan/amlodipine 160/5mg (16.4%) and valsartan/hydrochlorothiazide 160/12.5mg (14.8%), with other regimens being less prevalent. Patients were also given concomitant medications, such as diuretics (50%), calcium antagonists (40%), beta-blockers (33%), and ACE-inhibitors (47%). The main reasons for initiating valsartan as second-line treatment were uncontrolled BP (76%), poor treatment tolerance (10%), orboth (14%). At ~90 days, 16.7% of patients had discontinued study treatment. Those still on treatment were on valsartan 160mg (28.6%), followed by valsartan/amlodipine 160/5mg (15.2%) and valsartan/hydrochlorothiazide

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160/12.5mg (13.8%).

Physician Characteristics

The majority of 2349 GPs was male, certified and practicing solo to a mixed population of all ages. Mean(SD) age was 47.4(8.1) years and the average years of clinical practice was 20.7(8.9) years. The median number of hypertensive patients seen in the 12 months before baseline was 100 (mean[SD] 226.1[279.4]). On average, physicians spent 19.4(5.8) minutes in their first visit with a newly diagnosed hypertensive patient and saw new hypertensive patients 4.4(6.3) times in the first 3 months after diagnosis.

BP Values and Control (Table 3)

SBP decreased by a mean(SD) of 18.0(15.8)mmHg from a baseline mean(SD) of 155.4(15.1)mmHg to a ~90-day mean(SD) of 137.4(11.7)mmHg; and DBP by 9.5(10.1)mmHg from a baseline mean(SD) of 91.4(9.4)mmHg to a ~90-day mean(SD) of 81.8(7.5)mmHg. The SBP control rate had increased by 37.3% from a baseline rate of 6.7% to a 90-day rate of 44.0%; the DBP control rate by 43.2% from a baseline rate of 24.0% to a 90-day rate of 67.2%; and the combined SBP/DBP control rate by 34.2% from a baseline rate of 5.1% to a 90-day rate of 39.3%. These BP reductions and increases in BP control rates were statistically significant (all $p<0.0001$).

Modeling of BP Outcomes (Table 4)

BP Values at ~90 Days

At ~90 days, 24% of SBP and 26% of DBP variability was attributable to a physician class effect (ICC=0.22 and 0.25, respectively). The remaining 78% and 75% were accounted for by patient-related variables.

SBP at ~90 days increased as a function of higher SBP at diagnosis; diabetes; elevated total cholesterol; higher BMI; lower valsartan and/or HCTZ dose; concomitant treatment with alpha-blockers, beta-blockers, and/or ACE-inhibitors; increasing physician years in practice, physicians of male gender; and a study effect for the lower-dose PREVIEW study. Conversely,

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SBP decreased if patients had a history of cardiovascular disease, better patient adherence, and a study effect for the higher-dose INSIST study.

DBP at ~90 days increased as a function of higher DBP at diagnosis; elevated total cholesterol; higher BMI; lower valsartan and/or HCTZ dose; concomitant beta-blocker treatment; and increasing physician years in practice. DBP decreased as a function of age, if patients had history of cardiovascular disease, better patient adherence, and study effects for the higher-dose INSIST and IMPROVE studies.

BP Control at ~90 Days

Factors increasing the likelihood of controlled SBP at ~90 days included a history of cardiovascular disease, better patient adherence, and a study effect for the higher-dose INSIST study. Factors increasing the likelihood of controlled DBP comprised increasing patient age, history of cardiovascular disease, better patient adherence, and study effects for the higher-dose IMPROVE and INSIST studies. Factors increasing the likelihood of combined SBP/DBP control consisted of a history of cardiovascular disease, better patient adherence, and a study effect for the higher-dose INSIST study.

