

# “Later, lazier, and unluckier”: a heuristic profile of high vulnerability is an independent predictor of uncontrolled blood pressure (the PREVIEW study)

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**Objective:** Vulnerability profiling, an alternative to deterministic risk assessment, offers clinicians a more intuitive but empirically-grounded assessment of patient risk. This study aimed to determine whether a heuristic profile of high vulnerability is an independent predictor of uncontrolled hypertension.

**Methods:** Secondary analysis of prospective observational study data on 2999 hypertensive patients treated with valsartan. Predictive validity of vulnerability profiling for first-line, second-line, and first-or-second-line antihypertensive treatment was inferred from 1) logistic regression models with adequate statistical fit, 2) statistically significant odds ratios for uncontrolled BP for the high-vulnerability cluster exceeding 1.00, and 3) correct classification rates for patients' BP control status.

**Results:** All models of uncontrolled BP were significant ( $P < 0.001$ ); all odds ratios for the high-vulnerability cluster were greater than 1.00 and significant ( $P < 0.001$ ). Correct classification rates for the highly-vulnerability cluster on uncontrolled BP after first-line, second-line, or either treatment were 91.1%, 61.2%, and 93.5% for systolic BP; 74.5%, 65.8%, and 76.7% for diastolic BP; and 92.8%, 65.3%, and 94.6% for combined systolic and diastolic BP.

**Conclusion:** The heuristic profile of “later, lazier, and unluckier” is an intuitive and valid tool to help identify patients at greater risk for poor BP control seen in general practice.

**Keywords:** hypertension, heuristics, vulnerability, profiling, risk

## Introduction

Although different formal algorithms to determine cardiovascular outcomes are available (eg, Framingham risk score<sup>1</sup> and SCORE project<sup>2</sup>), these tools are seldom used in primary care. Because of the required data collection, calculations, and time demands, as well as the deterministic nature of the results, using such algorithms rarely fits into the clinical flow of primary care encounters. The implicit prescriptive nature of these algorithms and that they provide a probabilistic assessment of comparable patients may further limit their utility in planning individual patient care. Moreover, deterministic systems can be criticized for discounting clinicians' expertise in evaluating patients and assessing risk. Thus, clinically-intuitive methods for identifying patients at greater risk are important, particularly in control of hypertension, in which blood pressure (BP) targets are seldom reached<sup>3–6</sup> and patients are at high-risk for target organ damage.<sup>7,8</sup>

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We recently reported on determinants of BP outcomes and control after 90 days of second-line treatment with the angiotensin II receptor blocker valsartan.<sup>9</sup> The PREVIEW study was an observational trial involving 3194 patients in whom first-line treatment failed or was not tolerated. We used hierarchical cluster analysis to identify sub-cohorts of patients with differential vulnerability to uncontrolled hypertension. Cluster analysis, a subclass of data-mining,<sup>10</sup> was used to discover latent patterns of subject similarity based on factors identified from the literature and clinical experience.<sup>11,12</sup> We identified two clusters of patients with differential profiles of vulnerability to poor antihypertensive treatment outcomes.

As shown in Table 1, the highly-vulnerable cluster (HVC) of patients ( $n = 1063$  or 35.4%) differed from the remaining vulnerable cluster (VC) of patients by: a) having been diagnosed relatively late and with more severe hypertension, b) weighing and drinking more, and exercising less, c) presenting with greater general, cardiovascular, and renal/endocrine risk and more comorbid cardiovascular disease, d) having a family history of premature cardiovascular disease, and e) having a poor treatment response. Clinically, HVC patients had a higher propensity to be (only with helpful clinical mnemonics in mind, and without any derogatory intent) “later, lazier, and unluckier.” In the PREVIEW study, the vulnerability clusters were determinants of both BP values and BP control as defined by the JNC-7/ESH-ESC<sup>13,14</sup> guidelines (140/90 mmHg; for diabetics: 130/80 mmHg) in multivariate models.<sup>9</sup>

These initial aggregate findings indicate that being a HVC patient is predictive of BP outcomes in multivariate models that include other determinants. However, in order to be able to recommend the HVC profile as a means of identifying patients who may not respond to antihypertensive treatment, the profile must be further validated. This requires determining whether being a HVC patient is by and of itself a predictor of uncontrolled systolic BP (SBP), diastolic BP (DBP), and combined SBP/DBP – in the absence of other determinants. Further, the original analysis was limited to second-line treatment. It is also important to examine whether the HVC profile is predictive of uncontrolled BP after first-line treatment. These additional statistical analyses, which we report on in this present paper, are essential to determining the validity of the HVC profile as a predictor of poor response to antihypertensive treatment. Thus we examined the extent to which the HVC profile is an independent predictor of uncontrolled BP after first-line treatment (at physicians’ clinical discretion), after second-line treatment with valsartan, and after either first- or second-line treatment.

