

Nonadherence to Antihypertensive Treatment

Risk Factors for Nonadherence to Antihypertensive Treatment

Pankaj Gupta, Prashanth Patel, Branislav Štrauch, Florence Y. Lai, Artur Akbarov, Věra Marešová, Christobelle M.J. White, Ondřej Petrák, Gaurav S. Gulsin, Veena Patel, Ján Rosa, Richard Cole, Tomáš Zelinka, Robert Holaj, Angela Kinnell, Paul R. Smith, John R. Thompson, Iain Squire, Jiří Widimský Jr, Nilesh J. Samani, Bryan Williams, Maciej Tomaszewski

See Editorial Commentary, pp 1017–1018

Abstract—Nonadherence to antihypertensive treatment is a critical contributor to suboptimal blood pressure control. There are limited and heterogeneous data on the risk factors for nonadherence because few studies used objective-direct diagnostic methods. We used high-performance liquid chromatography-tandem mass spectrometry of urine and serum to detect nonadherence and explored its association with the main demographic- and therapy-related factors in 1348 patients with hypertension from 2 European countries. The rates of nonadherence to antihypertensive treatment were 41.6% and 31.5% in the UK and Czech populations, respectively. Nonadherence was inversely related to age and male sex. Each increase in the number of antihypertensive medications led to 85% and 77% increase in nonadherence ($P < 0.001$) in the UK and Czech populations, respectively. The odds of nonadherence to diuretics were the highest among 5 classes of antihypertensive medications ($P \leq 0.005$ in both populations). The predictive model for nonadherence, including age, sex, diuretics, and the number of prescribed antihypertensives, showed area under the curves of 0.758 and 0.710 in the UK and Czech populations, respectively. The area under the curves for the UK model tested on the Czech data and for the Czech model tested on UK data were calculated at 0.708 and 0.756, respectively. We demonstrate that the number and class of prescribed antihypertensives are modifiable risk factors for biochemically confirmed nonadherence to blood pressure-lowering therapy. Further development of discriminatory models incorporating these parameters might prove clinically useful in assessment of nonadherence in countries where biochemical analysis is unavailable. (*Hypertension*. 2017;69:1113-1120. DOI: 10.1161/HYPERTENSIONAHA.116.08729.)

Key Words: adherence ■ blood pressure ■ diuretics ■ hypertension ■ polypharmacy

The number of adult patients with hypertension was estimated at 972 million in 2000.¹ This number is projected to increase by 60%, bringing a total number of hypertensives to 1.56 billion in 2025.¹ Antihypertensive medications have been the mainstay of cardiovascular care during the past few decades. They are effective in lowering blood pressure (BP), preventing target organ damage, overt cardiovascular disease, and reducing mortality. Despite the documented effectiveness of antihypertensive treatment, targets of BP are achieved only in 40% to 50% of patients with hypertension,^{2,3} and high BP is the leading single risk factor for health loss and premature death globally,

exceeding the burden of disease attributable to smoking and excessive weight.¹ Nonadherence to antihypertensive treatment is increasingly recognized as a main contributor to suboptimal BP control at the population level, high prevalence of resistant hypertension, and high financial burden for healthcare.^{4–13} One of the major obstacles in management of nonadherence to antihypertensive treatment has been the lack of direct, sufficiently sensitive, and reproducible methods of its detection in clinical practice.^{14–16} We and others have recently developed an objective high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)-based assay to screen

Received November 9, 2016; first decision November 28, 2016; revision accepted March 1, 2017.

From the Department of Metabolic Medicine and Chemical Pathology, University Hospitals of Leicester NHS Trust, United Kingdom (P.G., P.P., R.C., A.K., P.R.S.); National Institute of Health Research, Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, United Kingdom (P.G., P.P., F.Y.L., G.S.G., I.S., N.J.S.); Department of Cardiovascular Sciences, British Heart Foundation Cardiovascular Research Centre (P.G., P.P., F.Y.L., C.M.J.W., G.S.G., I.S., N.J.S.) and Department of Health Sciences (J.R.T.), University of Leicester, United Kingdom; Third Department of Medicine, Department of Endocrinology and Metabolism, Hypertension Centre, General University Hospital (B.S., O.P., J.R., T.Z., R.H., J.W.), Institute of Forensic Medicine and Toxicology, General University Hospital (V.M.), and Cardiocentre, University Hospital Královské Vinohrady (J.R.), Charles University, Prague, Czech Republic; Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, University of Manchester, United Kingdom (A.A., M.T.); University Hospitals of Leicester NHS Trust, United Kingdom (G.S.G.); Derby Teaching Hospitals NHS Foundation Trust, United Kingdom (V.P.); Institute of Cardiovascular Science, University College London, United Kingdom (B.W.); National Institute for Health Research, University College London Hospitals, Biomedical Research Centre, United Kingdom (B.W.); and Division of Medicine, Central Manchester NHS Foundation Trust, Manchester Academic Health Science Centre, United Kingdom (M.T.).

Correspondence to Maciej Tomaszewski, Institute of Cardiovascular Sciences, Faculty of Biology, Medicine and Health, University of Manchester, 5th Floor, AV Hill Bldg, Manchester M13 9PT, United Kingdom. E-mail maciej.tomaszewski@manchester.ac.uk

© 2017 American Heart Association, Inc.