Conversely, factors decreasing the likelihood of SBP control included increasing patient age, higher SBP at diagnosis, diabetes, elevated total cholesterol, higher BMI, lower valsartan and/or HCTZ dose, increasing physician years in practice, physicians of male gender, and a study effect for the lower-dose PREVIEW study. Factors decreasing the likelihood of DBP control consisted of higher DBP at diagnosis of hypertension, diabetes, elevated total cholesterol, higher BMI, lower valsartan and/or HCTZ dose, and increasing physician years in practice. Factors decreasing the likelihood of combined SBP/DBP control comprised higher SBP at diagnosis of hypertension, diabetes, elevated total cholesterol, lower valsartan and/or HCTZ dose, increasing physician years in practice, physicians of male gender, and a study effect for the lower-dose PREVIEW study.

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DISCUSSION

In this pooled analysis of 11,999 patients contributed by 2,349 GPs, we found that treatment with valsartan-based regimens reduces BP values and improves BP control within a ~90-day follow-up period in patients with hypertension in whom first-line treatment failed or was not tolerated. We also identified several physician- and patient-related determinants associated with variations in BP values and the odds of BP control using hierarchical modeling. While our findings confirm prior studies, including those included in the pooled analysis, its novelty is fourfold. First, unlike patients in clinical trials, patients presented with significant comorbidities – in type and in number. Second, the large sample size lends major statistical power to the study and therefore robustness to the observed BP outcomes and associated determinants. Third, clinically, the findings quantify convincingly and consistently that adherence is a major determinant of BP outcomes and should be evaluated routinely. We have shown elsewhere that asking a single question ("Do you recall not having taken your medication sometime in the past 4 weeks?") is associated with better BP outcomes. Lastly, up to 25% of the variance in BP values at ~90 days is unrelated to the patient but attributable to their treating GP.[12]

Our findings for BP values and BP control rates should be compared with previous observations. In a meta-analysis of 354 randomized trials, Law et al. reported SBP and DBP reductions of, respectively, 10.3mmHg and 5.7mmHg at dose of 80mg, and 12.3mmHg and 6.5mmHg at dose of 160mg, in patients treated with ARBs.[13] These values are well below the average decline of 18.0mmHg in SBP and 9.5mmHgmmHg in SBP in our study. However, the Law et al.[13] BP values are for monotherapy, whereas our analyses included many patients receiving other antihypertensive medications in various combination therapies. Further, our control rates for SBP (44.0%), DBP (67.2%), and combined SBP/DBP (39.3%) were similar to, but mainly higher than, those reported by others. For example, Bramlage et al.[14] evaluated national and regional BP control and found that in Northern European countries (Belgium, Germany, Sweden, and Switzerland) BP was controlled in 17.5% (systolic), 35.5% (diastolic),

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and 13.4% (combined systolic/diastolic) of patients. In their study of low- and high-risk patients, Fagard et al.[15] reported combined SBP/DBP control rates of 46% in low-risk patients and 31% in high-risk patients. When we simulated their stratification, we obtained a similar SBP/DBP control rate 49.1% for low-risk patients, but a much lower SBP/DBP control rate of 8.5% for high-risk patients (data not shown). With diabetes being a key clinical marker of high-risk, this finding is consistent with the notion that diabetes is a major barrier to achieving blood pressure control.

Hierarchical modeling identified both patient-level and physician-level determinants of BP outcomes, as also summarized conceptually in **Table 5.** The findings about age impacting SBP negatively but DBP positively is consistent with established evidence. The finding that the higher the SBP and DBP at the time that hypertension is diagnosed underscores the importance of early detection and intervention, and hence the importance of screening and monitoring. Diabetes, elevated cholesterol levels, and being overweight or obese (as measured by the BMI) are known independent and inter-related risk factors – which can be managed or modified by lifestyle modifications and pharmacotherapy tailored to individual patient needs and thus lead to better BP outcomes. It also confirms that diabetes is a barrier to improving BP outcomes. The critical importance of patient adherence to antihypertensive treatment has long been established. Thus, it is not surprising that adherence was associated with improved BP outcomes in our pooled analysis. Further, our patient-level results show that more aggressive, higher-dose antihypertensive therapy, whether mono- or combination therapy, is associated with greater reductions in BP values and better BP control rates. Escalation to higher doses of agents and more anti-hypertensive agents were consistently associated with greater reductions in BP values and higher BP control rates – as evidenced by the coefficients for individual agent and dose variables, but also by the coefficients for the study effects associated with each of the six studies. The latter validated our assumption that each study was a proxy of increasingly stronger mono- and combination valsartan regimens. It also lends support to the notion that this

