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CLINICAL RESEARCH

Modelling of blood pressure and total cardiovascular risk outcomes after second-line valsartan therapy: The BSCORE study

Modélisation de la pression artérielle et du risque cardiovasculaire total après traitement de deuxième ligne par valsartan : l'étude BSCORE

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KEYWORDS

Hypertension;
Blood pressure;
Valsartan;
Angiotensin II type 1;
Receptor blockers

Summary

Background. — European guidelines recommend that antihypertensive management should be graded as a function of total cardiovascular risk.

Aims. — To examine the multilevel (patient- and physician-level) determinants of blood pressure and residual total cardiovascular risk outcomes associated with second-line valsartan therapy.

Methods. — The BSCORE study was a prospective, multi-centre, pharmacoepidemiological study of the “real-world” effectiveness of second-line valsartan with or without hydrochlorothiazide.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; ESC, European Society of Cardiology; ESH, European Society of Hypertension; GP, general practitioner; ICC, intraclass correlation coefficient; OR, odds ratio; SBP, systolic blood pressure; SCORE, Systematic COronary Risk Evaluation; SD, standard deviation; TCVR, total cardiovascular risk.

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Treatment effectiveness

Results A total of 3497 patients were recruited by 354 physicians. Mean age was 63.8 ± 12.0 years; 52.3% were male; 20.9% were smokers; 47.7% were dyslipidaemic; and 23.6% had diabetes. On average, reductions in blood pressure and increases in the proportions of patients with controlled blood pressure after 90 days were statistically significant (all $P < 0.001$). Twenty-one percent of systolic blood pressure and 25.6% of diastolic blood pressure variability at follow-up was attributable to physician-level characteristics. Significant reductions in total cardiovascular risk were observed ($P < 0.001$); with 12.5% of the variability in total cardiovascular risk change attributable to physician-level characteristics. Several independent determinants of blood pressure outcomes were identified, many of which are modifiable.

Conclusions. – Second-line valsartan therapy improves blood pressure outcomes under variable real-world conditions, and is associated with a decrease in total cardiovascular risk. Optimizing antihypertensive effectiveness, including the reduction of residual cardiovascular risk, involves managing concomitant conditions and risk factors, improving adherence, and identifying physician-level factors amenable to intervention.

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MOTS CLÉS

Hypertension ;
Tension artérielle ;
Valsartan ;
Dresseurs de récepteur de type 1 de l'angiotensine II ;
Efficacité de traitement

Résumé

Justification. – Les recommandations européennes indiquent que la prise en charge de l'hypertension artérielle doit être basée sur l'évaluation du risque cardiovasculaire global.

Objectifs. – Examiner les déterminants à deux niveaux (patients et médecins) de la pression artérielle ainsi que le risque cardiovasculaire global, associés à un traitement par valsartan de deuxième ligne.

Méthodes. – L'étude BSCORE est une étude prospective, multicentrique, pharmaco-épidémiologique d'évaluation de l'efficacité dans le monde réel d'un traitement par valsartan de seconde ligne, avec ou sans hydrochlorothiazide.

Résultats. – Trois mille quatre cent quatre-vingt-dix-sept patients ont été recrutés par 354 médecins. L'âge moyen était de $63,8 \pm 12$ ans ; 52,3% des patients étaient des hommes, 20,9% des fumeurs ; 40,7% présentaient une dyslipidémie et 23,6% un diabète. En moyenne, la réduction de la pression artérielle et l'augmentation de la proportion de patients ayant une pression artérielle contrôlée dans les 90 jours étaient statistiquement significatives ($P < 0,001$). Vingt-et-un pour cent des chiffres de pression artérielle systolique et 25,6% de la variabilité des chiffres de pression artérielle diastolique lors du suivi étaient attribuables à l'intervention médicale. Une réduction significative du risque cardiovasculaire global a été observée ($P < 0,001$) ; avec une variabilité de 12,5% du risque cardiovasculaire global lié aux caractéristiques de l'intervention médicale. Plusieurs déterminants indépendants de l'évolution de la pression artérielle ont été identifiés dont plusieurs sont des facteurs de risque modifiables.