Hypertension is available at <http://hyper.ahajournals.org>

DOI: 10.1161/HYPERTENSIONAHA.116.08729

for nonadherence to most commonly prescribed antihypertensive medications using an analysis of spot urine or blood sample.^{6,7,17–19} Biochemically confirmed nonadherence to antihypertensive treatment shows a tight correlation with the magnitude of BP elevation⁷ and remains the most common reason for pseudo-resistant hypertension.¹² In the absence of HPLC-MS/MS-based urine analysis, it is difficult to confirm the nonadherence to antihypertensive treatment.^{15,16,20,21} Patient-, treatment-, physician-, and healthcare-specific barriers are known to prevent regular administration of medications and are recognized risk factors of therapeutic nonadherence.²² Of those, therapy-related factors (such as the number and choice of antihypertensive medication) are easiest to quantify, monitor, and modify. However, to date, there has been no comprehensive analysis of the potential effects of the number of prescribed antihypertensives and classes of BP-lowering medications on the risk of objectively measured biochemical nonadherence. Mindful of potential practical applications of such studies, we examined the associations between both the burden and choice of BP-lowering therapy in the largest to date analysis of ≈1400 patients whose urine/serum samples were examined by HPLC-MS/MS in 2 European countries.

Methods

Populations

A total of 676 UK patients with hypertension were included in this project. This population consisted of patients whose spot urine samples were received for screening of nonadherence to antihypertensive treatment from 15 British centers by the University Hospitals of Leicester between 2011 and 2014. The main criterion for screening and the inclusion in this analysis was suspected therapeutic nonadherence by a referring clinician.

We included 672 patients recruited between 2010 and 2016 in Hypertension Unit of the Third Department of Medicine, General University Hospital in Prague (Czech Republic) for replication purposes. Serum samples from all these patients were screened for nonadherence to antihypertensive therapy because of difficulty to manage hypertension/suboptimal BP control. Of those, 475 attended the outpatient service, and 197 were admitted to hospital.

Apart from age, sex, and the details of prescribed antihypertensive treatment, no other clinical information was collected for the purpose of this analysis.

In both centers, the patients were informed about the purpose of urine/blood analysis (screening for nonadherence to antihypertensive medications) by the clinical staff. This information was provided on the day of the sample collection. In the University Hospitals of Leicester, the patients provided a verbal consent for the urine analysis, and the data were collected as a part of the approved clinical audit (no: 7235). All Czech patients provided written consent for use of their anonymized laboratory and clinical data for the purpose of retrospective analysis. The study was granted institutional approval by General University Hospital (VFN/004704). All results of HPLC-MS/MS-based analyses were collected as a part of routine clinical service, and data were retrieved from the existing clinical files and electronic systems.

Biochemistry

All urine (UK cohort) or serum (Czech cohort) samples were examined in single centers—the Department of Metabolic Medicine and Chemical Pathology, University Hospitals of Leicester NHS Trust, Leicester (UK patients), or the Toxicological Laboratory of the Institute of Forensic Medicine and Toxicology, General University Hospital, Charles University, Prague (Czech patients).

The biochemical analysis of UK samples was conducted on an Agilent Technologies 1290 series High Pressure Liquid Chromatograph interfaced with an Agilent Technologies 6460 Triple

Quadrupole Mass Spectrometer fitted with a Jetstream electrospray ionization source, as previously reported.⁷

In the Czech Republic center, serum concentrations of amlodipine, verapamil, betaxolol, bisoprolol, metoprolol, doxazosin, losartan, telmisartan, hydrochlorothiazide, perindoprilate, ramiprilate, urapidil, rilmenidine, canrenoate (metabolite of spironolactone), and furosemide were measured as reported previously.^{17,23–25} In outpatients, the sample was taken on the first visit to the outpatient department; in inpatients, the sample was taken on the day of admission to hospital. The chromatographic separation was performed on an Agilent Technologies 1200 Rapid Resolution Liquid Chromatography consisting of a degasser, binary pump, autosampler, and thermostatted column compartment. The mass spectrometry analysis was performed using an MDS Sciex3200 Q-trap triple quadrupole/linear ion trap mass spectrometer with a Turbo Ion Spray source.

Any deviation from prescribed antihypertensive treatment (absence of at least 1 prescribed BP-lowering medications/their metabolites in body fluids on biochemical analysis) was defined as nonadherence to antihypertensive treatment. Partial/total nonadherence was further identified as incomplete presence/complete absence of prescribed antihypertensive medications in urine/serum on this analysis, respectively.

Statistical Analysis

Demographic and clinical characteristics of both populations are shown as means (SDs), medians (interquartile ranges), and counts (percentages).

Medication class-specific nonadherence was examined after categorizing antihypertensives into 5 classes (A, angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, and renin inhibitors; B, β -blockers; C, calcium channel blockers; D, diuretics; and E, other antihypertensive medications). Population-level average effects were derived from generalized estimating equations (geeR package)^{26,27} taking into account the correlated nature of observations across the above 5 medication classes. The response variable was a binary indicator of medication class-specific nonadherence defined as absence of at least 1 medication from the associated class in the HPLC-MS/MS-based test results. The models were adjusted for age, sex, and total number of antihypertensive medications prescribed.

Prediction models for the overall nonadherence, defined as nonadherence to at least 1 medication of any class, were built using logistic regression with logit link function adjusting for age, sex, number of prescribed antihypertensive medications, and a binary variable indicating whether a patient was given diuretics (D). The discriminatory power of the models was evaluated using area under the curve.