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pooled set of patients, most of whom had failed first-line treatment, may have included many difficult-to-treatment and treatment-resistant patients. Lastly, a history of cardiovascular disease (MI or coronary) was associated with better outcomes – which seems paradoxical. This is a finding that has come up in some of the reports on the constituent six studies; that is, GPs may have paid closer attention to patients with a prior myocardial infarction or established coronary disease.[11]

Patients seen by the same physician are affected by that particular physician's knowledge, experience, and practice patterns, among other factors. This was evident from the proportions of variance in BP values at ~90 days attributable to a physician class effect physician-related: 22% for SBP and 25% for DBP – with the remaining 78% and 75% attributable to variation in patients. At the physician-level, number of years in practice was consistently associated with worse BP outcomes. This possibly indicates that younger physicians are more likely to intensify therapy when observing poor BP outcomes, In contrast, older colleagues may exhibit therapeutic inertia[16]: failure to initiate or intensify BP therapy when indicated due to overestimation of the care provided, use of "soft" reasons to avoid intensification of therapy, and lack of education, training, and practice organization aimed at achieving therapeutic goals.[17] However, Redon et al. have argued that factors explaining therapeutic inertia are not completely understood.[18]

Conversely, having seen more hypertension patients over the past 12 months, knowing BP targets, and practicing in accordance with evidence-based guidelines were associated with more favorable BP outcomes in our analysis. Chen et al.[19] showed that the average accuracy rate of hypertension prevention knowledge among general practitioners in Xuhui district in Shanghai, China was 49.2%, ranging from 10.5% to 94.7%. The factors associated with accuracy were physician's education level (medical university vs. professional school) and type of center in which they practiced (training base vs. community healthcare center). A case report-based survey by Ekesbo et al.[20] among GPs in southern Sweden confirmed a general lack of

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adherence to hypertension guidelines and was associated with both under- and overtreatment in the majority of cases presented. Further, most GPs used target BP levels but seldom considered cardiovascular risk factors. A systematic review of barriers to guideline adherence concluded that physicians are not adherent to guidelines because of lack of awareness, lack of familiarity, lack of agreement, lack of self-efficiency, lack of outcome expectancy, inertia of previous practice, and external guideline-related, patient-related, and environmental related barriers.[21]

This pooled analysis has limitations. Patients and physicians were from one country. Confounding from unmeasured variables may have influenced the results. Our study is limited to valsartan-centric regimens and did not cover other ARBs. Our findings were not from pooled RCTs.

The optimal approach for evaluating treatment efficacy is based on RCTs; i.e., does the treatment work under ideal circumstances. However, RCT conditions may not be representative of those seen in routine clinical practice. For example, physicians are likely to range from novice to expert, vary in clinical training, and may performed above or below their medical peers. Patients may also be of different age, with varying comorbid conditions, and compromising personal or family histories. It is not surprising, then, that the real-world effectiveness of antihypertensive treatment may differ, positively or negatively, from the efficacy seen in RCTs.[11] The studies included in this pooled analysis were highly similar, which strengthens the assumption that the observed results were indeed a function of the variables studied.