Conclusions. – Un traitement par valsartan de deuxième ligne améliore le contrôle de la pression artérielle, dans les conditions d'évaluation du monde réel, et est associé à une diminution du risque cardiovasculaire global. Optimiser l'efficacité du traitement hypotenseur en incluant la réduction du risque cardiovasculaire global, implique la prise en charge des pathologies associées concomitantes et des facteurs de risque, contribue à l'amélioration de l'observance, et permet d'identifier des facteurs modifiables par une intervention thérapeutique liée au médecin.

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Introduction

Approximately 50% of cardiovascular disease can be attributed to suboptimal BP control [1]. The ESH-ESC Guidelines [2] and the 2009 ESH guideline reappraisal [3] advocate quantifying patients' TCVR based on BP values and other risk factors or associated organ damage, and grading the intensity of antihypertensive management as a function of TCVR. The SCORE project developed 10-year risk models of fatal cardiovascular disease for various European countries [4]. The Belgian model (B-SCORE), which incorporated gender, age, smoking status, systolic BP, and total cholesterol level, was calibrated based on national mortality statistics and

prevalence estimates of major cardiovascular risk factors [5]. The ESH-ESC has recommended that TCVR classification should be part of clinical assessment and treatment planning, but it has not been used as an effectiveness outcome.

We recently applied a novel analytical framework for observational "real world" effectiveness studies to examine the determinants and outcomes of second-line antihypertensive treatment with valsartan (the PREVIEW study) [6–9]. This framework assumes that patients seen by the same physician share a commonality defined by that physician's knowledge, experience, and expertise (physician class effect). As such, statistical independence of patients "nested" under physicians cannot be assumed, and hierar-

chical (or multilevel) analytical approaches are warranted [10]. From a sample of 3194 Belgian patients cared for by 504 GPs, we found that about a quarter of the variability in BP values at 90 days was attributable to the compliance of these GPs with the ESH-ESC recommended triggers for treatment initiation and intensification, their practice patterns, experience in treating hypertension, and years in practice [6]. The remainder of the variance in BP was accounted for by patient-level variables, many of which were modifiable and manageable by evidence-based medical care and effective patient self-care. Similar factors were identified in an analysis of why certain patients did not achieve BP control.

PREVIEW was the first observational study of its kind in hypertension, and we believe it is in need of replication. The B-SCORE risk classification model enabled us to not only replicate the PREVIEW study, but also to assess physician- and patient-level variables influencing changes in TCVR and to identify determining factors reducing TCVR after second-line treatment with valsartan with or without hydrochlorothiazide (hereafter referred to as valsartan).

Methods

The observational BSCORE study (so named to emphasize its link to the B-SCORE risk model) was designed as a prospective, open-label, multicentre, multilevel (patients nested under physicians) pharmacoepidemiological study of predictors of, and changes in, BP and TCVR in patients with hypertension after 90 days of treatment with valsartan. Being partly a replication of PREVIEW, the methodology was virtually identical to the PREVIEW study [6], except for the addition of TCVR calculation according to the B-SCORE model. Only key elements of the methodology are summarized below. Further details are available from the corresponding author on: recruitment, screening and enrolment procedures; sample size calculations; schedule of assessment; complete data model; details on variables and measurement; procedures for data collection and management; and statistical analysis methods.