The generalizability of the models, that is, their ability to predict outcomes using unseen/new data, was evaluated by measuring each population's model's area under the curve on the data of the other. The goodness-of-fit was examined using Stukel test. The percentage of variation in the outcome explained by independent variables was expressed by Nagelkerke pseudo R^2 .

Sensitivity analyses stratified on the source for referral (inpatient and outpatient) were conducted on the data from the Czech population.

Results

Basic Demographic and Clinical Characteristics

The demographic characteristics of 1348 patients with hypertension stratified by population are presented in Table 1.

Nonadherence to Antihypertensive Treatment Is Common in United Kingdom and Czech Republic

In 676 UK patients with hypertension whose urine sample underwent HPLC-MS/MS analysis, the rates of any, partial, and total nonadherence were 41.6%, 27.1%, and 14.5%, respectively (Table 1). Of 2562 medications prescribed to 676 British patients, 815 (31.8%) were not detected in urine on HPLC-MS/MS analysis.

Table 1. Demographic and Clinical Characteristics by Population

Phenotype	United Kingdom	Czech Republic
No. of patients	676	672
Age, y	55.8 (14.6)	54.4 (11.6)
Men	328 (48.5%)	393 (58.5%)
No. of medications prescribed		
Total number	4 (3–5)	3 (2–4)
1	59 (8.7%)	20 (3%)
2	86 (12.7%)	254 (37.8%)
3	128 (18.9%)	177 (26.3%)
4	191 (28.3%)	137 (20.4%)
5	130 (19.2%)	61 (9.1%)
6+	82 (12.1%)	23 (3.4%)
No. of medications detected		
Total number	3 (1–4)	2 (2–3)
0	98 (14.5%)	81 (12.1%)
1	102 (15.1%)	72 (10.7%)
2	129 (19.1%)	246 (36.6%)
3	118 (17.5%)	144 (21.4%)
4	132 (19.5%)	91 (13.5%)
5+	97 (14.3%)	38 (5.7%)
Any nonadherence	281 (41.6%)	212 (31.5%)
Partial nonadherence	183 (27.1%)	131 (19.5%)
Total nonadherence	98 (14.5%)	81 (12.1%)
Total adherence	395 (58.4%)	460 (68.5%)
No. of medications prescribed by class, n (%)		
A	601 (88.9)	372 (55.4)
B	348 (51.5)	280 (41.7)
C	507 (75)	451 (67.1)
D	484 (71.6)	361 (53.7)
E	325 (48.1)	440 (65.5)
No. of medications detected by class, n (%)		
A	447 (74.4)	294 (79.0)
B	265 (76.1)	209 (74.6)
C	361 (71.2)	360 (79.8)
D	311 (64.3)	262 (72.6)
E	230 (70.8)	348 (79.1)

Data are counts (percentages), means (SDs), and medians (interquartile ranges). A indicates angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, and renin inhibitors; B, β -blockers; C, calcium channel antagonists; D, diuretics; and E, other antihypertensive medications.

The prevalence of any, partial, and total nonadherence was 31.5%, 19.5%, and 12.1%, respectively, among 672 patients recruited in the Czech Republic (Table 1). The overall percentage of prescribed antihypertensive medications undetected

Table 2. Clinical Predictors of Nonadherence to Antihypertensive Treatment

Phenotype	United Kingdom		Czech Republic	
	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age	0.67 (0.59–0.77)	<0.001	0.69 (0.59–0.80)	<0.001
Women	1.65 (1.16–2.33)	0.005	1.55 (1.09–2.20)	0.014
No. of med.	1.85 (1.58–2.16)	<0.001	1.77 (1.47–2.12)	<0.001
Prescribed diuretics	1.65 (1.01–2.70)	0.047	1.18 (0.76–1.83)	0.457

Data are ORs with respective 95% CIs and levels of statistical significance (*P* value) from adjusted logistic regression models. CI indicates confidence interval; No. of med., total number of prescribed antihypertensive medications; and OR, odds ratio.

on HPLC-MS/MS–based serum analysis was 24.1% in this population.

Age and Sex Are Associated With Nonadherence to Antihypertensive Treatment

Women were more commonly nonadherent to antihypertensive treatment in both populations—the odds of the overall nonadherence were \approx 65% and 55% higher in women than in men in the UK and Czech patients, respectively (Table 2). Age showed an inverse association with nonadherence to antihypertensive treatment—every 10-year increase in age was associated with just >30% reduction in the odds of nonadherence in the UK and the Czech populations (Table 2).

Number of Prescribed Antihypertensive Medications Is a Strong Risk Factor for Nonadherence to Antihypertensive Treatment

Our analysis of UK patients showed that the risk of nonadherence increases with the number of prescribed BP-lowering medications (Figure 1). Although nonadherence among those who were prescribed only 1 antihypertensive was minimal, the majority (79.3%) of UK patients prescribed \geq 6 BP-lowering medications were nonadherent to antihypertensive treatment (Figure 1). This association was independent of age, sex, as well as the class of prescribed antihypertensive medications (Tables 2 and 3). We replicated these findings in the Czech population—the number of prescribed antihypertensive medications showed a strong association with the risk of nonadherence to treatment even after adjusting for basic demographics and the classes of prescribed antihypertensives (Figure 1; Tables 2–3). On average, every increase in the number of prescribed antihypertensive medications was associated with 85% and 77% increase in the odds of the nonadherence in the UK and Czech populations, respectively (Table 2).