CONCLUSION

Our pooled analysis confirms that valsartan-based regimens prescribed by GPs are effective in the real world for patients with known comorbidities in whom first-line antihypertensive treatment failed or was not tolerated. In its different formulations, valsartan has major therapeutic benefits in lowering and controlling BP within a ~90-day follow-up period, with a trend for higher-dose mono- and combination therapies to yield better BP outcomes. Many of

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the determinants of BP outcomes identified in our analysis are modifiable and manageable through effective clinical interventions and responsive patient engagement.

Table 1. Studies, patients, and valsartan formulations included in pooled analysis

Study	PREVIEW	IMPROVE	INSIST	eNOVA	BSCORE	EXCELLENT	Total
Patients	2599	3028	592	636	2238	2906	11999
Physicians	455	502	251	230	293	618	2349
Patient characteristics							
Age, y, mean (SD)	63.4 (11.8)	63.6 (11.8)	63.7 (11.4)	64.0 (11.8)	63.9 (11.6)	63.8 (11.5)	
Gender, % male	48.7	49.5	51.0	51.2	55.9	55.0	
Diabetes mellitus, %	20.6	22.4	28.9	25.6	24.8	27.4	
Valsartan formulations							
80mg	✓	✓		✓	✓		
160mg	✓	✓		✓	✓		
80mg + 12.5mg HCTZ	✓	✓		✓	✓		
160mg + 12.5mg HCTZ		✓		✓	✓		
160mg + 25mg HCTZ		✓	✓		✓		
80mg + 5mg amlodipine						✓	
160mg + 5mg amlodipine						✓	
160mg + 10mg						✓	

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	amlodipine

SD, standard deviation; HCTZ, hydrochlorothiazide; y, year.

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Table 2. Patient characteristics at baseline [a]		
Age, y, mean (SD)	64 (11.7)	
Male, %	52.0	
History of disease [b]		
Myocardial infarction	8.6%	
Coronary artery disease	8.9%	
Heart failure	4.4%	
Cerebrovascular conditions	9.3%	
Peripheral arterial disease	6.2%	
Renal impairment [c]	3.8%	
Risk factors, %		
Smoker	25.2%	
Diabetes	24.2%	
Cholesterol-lowering treatment	55.5%	
Body mass index >25kg/m^2	74.0%	
Total cholesterol, mg/dL, mean (SD)	212.7 (40.0)	
Height, cm, mean (SD)	169.2 (9.2)	
Weight, kg, mean (SD)	81.0 (15.6)	
Valsartan treatment, %	Baseline	90 days
Discontinuation	-	16.7%
Valsartan 160mg	39.1%	28.6%
Valsartan/amlodipine 160mg/5mg	16.4%	15.2%
Valsartan/HCTZ 160/12.5mg	14.8%	13.8%
Valsartan/HCTZ 160/25mg	8.7%	6.3%
Valsartan/HCTZ 80/12.5mg	6.6%	6.9%
Valsartan 80mg	6.5%	3.6%
Valsartan/amlodipine 160mg/10mg	5.1%	6.8%

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Valsartan/amlodipine 80mg/5mg	2.7%	2.2%

SD, standard deviation; HCTZ, hydrochlorothiazide; y, year

[a] Missing data not reported; thus, total may not equal 100%.

[b] Categories are not mutually exclusive.

[c] Renal impairment defined as serum creatinine>1.5mg/dL.

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Table 3. Blood pressure at baseline and ~90 days

	BP values, mmHg (SD)				BP control rate (%)			
	Baseline	~90 days	Δ	p	Baseline	~90 days	Δ	p
SBP	155.4 (15.1)	137.4 (11.7)	-18.0 (15.8)	<0.0001	6.7 %	44.0 %	+37.3 %	<0.0001
DBP	91.4 (9.4)	81.8 (7.5)	-9.5 (10.1)	<0.0001	24.0 %	67.2 %	+43.2 %	<0.0001
SBP/DBP					5.1 %	39.3 %	+34.2 %	<0.0001

BP, blood pressure; SD, standard deviation; Δ, change.