To be eligible, patients had to be consenting adults (male or female) who did not tolerate and/or who did not benefit sufficiently from prior antihypertensive treatment, as evidenced by systolic BP (SBP) ≥ 140 mmHg and/or diastolic BP (DBP) ≥ 90 mmHg (except for patients with diabetes, in which case investigators were asked to consider the 2007 ESH-ESC recommended levels of SBP ≥ 130 mmHg and DBP ≥ 80 mmHg); and who were started de novo on one of the following commercially available valsartan formulations: 80 mg, 160 mg, 80 mg/12.5 mg hydrochlorothiazide, 160 mg/12.5 mg hydrochlorothiazide, or 160 mg/25 mg hydrochlorothiazide. Patients could be on either valsartan mono- or combination therapy. Patients who did not tolerate prior antihypertensive treatment were eligible, hence the presence of 2% of patients with baseline normal and high normal BP in the sample. The evaluable sample, defined primarily as patients with baseline and follow-up BP values, included 3497 patients contributed by 354 from all over Belgium.

Patient baseline data included: demographics; anthropometrics; hypertension and cardiovascular history; comorbidities; lifestyle; prior antihypertensive medications; BP;

TCVR; clinical status; starting valsartan dose; concomitant antihypertensive and other relevant medications; and adherence. Data recorded at 90-day follow-up were: BP; residual TCVR; clinical status; changes in valsartan dose since previous visit; concomitant medication(s) taken or changed since previous visit; self-reported adherence within the past 4 weeks; and side-effects over the past 90 days. Only patient data collected routinely in clinical practice were recorded; no additional tests or exams were ordered.

Separately, and using a specially developed questionnaire, we also assessed several physician variables that might influence BP or TCVR outcomes: practice type, location/setting, patient mix; demographics; sources of information and knowledge related to hypertension; hypertension management practices; prescription patterns; management of adverse effects; SBP/DBP thresholds for treatment initiation and intensification; perceptions of patient adherence; and knowledge of practice guidelines.

BP was measured three times at 1–2-minute intervals, in a sitting position after 5 minutes of rest. The mean was recorded as the mean sitting SBP and mean DBP. BP control was defined as per the 2007 ESH-ESC guidelines as SBP < 140 mmHg and DBP < 90 mmHg; except for patients with diabetes mellitus and/or high or very high TCVR, in which case targets were SBP < 130 mmHg and DBP < 80 mmHg [2]. Of note, the 2009 update [3] advocates a 140/90 mmHg cut-off for all populations, but our study was conducted under the 2007 guidelines [2].

TCVR was computed based on the cross-classification of BP by risk factors (e.g. smoking and dyslipidaemia), metabolic syndrome, organ damage, diabetes, and established cardiovascular or renal disease (myocardial infarction, coronary blood vessel disease, heart failure, cerebrovascular conditions, peripheral vascular conditions, and renal conditions [defined as serum creatinine > 1.5 mg/dL]) [2]. Possible classifications included: average risk, low added risk, moderate added risk, high-added risk, and very high-added risk. We computed "change in TCVR" by subtracting TCVR at baseline from TCVR at the end of treatment, yielding possible scores from -4 (greatest TCVR improvement possible; from very high added to average risk) to $+4$ (greatest TCVR worsening; from average to very high added risk). Patients with established cardiovascular or renal disease were not included in the TCVR calculations and analyses as they cannot improve according to the ESH-ESC TCVR classification. We also classified patients dichotomously as having achieved, or not, a reduction of at least one level of TCVR at 90 days (excluding patients who were in the average risk category at baseline and those with established cardiovascular or renal disease).

The ESH-ESC guidelines [2], recommend different BP thresholds for the general population and for patients with diabetes and/or high/very high risk. Hence, using baseline data, we classified patients in a binary manner as average to moderate added risk (LOW risk) or diabetes and/or high added/very high-added risk (HIGH risk). This classification was used in the evaluation of BP values and BP control over the 90-day study period.

Descriptive statistics of frequency, central tendency, and dispersion were applied under consideration of levels of measurement. The *t*-test for dependent samples was used to measure BP changes over time; the McNemar test was

Table 1 Effectiveness outcomes at baseline and after 90 days of treatment.