Diuretics Are Associated With the Highest Odds of Biochemical Nonadherence Among 5 Classes of Antihypertensive Medications

Antihypertensive medications acting on the renin–angiotensin system (A) were the most commonly prescribed class of antihypertensive medications in the UK population and were used as the reference for comparisons with other classes in both

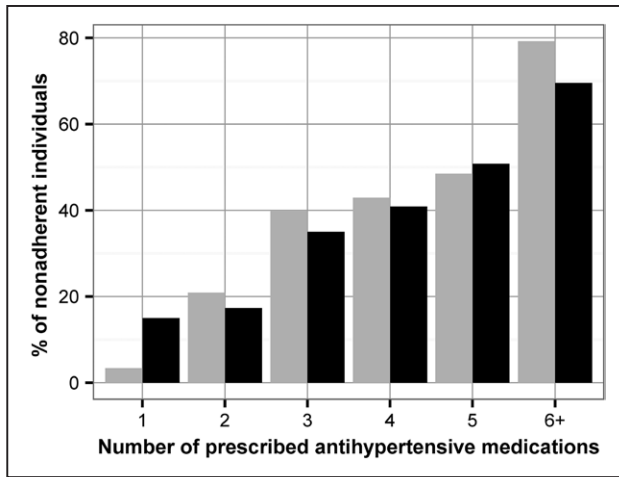


Figure 1. Association between the number of prescribed antihypertensive medications and the risk of nonadherence by population (gray, United Kingdom; black, Czech Republic).

population samples (Table 2). After adjustment for age, sex, and the number of prescribed medications, the odds of nonadherence to diuretics were the highest among 5 classes of antihypertensive medications, ≈1.8- and 1.6-fold higher than the reference category (A) in the UK and Czech populations, respectively (Table 3).

Prediction of the Overall Nonadherence to Antihypertensive Treatment Based on 4 Basic Clinical Parameters

Based on the 4 parameters (age, sex, number of prescribed antihypertensives, and prescribed diuretics) associated with nonadherence, we built its predictive models in both populations. We fitted discrimination models in each population as a discovery cohort and then tested the performance of these models in the other data set (replication; Table 4). The area

Table 3. Antihypertensive Class-Specific Nonadherence Across 5 Groups of Prescribed BP-Lowering Medications

Phenotype	United Kingdom		Czech Republic	
	Adjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Age	0.64 (0.59–0.69)	<0.001	0.66 (0.60–0.73)	<0.001
Women	2.40 (1.96–2.94)	<0.001	1.85 (1.48–2.31)	<0.001
No. of med.	1.71 (1.58–1.84)	<0.001	1.56 (1.43–1.71)	<0.001
Antihypertensive medication classes				
A	1	...	1	...
B	0.69 (0.50–0.96)	0.025	1.07 (0.74–1.56)	0.708
C	1.02 (0.77–1.35)	0.899	0.96 (0.67–1.36)	0.800
D	1.76 (1.33–2.33)	<0.001	1.63 (1.16–2.30)	0.005
E	1.05 (0.77–1.44)	0.757	1.10 (0.78–1.56)	0.583

Data are OR with respective 95% CIs and levels of statistical significance (P value). A indicates angiotensin-converting enzyme inhibitors, angiotensin II type 1 receptor antagonists, and renin inhibitors; B, β-blockers; BP, blood pressure; C, calcium channel antagonists; CI, confidence interval; D, diuretics; E, other antihypertensive medications; No. of med., total number of prescribed antihypertensive medications; and OR, odds ratio.

Table 4. Model Diagnostics and Performance Measures

Statistic	Population	
	United Kingdom	Czech Republic
AUC: UK model	0.758	0.708
AUC: Czech model	0.756	0.710
Stukel test	0.443	0.348
Nagelkerke pseudo R ²	0.269	0.165

AUC indicates area under the curve; Nagelkerke pseudo R², proportion of variation explained by models; and Stukel test, model calibration test.

under the curves on the data used for model fitting were 0.758 and 0.710 for the UK and Czech data, respectively, both consistent with fair discriminatory power (Table 4). Similar levels of area under the curve were observed when the UK model was tested on the Czech data (0.708) and vice versa for the Czech model (0.756; Table 4). The goodness-of-fit tests using Stukel test did not reveal any model misspecification (Table 4). The amount of variation in the overall nonadherence explained by the independent variables, measured by Nagelkerke pseudo R², was 27% and 16% in the UK and Czech models, respectively (Table 4). The probabilities of the overall nonadherence derived from these models are shown in Figure 2. For example, the probability of nonadherence in middle-aged women (aged, 35–55 years) on >6 antihypertensive medications was >75% in both populations.

Sensitivity Analysis

The outpatient/inpatient indicator in the prediction model for the Czech Republic data had P value of 0.054. Its inclusion in the model had no effect on the odds ratio estimates for age and sex and reduced only slightly the odds ratio for the total number of prescribed medications from 1.77 (1.47–2.12) to 1.72 (1.43–2.07). The indicator variable for whether patients were prescribed diuretics or not was kept in the model to enable comparison with the UK model. For the same reason—consistent comparison with the UK model—the outpatient/inpatient variable was dropped from the medication class-specific model for the Czech Republic data because it was not a significant predictor of nonadherence (P=0.450).

Discussion

This study has provided several important insights into the nonadherence to antihypertensive medications and the management of hypertension. First, our data reveal a widespread prevalence of nonadherence, irrespective of the region/country of recruitment. Second, we show that both the number and the class of prescribed antihypertensives are strong independent risk factors for biochemically confirmed nonadherence to antihypertensive treatment. The similarity in the direction and the magnitude of association between nonadherence to antihypertensive medications and both predictors across 2 different health systems in 2 countries and by analysis of 2 different biological fluids make our results extremely robust. Finally, we show that diagnostic models based on 4 cost free and easy to collect clinical parameters show a fair discrimination between adherence and nonadherence to treatment in patients with hypertension.