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Table 4. Hierarchical linear and logistic modeling of BP outcomes at ~90 days

A. Hierarchical linear modeling of SBP and DBP at ~90 days

SBP at ~90 days			ICC	0.22
		mmHg	SE	p
	Intercept	106.56	1.5154	<0.0001
Patient variables				
SBP at diagnosis of hypertension, per mmHg		0.1257	0.0068	<0.0001
Cardiovascular disease (MI and coronary)		-1.2169	0.3214	0.0002
Diabetes		0.8091	0.2489	0.0012
Total cholesterol, per mg/dL		0.0171	0.0027	<0.0001
Body mass index, per kg/m^2		0.0298	0.0125	0.0176
Valsartan dose (80/160mg)		1.3551	0.2562	<0.0001
HCTZ dose (0/12.5/25mg)		2.7347	0.2532	<0.0001
Concomitant medication: alpha-blocker		1.5905	0.6358	0.0124
Concomitant medication: beta-blocker		1.1841	0.2367	<0.0001
Concomitant medication: ACE-inhibitor		2.0032	0.6253	0.0014
Patient adherence		-2.1380	0.2372	<0.0001
Physician variables				
Years in practice, y		0.0717	0.0187	0.0001
Male gender		1.1065	0.4587	0.0159
Study effect (reference: EXCELLENT)				
INSIST		-3.3611	0.7926	<0.0001
PREVIEW		2.0951	0.4792	<0.0001
DBP at ~90 days			ICC	0.25
		mmHg	SE	p
	Intercept	70.75	0.9525	<0.0001
Patient variables				

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Age, y	-0.0419	0.0057	<0.0001
DBP at diagnosis of hypertension, per mmHg	0.1051	0.0066	<0.0001
Cardiovascular disease (MI and coronary)	-0.5398	0.1992	0.0067
Total cholesterol, per mg/dL	0.0089	0.0017	<0.0001
Body mass index, per kg/m^2	0.0260	0.0078	0.0009
Valsartan dose (80/160mg)	0.3744	0.1545	0.0154
HCTZ dose (0/12.5/25mg)	1.4812	0.1578	<0.0001
Concomitant medication: beta-blocker	0.4794	0.1450	0.0010
Patient adherence	-1.4176	0.1486	<0.0001
Physician variables			
Years in practice, y	0.0337	0.0113	0.0029
Study effect (reference: EXCELLENT)			
INSIST	-2.2002	0.4919	<0.0001
IMPROVE	-0.8513	0.2959	0.0040

B. Hierarchical logistic modeling of blood pressure control at ~90 days

SBP control at ~90 days	OR (95% CI)	p
Patient variables		
Age, per 1 y	0.991 (0.987-0.995)	<0.0001
SBP at diagnosis of hypertension, per mmHg	0.982 (0.978-0.985)	<0.0001
Cardiovascular disease (MI and coronary)	1.183 (1.035-1.352)	0.0134
Diabetes	0.162 (0.142-0.185)	<0.0001
Total cholesterol, per mg/dL	0.997 (0.995-0.998)	<0.0001
Body mass index, per kg/m^2	0.989 (0.979-1.000)	0.0539
Valsartan dose (80/160mg)	0.768 (0.686-0.859)	<0.0001
HCTZ dose (0/12.5/25mg)	0.704 (0.629-0.787)	<0.0001
Patient adherence	1.404 (1.264-1.560)	<0.0001
Physician variables		