	Mean \pm SD BP (mmHg)			Patients meeting recommended target		
	Baseline	90 days	Δ	Baseline (%)	90 days (%)	Δ by factor of
SBP						
All patients ($n = 3497$)	154.7 \pm 15.3	135.3 \pm 11.5	-19.5 \pm 16.2	4.6	36.9	8.0
LOW risk ($n = 1359$)	152.1 \pm 11.4	135.0 \pm 10.4	-17.2 \pm 13.1	8.0	60.2	7.5
HIGH risk ($n = 2116$)	156.4 \pm 17.1	135.5 \pm 12.2	-20.9 \pm 17.8	2.4	22.0	9.2
DBP						
All patients ($n = 3497$)	90.7 \pm 9.8	80.7 \pm 7.7	-10.0 \pm 10.4	16.5	48.8	3.0
LOW risk ($n = 1359$)	89.9 \pm 8.6	80.8 \pm 7.5	-9.1 \pm 9.4	33.1	83.7	2.5
HIGH risk ($n = 2116$)	91.2 \pm 10.5	80.7 \pm 7.9	-10.5 \pm 11.0	5.9	26.4	4.5
Combined SBP/DBP						
All patients ($n = 3497$)				3.0	28.7	9.6
LOW risk ($n = 1359$)				6.2	56.2	9.1
HIGH risk ($n = 2116$)				0.9	11.1	12.3
TCVR		Mean \pm SD change in TCVR score			Reduction in TCVR (%)	
All patients ($n = 2344$)		-0.75 \pm 0.94			60.9	
LOW risk ($n = 1370$)		-0.68 \pm 0.85			62.5	
HIGH risk ($n = 974$)		-0.85 \pm 1.05			58.5	

BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic blood pressure; SD: standard deviation; TCVR: total cardiovascular risk. Note that the 2007 ESH-ESC-recommended BP targets differ for the general population (those with no or low cardiovascular risk [LOW risk]) than for those with diabetes and/or high/very high cardiovascular risk (HIGH risk) [2]. The targets are SBP < 140 mmHg and DBP < 90 mmHg in LOW-risk and SBP < 130 mmHg and DBP < 80 mmHg in HIGH-risk patients. The % of patients meeting recommended targets was derived from a total of 3475 patients as 22 patients could not be classified due to missing data related to risk factors.

used for changes in proportions in BP control and TCVR reduction of at least one level. We used conditional hierarchical/multilevel linear modelling to identify patient- and physician-level determinants of changes in BP and TCVR; unconditional hierarchical/multilevel linear modelling to calculate the proportion of variability in these variables attributable to physicians (ICC); and logistic regression modelling to identify independent predictors of uncontrolled BP and improvement in TCVR.

Results

Patients

Among 3497 patients, the mean age was 63.8 \pm 12.0 years (range 19–98 years); 13.0% were < 50 years old, 52.4% were aged 50–69 years, and 34.6% were \geq 70 years old. Around half were male (52.3%), 20.9% were smokers, 23.6% had diabetes, and 47.7% were dyslipidaemic. With regard to cardiovascular conditions, 11.0% had coronary blood vessel disease, 8.9% peripheral vascular conditions, 8.3% had a history of myocardial infarction, 7.6% had cerebrovascular conditions, and 5.5% had heart failure. Only 3.6% had renal disease, and 19.7% had no pre-existing conditions.

For the 3475 patients (99.4%) for whom binary risk status at baseline could be calculated, 1359 patients (39.1%) were in the LOW-risk and 2116 patients (60.9%) were in the HIGH-risk category at baseline. TCVR could be calculated for 2344 patients (67.0%) who had data available at both baseline and follow-up. Note that 2% of patients had normal or high

normal BP at baseline. These were patients who, despite therapeutic benefits, did not tolerate prior BP-lowering treatment and were converted to a valsartan regimen.