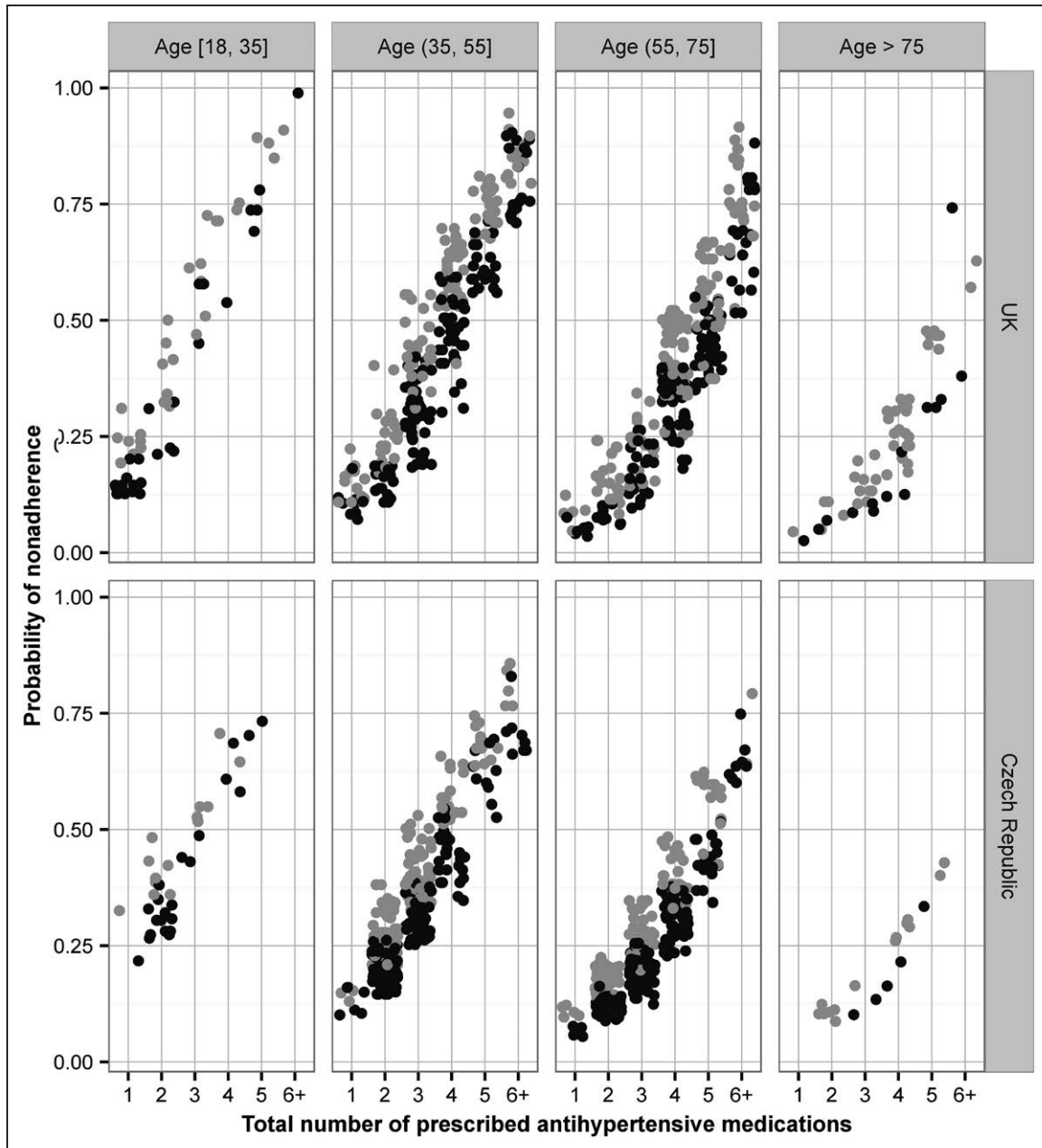


Figure 2. Predicted probability of nonadherence by age, sex, and total number of prescribed medications for both United Kingdom and Czech Republic populations (gray, females; black, males).

The correlation between the count of antihypertensive medications and the increased risk of nonadherence was assessed in previous studies.^{14,28,29} Some investigations (mostly relying on indirect measures of adherence) proposed neutral³⁰ or even positive³¹ effect of the number of prescriptions on the concordance with therapy. To this end, the consistency of almost 2-fold increase in odds of directly confirmed nonadherence with each additional prescribed medication in 2 independent populations demonstrated here provides a strong line of evidence for polypharmacy as a potential risk factor for nonadherence to antihypertensive treatment. Because of the retrospective nature of our analysis, we are unable to assign directional causality to this association. Although it seems intuitive that the higher number of medications might increase

the susceptibility to nonadherence, we should acknowledge that concealed nonadherence could also stimulate overprescribing (leading to the increasing number of antihypertensives). Future prospective clinical studies are warranted to provide clarity into the sequence and mechanisms of the demonstrated associations. Nevertheless, the relationship between the number of prescribed antihypertensives and the nonadherence is an extremely important finding with direct implications for treatment escalations in difficult to treat patients with hypertension. Given the increase in nonadherence with every additional prescribed antihypertensive medication, the strategy of using more fixed dose combinations may be effective, as demonstrated before in patients with hypertension.²⁸ However, because partial deviation from the prescribed

antihypertensive treatment is the most common type of nonadherence, one should consider that on fixed dose combinations, some partially nonadherent patients might end up missing more prescribed medications than on individual antihypertensives. Further prospective studies using HPLC-MS/MS-based urine analyses will be necessary to confirm directly whether fixed dose combinations of antihypertensive medications can reduce the overall burden of nonadherence in hypertensive population.