## Methods

### Procedures

Procedures for sampling, variables and measurements, data collection and management, statistical analysis, and management of confounding variables are described in detail in the referent article.<sup>9</sup>

**Table 1** Profiling of patients’ vulnerability to uncontrolled hypertension

	Vulnerable patients ( $n = 1936$ )	Highly-vulnerable patients ( $n = 1063$ )	
	Mean ( $\pm$ SD)	Mean ( $\pm$ SD)	P-value
SBP when diagnosed	159.49 ( $\pm$ 9.33)	182.13 ( $\pm$ 14.20)	<0.001
DBP when diagnosed	94.07 ( $\pm$ 6.90)	104.12 ( $\pm$ 11.38)	<0.001
General risk <sup>a</sup>	2.4060 ( $\pm$ 1.54)	2.6058 ( $\pm$ 1.55)	0.001
Cardiovascular risk <sup>b</sup>	0.6410 ( $\pm$ 1.12)	0.7846 ( $\pm$ 1.26)	0.002
Renal/endocrine risk <sup>c</sup>	0.1865 ( $\pm$ 0.61)	0.2389 ( $\pm$ 0.67)	0.038
	% (95% CI)	% (95% CI)	P-value
Left ventricular hypertrophy	11.4% (10.3–12.5)	16.8% (15.6–18.0)	<0.001
Excessive alcohol use	16.0% (14.9–17.1)	18.9% (17.6–20.2)	0.023
Lack of exercise	55.8% (54.2–57.4)	61.1% (59.5–62.7)	0.005
Obesity	42.5% (40.9–44.1)	48.4% (46.7–50.1)	0.001
Family history of early cardiovascular disease	16.6% (15.4–17.8)	19.5% (18.2–20.8)	0.027
SBP controlled at start of treatment	10.4% (9.4–11.4)	6.1% (5.3–6.9)	<0.001
DBP controlled at start of treatment	27.9% (26.4–29.4)	21.3% (19.9–22.7)	<0.001

**Notes:** Data adapted from Van der Niepen et al.<sup>9</sup> <sup>a</sup>Composite score of occurrence of hypercholesterolemia, diabetes mellitus, smoking, excess alcohol use, lack of regular physical exercise, obesity, advanced retinopathy; <sup>b</sup>Composite score of occurrence of myocardial infarction, angina, coronary revascularization, left ventricular hypertrophy, ischemic and/or hemorrhagic cerebrovascular accident, transient ischemic attacks, intermittent claudication, peripheral bypass or stent, and amputation; <sup>c</sup>Composite score of occurrence of microalbuminuria, renal impairment (serum creatinine >1.5 mg/dL), diabetic nephropathy, and proteinuria; (hemorrhages, exudates, papilloedema), C-reactive protein  $\geq 1$  mg/dL, and family history of premature cardiovascular disease (at age <55 for men, <65 for women).

**Abbreviations:** DBP, diastolic blood pressure; SBP, systolic blood pressure.

## Modeling

Logistic regression modelling<sup>15</sup> was used to model uncontrolled SBP, DBP, and SBP/DBP at 90 days. In this analysis, it was assumed that predictive validity could be inferred if four conditions were met. First, statistically significant logistic regression models could be fit using vulnerability profiles to predict uncontrolled BP. Second, odds ratios (ORs) for uncontrolled BP as a function of being highly vulnerable exceed 1.00, and the associated 95% confidence intervals (CIs) do not cross 1.00. Third, each model is sufficiently sensitive to correctly classify patients' BP control status as indicated by the correct classification rate (CCR). Fourth, given the availability of data on initial BP control, and BP control after valsartan treatment, the first three conditions are met for first-line, second-line, and first-or-second-line antihypertensive treatment.

## Results

Table 2 summarizes the logistic regressions for uncontrolled SBP, DBP, and combined SBP/DBP for HVC patients. All models were significant at  $P < 0.001$ . All ORs for HVC were statistically greater than 1.00 and none had 95% CIs crossing 1.00 (all  $P < 0.001$ ). CCRs for uncontrolled BP after first-, second-, or either treatment were 91.1%, 61.2%, and 93.5% for SBP; 74.5%, 65.8%, and 76.7% for DBP; and 92.8%, 65.3%, and 94.6% for combined SBP/DBP.

## Discussion

We accurately identified patients who had been diagnosed relatively late and with more severe hypertension (later); those weighing more, drinking more, and exercising less (lazier); and those who present with greater general, cardiovascular,

and renal/endocrine risk and have a family history of premature cardiovascular disease (unluckier) as being highly-vulnerable to poor BP control. Again, the profile's labelling is only with clinical mnemonics in mind and without any derogatory intent.

Being a highly-vulnerable patient was significantly associated with uncontrolled BP after first-line antihypertensive therapy with excellent predictive power. Thus, if patients presenting in the clinic fit the general profile of "later, lazier, and unlucky", this should serve as a strong warning signal to clinicians that this subgroup of patients is much less likely to meet BP targets after first-line therapy, leaving them more prone to end-organ damage and requiring transition to second-line treatment. Likewise, this general profile was helpful in identifying patients who were less likely to achieve BP control after either first- or second-line treatment, with minimally higher predictive validity compared to first-line therapy alone.