Effectiveness outcomes

Blood pressure

Reductions in mean SBP and DBP, and increases in the proportions of patients with controlled BP after 90 days on valsartan (Table 1), were statistically significant in the entire sample and in the LOW-risk and HIGH-risk groups (all $P < 0.0001$). At baseline, the HIGH-risk group had significantly higher mean SBP and DBP levels than the LOW-risk group (both $P < 0.001$). However, this was not the case at follow-up, indicating a proportionately higher reduction in BP among HIGH-risk patients.

Total cardiovascular risk

Of the 2344 patients for whom TCVR could be calculated, 60.9% showed a reduction in TCVR classification by at least one category after 90 days of valsartan treatment (Table 1). Mean TCVR reduction was significantly higher among HIGH-risk than LOW-risk patients ($P < 0.001$). The difference in proportions of patients achieving versus not achieving a reduction in TCVR was not statistically significant between HIGH- and LOW-risk patients.

Modelling of blood pressure outcomes

Hierarchical/multilevel modelling revealed that 21.0% of SBP and 25.6% of DBP variability at follow-up was

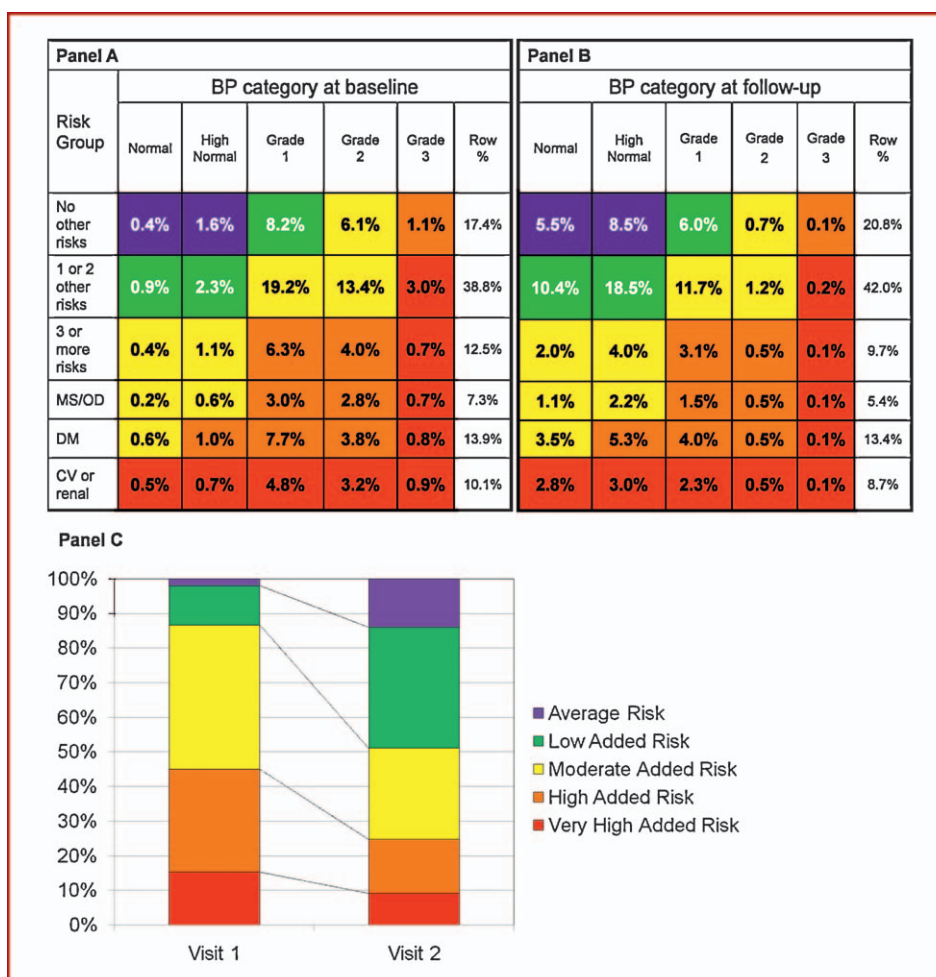


Figure 1. Distribution of TCVR (A) at baseline and (B) after 90 days of treatment with valsartan, for those patients for whom TCVR could be calculated at both time points; and the shifts in proportions from baseline to follow-up (C; dependent samples *t*-test significant with $P < 0.0001$). BP: blood pressure; CV: cardiovascular; DM: diabetes mellitus; MS: metabolic syndrome; OD: subclinical organ damage; TCVR: total cardiovascular risk.