The highest risk for nonadherence to diuretics is in keeping with previously published meta-analysis.³² Well-known side effects of diuretics directly affecting the quality of life may probably explain the highest risk of nonadherence (driven by low persistence) for this class of BP-lowering medications. However, we should also acknowledge that diuretics are often added to antihypertensive treatment later than other BP-lowering drugs, such as calcium channel antagonists or blockers of renin-angiotensin system. Thus, the increase in nonadherence to diuretics when compared with the usual first line antihypertensive therapies could be potentiated by the relationship between the existing burden of prescribed medications and deviation from the antihypertensive therapy.

The mechanisms underlying the strong relationship between sex and biochemically confirmed nonadherence to antihypertensive medications in both populations are less clear. Previous studies showed either no association between sex with adherence³³ or that females are more susceptible to nonadherence than males.³⁴ Although our data seem consistent with the previously demonstrated female disadvantage in nonadherence, in the absence of information on sex distribution of patients attending each referring center (from where the population samples were derived), we cannot fully exclude a potential contribution of sex referral bias to the detected association. This will require further confirmation in well-designed prospective studies.

The published evidence for the association between nonadherence and age is also inconsistent. Nonadherence to antihypertensive treatment was reported to correlate with younger age^{35,36} and older age³⁴ and was not associated with age at all.^{29,33} This inconsistency in associations between the nonadherence and basic demographics is likely to arise from the subjective or semiobjective measures used to assess nonadherence in the previous studies (ie, self-reported measures and retrospective pharmacy database reviews).^{4,14,15,37} We speculate that younger patients are more reluctant to accept the regular administration of medication for a chronic and generally asymptomatic condition, in particular, if the therapy regime interferes with work/daily routine. What also transpires from interviews with some of our nonadherent patients is a perception that regular administration of medications heralds the "end of youth." This self-belief may have a negative impact on adherence to antihypertensive treatment.

The fair discriminatory power of our prediction algorithms across both cohorts suggests that the number/classes of antihypertensive medications together with age and sex might be a helpful template for further development of tools to estimate the risk of nonadherence in centers where HPLC-MS/MS is unlikely to become available. We accept that the

simple predictive algorithms demonstrated in this study are not yet ready for immediate introduction to clinical practice. However, their fair power to discriminate between adherence and nonadherence based on only 4 cost free and easy to collect clinical parameters should provide an impetus for their further advancement in future studies. These investigations should pave the way to develop tools that could (at least to some extent) substitute subjective and often insensitive methods of assessing adherence in healthcare systems with limited financial resources. Indeed, we should appreciate that HPLC-MS/MS-based analysis (because of the costs of the test and related infrastructure) is unlikely to become available in many developing countries. This is recognized in the medical literature including the recent conclusions by the Lancet Commission on hypertension.³⁸ The rates of nonadherence to antihypertensive therapy in those countries are not lower than in the westernized societies. Therefore, we argue that inexpensive (or in fact cost free) predictive tools developed based on objective and direct methods of assessing nonadherence have a potential to equip clinicians practicing in such countries with more sensitive methods of estimating the risk of nonadherence than clinical impression.

Our analysis has several strengths. It is the largest to date study into the risk factors of nonadherence defined by a robust, direct, and objective method of its detection. We also demonstrate a unique replication for each of the identified associations between nonadherence and the examined parameters by using 2 separate populations. However, we are aware of some limitations of our study. First, our data collection was based on retrospective analysis of clinical files and as such is not immune from a potential bias because of selection and incomplete information. Second, the rates of nonadherence reported here are probably higher than those in the general hypertensive population given the selection criteria (patients with hypertension with suspected nonadherence and those with suboptimal BP control). Indeed, the magnitude of BP elevation shows a strong positive association with the risk of nonadherence.⁷ Furthermore, patients selected for HPLC-MS/MS screening specifically based on suboptimal BP control exhibit much higher prevalence of nonadherence than those in whom the suspicion of nonadherence or suboptimal BP control was not the exclusive reason for screening.⁷ Finally, we accept the biochemical limitations of our method of diagnosing nonadherence to antihypertensive treatment. For example, HPLC-MS/MS-based urine analysis is not immune to detection of toothbrush adherence.³⁹ This means that patients activating their adherence before the clinical appointments (similar to the behavior of patients brushing teeth before seeing a dentist) might be classified as biochemically adherent despite being therapeutically nonpersistent. Furthermore, a majority of antihypertensive medications retain their presence in bodily fluids long after the last pill had been ingested (because of their long half-lives). That means that for several medications (ie, indapamide—4 half-lives: 60 hours),⁴⁰ intermittent adherence/nonadherence might go undetected. Because of these limitations, we suspect that our method probably underestimates the genuine burden of nonadherence to antihypertensive treatment. A combination of electronic monitoring with direct biochemical HPLC-MS/

MS-based analysis should provide better measures of defining nonadherence in such patients.