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Years in practice, per 1 y	0.992 (0.985-0.998)	0.0146
Male gender	0.853 (0.738-0.985)	0.0304
Study effects (reference: EXCELLENT)		
INSIST	1.476 (1.075-2.028)	0.0161
PREVIEW	0.685 (0.578-0.811)	<0.0001
DBP control at ~90 days		
Patient variables		
Age, per 1 y	1.008 (1.004-1.012)	0.0003
DBP at diagnosis of hypertension	0.969 (0.964-0.975)	<0.0001
Cardiovascular disease (MI and coronary)	1.326 (1.144-1.537)	0.0002
Diabetes	0.065 (0.057-0.074)	<0.0001
Total cholesterol, per mg/dL	0.998 (0.997-0.999)	0.0027
Body mass index, per kg/m^2	0.994 (0.989-1.000)	0.0402
Valsartan dose (80/160mg)	0.808 (0.720-0.908)	0.0003
HCTZ dose (0/12.5/25mg)	0.693 (0.615-0.781)	<0.0001
Patient adherence	1.454 (1.310-1.613)	<0.0001
Physician variables		
Years in practice, per 1 y	0.993 (0.986-1.000)	0.0511
Study effects (reference: EXCELLENT)		
IMPROVE	1.325 (1.100-1.597)	0.0031
INSIST	1.737 (1.229-2.455)	0.0018
Combined SBP/DBP control at ~90 days		
Patient variables		
SBP at diagnosis of hypertension, per mmHg	0.982 (0.979-0.985)	<0.0001
Cardiovascular disease (MI and coronary)	1.198 (1.054-1.362)	0.0057
Diabetes	0.085 (0.072-0.100)	<0.0001
Total cholesterol, per mg/dL	0.997 (0.996-0.998)	<0.0001

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Valsartan dose (80/160mg)	0.809 (0.726-0.902)	0.0001
HCTZ dose (0/12.5/25mg)	0.703 (0.630-0.784)	<0.0001
Patient adherence	1.388 (1.259-1.529)	<0.0001
Physician variables		
Years in practice, per 1 y	0.991 (0.985-0.998)	0.0067
Male gender	0.856 (0.738-0.992)	0.0384
Study effects (reference: EXCELLENT)		
INSIST	1.493 (1.094-2.038)	0.0115
PREVIEW	0.737 (0.623-0.872)	0.0004

CI, confidence interval; DBP, diastolic blood pressure; HCTZ, hydrochlorothiazide; ICC, intraclass correlation coefficient; MI, myocardial infarction; OR, odds ratio; SBP, systolic blood pressure; SE, standard error; y, year.

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Table 5. Summary of hierarchical linear and logistic regression models in terms of negative (–) [a] or positive (+) [b] impact on ~90-day BP values and control

	BP values		BP control		
	SBP	DBP	SBP	DBP	SBP/DBP
Patient variables					
Age		+	–	+	
SBP at diagnosis of hypertension	–		–		–
DBP at diagnosis of hypertension		–		–	
Cardiovascular disease (MI and coronary)	+	+	+	+	+
Diabetes	–		–	–	–
Total cholesterol	–	–	–	–	–
Body mass index	–	–	–	–	
Valsartan dose	–	–	–	–	–
HCTZ dose	–	–	–	–	–
Concomitant medication: alpha-blocker	–				
Concomitant medication: beta-blocker	–	–			
Concomitant medication: ACE-inhibitor	–				
Patient adherence	+	+	+	+	+
Physician variables					
Years in practice	–	–	–	–	–
Male gender	–		–		–
Study effects (reference: EXCELLENT) [c]					
INSIST (160/25mg HCTZ)	+	+	+	+	+
PREVIEW (80mg, 160mg, 80/12.5mg HCTZ)	–		–		–
IMPROVE (80mg, 160mg, 80/12.5mg HCTZ, 160/12.5mg HCTZ, 160/25mg HCTZ)		+		+	

BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MI, myocardial

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infarction; HCTZ, hydrochlorothiazide.

[a] Negative impact is denoted by a minus (–) sign: increases BP values and decreases odds of BP control.

[b] Positive impact is denoted by a plus (+) sign: decreases BP values and increases odds of BP control.

[c] EXCELLENT (80/5mg amlodipine, 160/5mg amlodipine, 160/10mg amlodipine)

[‡] Defined as the correct responses to 3 hypertension management questions.

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