attributable to physician-level characteristics (ICCs = 0.210 and 0.256, respectively). SBP increased from an intercept of 112.0 mmHg as a function of SBP at diagnosis of hypertension (+0.0621 mmHg per prior mmHg; $P < 0.001$) and at baseline (+0.1859 mmHg per prior mmHg; $P < 0.001$), and of concurrent treatment with a calcium antagonist (+0.8568 mmHg; $P = 0.049$); but decreased based on physician-rated patient adherence (−0.1859 mmHg for each point on a scale of 0–100; $P < 0.001$). DBP increased from an intercept of 71.8 mmHg as a function of DBP at diagnosis of hypertension (+0.0333 mmHg per prior mmHg; $P < 0.011$) and at baseline (+0.1817 mmHg per prior mmHg; $P < 0.001$), and whether physicians could identify the appropriate initial antihypertensive treatment for patients without known risk factors (+1.3153 mmHg; $P < 0.001$). DBP decreased based on physician-rated patient adherence (−0.0899 mmHg for each point on a scale of 0–100; $P < 0.001$), patients' self-report of being adherent (−0.6802 mmHg; $P = 0.030$), and patient age (−0.0422 mmHg per year of age; $P < 0.001$).

Logistic regression modelling showed that the sole predictor of uncontrolled SBP at follow-up was a TCVR classification of high-added risk ([OR] 8.55, 95% confidence

interval [CI] 2.01–36.40; $P = 0.004$). Predictors of uncontrolled DBP included TCVR status of very high (OR = 39.44, 95% CI 5.19–299.95; $P < 0.001$), high (OR = 43.75, 95% CI 5.78–331.30; $P < 0.001$), and moderate added risk (OR = 8.25, 95% CI 1.07–63.62; $P = 0.043$) status. Predictors of both uncontrolled SBP and DBP were very high (OR = 27.17 [95% CI 3.47–212.96]; $P = 0.002$), high (OR = 7.50, 95% CI 2.60–21.58; $P < 0.001$), and moderate added risk (OR = 2.22, 95% CI 1.05–4.68; $P = 0.037$).

Modelling of TCVR

Change in total cardiovascular risk

Using the colour coding of the ESH-ESC classification [2], Fig. 1 shows the cross-classification of cardiovascular risk factors and BP at baseline (Fig. 1A) and follow-up (Fig. 1B) ($n = 2575$), as well as the statistically significant shift in proportions (Fig. 1C; $P < 0.001$). The change in TCVR scores ranged from −4 to +3 among the 2344 patients included in the computation (mean \pm SD = −0.75 \pm 0.94).

The proportion of variability in change in TCVR accounted for by the class effect of physicians was 12.5% (ICC = 0.125).

From an intercept of 0.982, residual TCVR decreased as a function of physician-rated patient adherence (-0.009 per point on a scale of 0–100; $P < 0.001$), of the absence of pre-existing cardiovascular risk factors (-0.395 ; $P < 0.001$), and of a very high (-3.263 ; $P < 0.001$), high (-2.215 ; $P < 0.001$), moderate (-1.644 ; $p < 0.001$), or low added risk (-0.932 ; $P < 0.001$) status at baseline. However, residual TCVR was increased by patients' SBP at the time of diagnosis of hypertension ($+0.0037$ per prior mmHg; $P = 0.001$), by the presence of diabetes ($+0.750$; $P < 0.001$) or dyslipidaemia ($+0.1925$; $P < 0.001$), and whether physicians knew the appropriate initial antihypertensive treatment for patients with one or two known risk factors ($+0.148$; $P = 0.027$).