Perspectives

Biochemical assessment of nonadherence to antihypertensive medications is a useful diagnostic test in management of patients with hypertension, in particular those with suboptimal BP control. A wider use of this test may prevent many unnecessary investigations and treatment escalations. We anticipate that the simple changes in antihypertensive treatment (such as a reduction in the number of prescribed medications or single pill combinations) inspired by the results of this test will improve adherence and translate into better BP control in many nonadherent patients with hypertension.

Disclosures

I. Squire has received modest honoraria from Novartis for participation in advisory boards and educational events and has received modest research support from Novartis and Servier. B. Williams has received modest honoraria from Novartis, Servier, Daiichi Sankyo, Boehringer Ingelheim, and Pfizer for lectures. The other authors report no conflicts.

References

- Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–223. doi: 10.1016/S0140-6736(05)17741-1.
- Kotseva K, Wood D, De Bacquer D, et al; EUROASPIRE Investigators. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol*. 2016;23:636–648. doi: 10.1177/2047487315569401.
- Yoon S, Fryar C, Carroll M. *Hypertension Prevalence and Control Among Adults: United States, 2011–2014*. NCHS Data Brief, No 220. Hyattsville, MD: National Center for Health Statistics. www.cdc.gov/nchs/data/data-briefs/db220.htm. Updated 2015. Accessed December 18, 2016.
- NICE. NICE clinical guideline 76: medicines adherence. www.nice.org.uk/CG76. Updated 2009. Accessed April 5, 2016.
- IMS Institute of Healthcare Informatics. Avoidable costs in US health care. www.imshealth.com/en_US/thought-leadership/ims-institute/reports/avoidable-costs. Updated 2013. Accessed October 23, 2016.
- Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, Toennes SW. Resistant hypertension? Assessment of adherence by toxicological urine analysis. *J Hypertens*. 2013;31:766–774. doi: 10.1097/HJH.0b013e32835e2286.
- Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, Samani NJ, Gupta P, Madira W, Stanley A, Williams B. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) urine analysis. *Heart*. 2014;100:855–861. doi: 10.1136/heartjnl-2013-305063.
- Nieuwlaat R, Wilczynski N, Navarro T, et al. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev*. 2014;11:CD000011. doi: 10.1002/14651858.CD000011.pub4.
- Kolandaivelu K, Leiden BB, O’Gara PT, Bhatt DL. Non-adherence to cardiovascular medications. *Eur Heart J*. 2014;35:3267–3276. doi: 10.1093/eurheartj/ehu364.
- Mennini FS, Marcellusi A, von der Schulenburg JM, Gray A, Levy P, Sciatella P, Soro M, Staffiero G, Zeidler J, Maggioni A, Schmieder RE. Cost of poor adherence to anti-hypertensive therapy in five European countries. *Eur J Health Econ*. 2015;16:65–72. doi: 10.1007/s10198-013-0554-4.
- Rosa J, Widimský P, Toušek P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. *Hypertension*. 2015;65:407–413. doi: 10.1161/HYPERTENSIONAHA.114.04019.
- Patel P, Gupta PK, White CM, Stanley AG, Williams B, Tomaszewski M. Screening for non-adherence to antihypertensive treatment as a part of the diagnostic pathway to renal denervation. *J Hum Hypertens*. 2016;30:368–373. doi: 10.1038/jhh.2015.103.
- Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. *J Hum Hypertens*. 2016;30:83–89. doi: 10.1038/jhh.2015.38.
- Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. *Cochrane Database Syst Rev*. 2004;2:CD004804.
- Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int*. 2015;2015:217047. doi: 10.1155/2015/217047.
- Pandey A, Raza F, Velasco A, Brinker S, Ayers C, Das SR, Morisky DE, Halm EA, Vongpatanasin W. Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment-resistant hypertension. *J Am Soc Hypertens*. 2015;9:420–426.e2. doi: 10.1016/j.jash.2015.04.004.
- Gonzalez O, Iriarte G, Rico E, Ferreirós N, Maguregui MI, Alonso RM, Jiménez RM. LC-MS/MS method for the determination of several drugs used in combined cardiovascular therapy in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2010;878:2685–2692. doi: 10.1016/j.jchromb.2010.07.026.
- Strauch B, Petrák O, Zelinka T, Rosa J, Somlóová Z, Indra T, Chytil L, Marešová V, Kurcová I, Holaj R, Wichterle D, Widimský J Jr. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. *J Hypertens*. 2013;31:2455–2461. doi: 10.1097/HJH.0b013e3283283652c61.
- Florczak E, Tokarczyk B, Warchol-Celińska E, Szwencz-Pietrasz E, Prejzbisz A, Gosk M, Kabat M, Narkiewicz K, Januszewicz A, Kała M. Assessment of adherence to treatment in patients with resistant hypertension using toxicological serum analysis. A subgroup evaluation of the RESIST-POL study. *Pol Arch Med Wewn*. 2015;125:65–72.
- Bokhour BG, Berlowitz DR, Long JA, Kressin NR. How do providers assess antihypertensive medication adherence in medical encounters? *J Gen Intern Med*. 2006;21:577–583. doi: 10.1111/j.1525-1497.2006.00397.x.
- Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40:1280–1288. doi: 10.1345/aph.1H018.
- World Health Organisation. Adherence to long-term therapies: evidence for action. www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Updated 2003. Accessed October 12, 2016.
- Iriarte G, Gonzalez O, Ferreirós N, Maguregui MI, Alonso RM, Jiménez RM. Validation of a fast liquid chromatography-UV method for the analysis of drugs used in combined cardiovascular therapy in human plasma. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2009;877:3045–3053. doi: 10.1016/j.jchromb.2009.07.018.
- Chytil L, Cvačka J, Marešová V, Štrauch B, Widimský J Jr, Štícha M, Slanař O. Development of a fast LC-MS/MS method for quantification of rilmenidine in human serum: elucidation of fragmentation pathways by HRMS. *J Mass Spectrom*. 2010;45:1179–1185. doi: 10.1002/jms.1809.
- Chytil L, Strauch B, Cvačka J, Marešová V, Widimský J Jr, Holaj R, Slanař O. Determination of doxazosin and verapamil in human serum by fast LC-MS/MS: application to document non-compliance of patients. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2010;878:3167–3173. doi: 10.1016/j.jchromb.2010.09.032.
- R Core Team. *A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. www.R-project.org. Updated 2015. Accessed May 10, 2016.
- Carey V. Ported to R by Lumley T, Ripley B. Generalized estimation equation solver. R package version 4.13–19. https://CRAN.R-project.org/package=gee. Updated 2015. Accessed June 10, 2016.
- Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension*. 2010;55:399–407. doi: 10.1161/HYPERTENSIONAHA.109.139816.
- Morrison VL, Holmes EA, Parveen S, Plumpton CO, Clyne W, De Geest S, Dobbels F, Vrijens B, Kardas P, Hughes DA. Predictors of self-reported adherence to antihypertensive medicines: a multinational, cross-sectional survey. *Value Health*. 2015;18:206–216. doi: 10.1016/j.jval.2014.12.013.
- Grigoryan L, Pavlik VN, Hyman DJ. Predictors of antihypertensive medication adherence in two urban health-care systems. *Am J Hypertens*. 2012;25:735–738. doi: 10.1038/ajh.2012.30.
- Watanabe JH, Bounthavong M, Chen T, Ney JP. Association of polypharmacy and statin new-user adherence in a Veterans Health Administration