Many patients with hypertension are started on monotherapy and often require two or more antihypertensive agents in combination.<sup>13,14</sup> Being a HVC patient increased the odds of having uncontrolled BP after second-line treatment, but with somewhat less predictive power. This may be due to the fact that second-line agents are started on patients who may be resistant to antihypertensive treatment, or patients in whom other factors, such as comorbid conditions or poor adherence, have not been identified and/or sufficiently addressed. This may be due to the fact that by switching from one antihypertensive drug (first-line) to another (second-line) involved a change in antihypertensive class. In Belgium, thiazide diuretics are often prescribed as first-line antihypertensive drugs; thus, changing to valsartan often involved a switch from an antivolument to an antiresistance drug.<sup>16</sup> Fitting the general profile of "later, lazier, and unlucky", however, should serve as a caution for clinicians that this subgroup of patients is also less likely to meet BP targets after second-line treatment.

## Conclusion

With this additional evidence of the predictive validity of vulnerability profiling on BP control, clinicians have a more intuitive but empirically-grounded assessment of patient risk. The general profile of "later, lazier, unlucky" is helpful in identifying patients at greater risk for poor BP control.

## Disclosure

Drs Abraham, Lee, Song, and MacDonald are employees of Matrix45 and by company policy are prohibited from owning equity in client organizations. Dr Van der Niepen has consulted with and received research grants and contracts

**Table 2** Logistic regression results of uncontrolled blood pressure at follow-up as a function of membership in the high-vulnerability cluster

	OR	95% CI	CCR
After first-line treatment			
Uncontrolled SBP	1.789	1.338 to 2.391	91.1%
Uncontrolled DBP	1.443	1.200 to 1.711	74.5%
Uncontrolled SBP/DBP	1.550	1.137 to 2.115	92.8%
After second-line treatment with valsartan			
Uncontrolled SBP	1.562	1.331 to 1.833	61.2%
Uncontrolled DBP	1.534	1.309 to 1.797	65.8%
Uncontrolled SBP/DBP	1.717	1.455 to 2.028	65.3%
After either first- or second-line treatment			
Uncontrolled SBP	2.071	1.459 to 2.940	93.5%
Uncontrolled DBP	1.553	1.290 to 1.869	76.7%
Uncontrolled SBP/DBP	1.898	1.340 to 2.761	94.6%

**Abbreviations:** CCR, correct classification rate; CI, confidence interval; DBP, diastolic blood pressure; OR, odds ratio; SBP, systolic blood pressure.

from Novartis Pharma. Drs Vancayzeele and Brié and Ms Hermans are employees of Novartis Pharma.

## References

1. D'Agostino RBS, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.
2. Conroy RM, Pyörälä K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.
3. Berlowitz DR, Ash AS, Hickey EC, et al. Inadequate management of blood pressure in a hypertensive population. *New Engl J Med*. 1998;339:1957–1963.
4. Fagard RH, Van den Enden M, Leeman M, Warling X. Survey on treatment of hypertension and implementation of World Health Organization/International Society of Hypertension risk stratification in primary care in Belgium. *J Hypertens*. 2002;20:1297–1302.
5. Van der Niepen P, Giot C, van de Borne P. Prevalence of isolated uncontrolled systolic blood pressure among treated hypertensive patients in primary care in Belgium. Results of the I-inSYST survey. *J Hypertens*. 2008;26:2057–2063.
6. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension*. 2007;49:69–75.
7. Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: a quantitative overview updated until 2003 March 1. *J Hypertens*. 2003;21:1055–1076.
8. Kannel WB. Elevated systolic blood pressure as a cardiovascular risk factor. *Am J Cardiol*. 2000;85:251–255.
9. Van der Niepen P, Woestenburg A, Brié H, et al. Effectiveness vs efficacy of valsartan for treatment of hypertension: patient profiling and hierarchical modeling of determinants and outcomes. *Ann Pharmacother*. 2009;43:849–861.
10. Tan PN, Steinbach M, Kumar V. *Data Mining*. Boston, MA: Addison-Wesley; 2005.
11. Aldenderfer MS, Blashfield RK. *Cluster Analysis*. Thousand Oaks, CA: Sage; 1984.
12. Everitt BS, Landau B, Leese M. *Cluster analysis*. 2001. 4th ed. New York: Oxford University Press.
13. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC-7 report. *J Am Med Assoc*. 2003;289:2560–2572.
14. Guidelines Committee. 2003 European Society of Hypertension – European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21:1011–1053.
15. Kleinbaum DG, Klein M. *Logistic regression*. 2005. 2nd ed. New York, NY: Springer-Verlag.
16. Laragh JH. Abstract, closing summary, and table of contents for Laragh's 25 lessons in pathophysiology and 12 clinical pearls for treating hypertension. *Am J Hypertens*. 2001;14:1173–1174.

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