Reduction in total cardiovascular risk

Predictors of improvement in patients' TCVR by at least one level included: physician-rated patient adherence (OR = 1.03 per point on a scale of 0–100, 95% CI 1.02–1.05; $P < 0.001$); no pre-existing cardiovascular risk conditions (OR = 2.07, 95% CI 1.38–3.11; $P < 0.001$); baseline status of very high (OR = 104.28, 95% CI: 31.24–349.17; $P < 0.001$), high (OR = 11.12, 95% CI 2.31–12.95; $P < 0.001$), or moderate added risk (OR = 5.57, 95% CI 2.31–12.95; $P < 0.001$); and being treated concomitantly with another antihypertensive agent (OR = 2.28, 95% CI 1.11–4.68; $P = 0.025$), apart from alpha-blockers (OR = 0.51, 95% CI 0.26–0.99; $P = 0.046$). Improvement in TCVR was also impaired by being diabetic (OR = 0.19, 95% CI 0.14–0.27; $P < 0.001$) or dyslipidaemic (OR = 0.71, 95% CI 0.54–0.96; $P = 0.024$), and having both SBP and DBP controlled at baseline (OR = 0.50, 95% CI 0.28–0.92; $P = 0.025$).

Discussion

Perhaps most significant is our finding that 90-day second-line treatment with valsartan produces significant downward shifts in residual TCVR, in addition to improving BP outcomes. To the best of our knowledge, the BSCORE study is among the first to use the ESH-ESC TCVR classification as an outcome of antihypertensive therapy, rather than just a determinant. This study further confirms that valsartan is a highly effective antihypertensive agent for patients in whom prior treatment failed or was not tolerated [11], yet adds that this antihypertensive effect is achieved both in patients with average to moderate risk (LOW risk) and in those with diabetes and/or high/very high cardiovascular risk (HIGH risk) according to the ESC-ESH risk classification [2,3].

For instance, at baseline 45.0% of patients were in the high and very high-added risk categories, and after 90 days of valsartan treatment, this was reduced to 24.7%. Similarly, the proportion of patients in the moderate added risk group decreased from 41.6% at baseline to 26.4% at follow-up. Conversely, 90 days of valsartan treatment increased the group of patients with average or low added risk by a factor of 3.7 from 13.4% (2.0 and 11.4%, respectively) at baseline to 49.6% (14.0 and 35.6%, respectively). This confirms that when the room for improvement in TCVR is larger, such improvement is indeed likely to occur in many patients. In fact, the worse the TCVR score at baseline, the greater the odds for improvement. Conversely, patients with controlled

SBP and DBP at baseline (less room for improvement) were less likely to show improvement in TCVR, as these patients were started on valsartan because first-line treatment was not tolerated.

The physician class-effect was less pronounced in the change in TCVR (12.5%) compared to changes in SBP (21.0%) and DBP (25.6%). This could mean that details of the TCVR classification may be easier for clinicians to remember than the BP thresholds for treatment initiation or intensification. This validates the use of the TCVR classification as a support tool in the clinical management of hypertension.

The finding that physicians' knowledge of the appropriate antihypertensive treatment for patients with none, one, or two risk factors had a negative impact on outcomes may seem paradoxical. However, it may indicate that limited knowledge about high-risk patients impaired physicians' ability to treat more complex patients at second and, arguably, later lines of antihypertensive therapy. Also seemingly paradoxical, the weak ($P = 0.049$) SBP-elevating ($+0.86$ mmHg) effect of concomitant treatment with a calcium antagonist may be a proxy reference to a subgroup of patients who have comorbidities where such treatment is indicated (peripheral artery disease, angina, and metabolic syndrome).