- population: a retrospective cohort study. *Ann Pharmacother*. 2013;47:1253–1259. doi: 10.1177/1060028013502000.
32. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. *Circulation*. 2011;123:1611–1621. doi: 10.1161/CIRCULATIONAHA.110.983874.
 33. Swain S, Hariharan M, Rana S, Chivukula U, Thomas M. Doctor-patient communication: impact on adherence and prognosis among patients with primary hypertension. *Psychol Stud*. 2015;60:25–32.
 34. Degli Esposti L, Saragoni S, Benemei S, Batacchi P, Geppetti P, Di Bari M, Marchionni N, Sturani A, Buda S, Degli Esposti E. Adherence to antihypertensive medications and health outcomes among newly treated hypertensive patients. *Clinicoecon Outcomes Res*. 2011;3:47–54. doi: 10.2147/CEOR.S15619.
 35. Ross S, Walker A, MacLeod MJ. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. *J Hum Hypertens*. 2004;18:607–613. doi: 10.1038/sj.jhh.1001721.
 36. Maguire LK, Hughes CM, McElnay JC. Exploring the impact of depressive symptoms and medication beliefs on medication adherence in hypertension—a primary care study. *Patient Educ Couns*. 2008;73:371–376. doi: 10.1016/j.pec.2008.06.016.
 37. Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, Lohr KN. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. *JAMA Intern Med*. 2015;175:76–87. doi: 10.1001/jamainternmed.2014.5841.
 38. Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. *Lancet*. 2016;388:2665–2712. doi: 10.1016/S0140-6736(16)31134-5.
 39. Chatterjee JS. From compliance to concordance in diabetes. *J Med Ethics*. 2006;32:507–510. doi: 10.1136/jme.2005.012138.
 40. Moffat A, Osselton D, Widdop B, Watts J. *Clarke's Analysis of Drugs and Poisons*. 4th ed. London, UK: Pharmaceutical Press; 2011.

Novelty and Significance

What Is New?

- Biochemically confirmed nonadherence to antihypertensive treatment is inversely related to age and male sex. The risk of nonadherence increases by >75% with every increase in the number of prescribed antihypertensives. Biochemical nonadherence to diuretics is higher than to other classes of antihypertensive medications.

What Is Relevant?

- Biochemical analysis of urine/serum is a useful diagnostic strategy in screening for nonadherence to antihypertensive medications.

- The number and the choice of prescribed blood pressure-lowering medications should always be considered in management of nonadherence to antihypertensive treatment.

Summary

Nonadherence to antihypertensive treatment is common, in particular in patients on multiple blood pressure-lowering medications and diuretics.

Risk Factors for Nonadherence to Antihypertensive Treatment

Pankaj Gupta, Prashanth Patel, Branislav Strauch, Florence Y. Lai, Artur Akbarov, Vera Maresová, Christobelle M.J. White, Ondrej Petrák, Gaurav S. Gulsin, Veena Patel, Ján Rosa, Richard Cole, Tomáš Zelinka, Robert Holaj, Angela Kinnell, Paul R. Smith, John R. Thompson, Iain Squire, Jirí Widimský, Jr, Nilesh J. Samani, Bryan Williams and Maciej Tomaszewski

Hypertension. 2017;69:1113-1120; originally published online May 1, 2017;

doi: 10.1161/HYPERTENSIONAHA.116.08729

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2017 American Heart Association, Inc. All rights reserved.

Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://hyper.ahajournals.org/content/69/6/1113>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Hypertension* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Hypertension* is online at:
<http://hyper.ahajournals.org/subscriptions/>