The multilevel models were less detailed in terms of physician- and patient-level determinants than those in the PREVIEW study and some of its subgroup analyses that have been published [6–8] or are in progress (stratifications by cardiovascular risk, body mass index, hyperlipidaemia, diabetes, gender, and smoking). However, the proportions of variability in BP outcomes attributed to the class effect of physicians in BSCORE (21.0 and 25.6%) were comparable to those in PREVIEW [6]. Thus, future research should focus on identifying physician-level factors that are helpful in explaining variance in the effectiveness of antihypertensive treatment. To this end, several studies similar to PREVIEW and BSCORE are underway for a fixed-dose combination of valsartan and amlodipine, and for the new direct renin inhibitor, aliskiren, and its fixed-dose combination with hydrochlorothiazide.

An innovation in the BSCORE study is the use of the TCVR classification as an outcome variable in the assessment of the effectiveness of valsartan as second-line antihypertensive treatment. Given that BP control may continue to be a moving target, TCVR outcome data can provide critical information from which to estimate treatment effectiveness. As antihypertensive treatment needs to be based on both BP values and TCVR assessment, the BSCORE study provides preliminary evidence of the clinical relevance of incorporating TCVR as an index of treatment outcomes – even though the only factor impacted on in this study is BP, and the observed improvements in TCVR are attributable only to treatment.

Improvement in TCVR was a function of patient adherence and TCVR at baseline – with significant downward shifts among both LOW- and HIGH-risk patients. Dyslipidaemia and diabetes may inhibit this risk reduction effect of valsartan; however, dyslipidaemia is a modifiable factor and diabetes is a manageable factor. A treatment plan for a patient with hypertension should target the elevated BP, as well as dyslipidaemia and diabetes in order to optimize patient outcomes. Future studies are needed to evaluate how the comprehensive management of the various

elements of TCVR (e.g. lipids, glucose, and lifestyle risk factors), not just hypertension, translate into lower residual cardiovascular risk [12]—and ensuring that sufficient patients are enrolled, with the required data, to minimize the loss of subjects in analyses.

Conclusions

Ninety days of second-line antihypertensive therapy with valsartan reduced BP values and improved BP control under variable real-world conditions. Treatment was also associated with decreases in patients' TCVR status—including patients at advanced risk levels. ESH-ESC guidelines recommend that TCVR be used in the assessment of need for antihypertensive therapy. Yet our study also validates the use of the ESH-ESC classification of TCVR as an outcome variable when evaluating the efficacy and effectiveness of antihypertensive therapy.

Conflict of interest statement

R. L. Advisor to Novartis.

A. A., H. B., N. C., C. H., and S. V. Employees of Novartis Pharma.

I. A., C. L., K. M., N. M., and Y.M. S. Employees of Matrix45.

By company policy, employees are prohibited from owning equity in client organizations (except through mutual funds or other independently administered collective investment instruments) or contracting independently with client organizations. Matrix45 provides services similar to those described in this article to other biopharmaceutical companies on a non-exclusivity basis.

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Responsibility for data integrity and statistical analysis and independence of statistical analysis: K.M., Y.M.S., and I.A. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the statistical analysis. All statistical analyses were performed independently by K.M. and Y.M.S., and submitted to the investigators for review, feedback, and instructions, and to the sponsor for review and comment.

Independence of writing committee: The Writing Committee consisted of I.A. and K.M. All content decisions were made by the external authors. The sponsor had the right or review and comment; co-authors affiliated with the sponsor refrained from undue influence.

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Authorship contributions

- Study design: I. A., H. B., R. L., K. M., S. V.
- Study implementation: H. B., C. H.
- Data management: K. M., Y.M. S.
- Statistical analysis: I. A., K. M., Y.M. S.
- Interpretation of results: I. A., A. A., H. B., N. C., C. H., C.L., R. L., K.M., N.M., Y.M.S., S.V.
- Manuscript draft: I.A., C.L., K.M.
- Critical review of manuscript for intellectual content: A.A., H.B., N.C., C.H., C.L., R.L., Y.M.S., S.V.

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