


Drug adherence and psychological factors in patients with apparently treatment-resistant hypertension: Yes but which ones?

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Abstract

The aim of the study was to assess drug adherence, as well as association of psychological factors with both drug adherence and severity of hypertension in two subtypes of patients with apparently treatment-resistant hypertension (ATRH): younger patients with uncomplicated hypertension (YURHTN) versus patients ≥ 60 -year-old and/or with a history of cardio- or cerebrovascular complication (OCRHTN).

Drug adherence was assessed in urine by targeted Liquid Chromatography-Mass Spectrometry. The severity of hypertension was assessed by 24-h ambulatory blood pressure adjusted for the number of antihypertensive drugs and for drug adherence. Psychological profile was assessed using five validated questionnaires.

The proportion of totally non-adherent patients was three times higher (24.1 vs. 7.1%, $P = 0.026$) in the YURHTN ($n = 54$) than in OCRHTN subgroup ($n = 43$). Independent predictors of drug adherence in YURHTN were ability to use adaptive strategies, male sex and family history of hypertension, accounting for 39% of variability in drug

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adherence. In the same subgroup, independent predictors of severity of hypertension were somatization and lower recourse to planification, accounting for 40% of variability in the severity of hypertension. In contrast, in the OCRHTN subgroup, independent predictors of drug adherence and severity of hypertension were limited to the number of yearly admissions to the emergency room and the total number of prescribed drugs. In conclusion, poor drug adherence and altered psychological profiles appear to play a major role in younger patients with ATRH devoid of cardiovascular complication. This subgroup should be prioritized for chemical detection of drug adherence and psychological evaluation.

KEYWORDS

drug adherence, psychological profile, resistant hypertension

1 | INTRODUCTION

Resistant hypertension has been defined as the failure to achieve an office blood pressure (BP) < 140/90 mm Hg and a 24-h ambulatory BP < 130/80 mm Hg on optimal doses of at least three antihypertensive medications from different classes (ideally one of which is a diuretic).¹ It is characterized by a higher prevalence of target organ damage² and a higher incidence of cardiovascular events³ compared with other forms of hypertension. Many patients with seemingly treatment-resistant hypertension are in fact pseudo-resistant due to poor drug adherence.^{4,5,6} However, whatever the approach used, drug adherence is difficult to assess and varies over time.^{4,7} Therefore, the frontier between truly and pseudo-resistant hypertension is fluctuating, and patients with severe hypertension may shift from one group to the other and vice versa. Accordingly, many authors prefer to consider these patients in a single category, that is, “apparently treatment-resistant hypertension” (ATRH)^{4,8–11}.

Beyond classic demographic and health-related characteristics, we have demonstrated that psychological factors, mostly related to somatization and expression of emotions, are strong, independent predictors of both drug adherence and severity of hypertension in ATRH but not in controlled hypertensive patients.^{12,13} On the other side, it is well known that drug resistance is also influenced by arterial stiffness and vascular damage.^{2,3} The scope of the current study was to help identifying those patients in whom psychological factors play a predominant role in the pathogenesis of ATRH, either directly or through the mediation of poor drug adherence versus patients in whom drug resistance may primarily or secondarily result from vessel-related mechanical factors. In order to achieve this aim, we split our cohort of patients with ATRH in patients aged 60 or older and/or with a history of cardio- or cerebrovascular complication (OCRHTN) versus patients without these characteristics, that is, patients < 60-year-old with uncomplicated hypertension (YURHTN) and assessed drug adherence and predictors of both drug adherence and severity of hypertension in these two subgroups.

2 | METHODS

2.1 | Study population

Eligible patients were recruited during the hypertension consultations performed at the Hypertension Clinic of the Cliniques Universitaires Saint-Luc (Brussels, Belgium, October 2017 to June 2021) and at Torino Hypertension Center (Torino, Italy, January 2019 to June 2021).

All consecutive patients with ATRH confirmed by ambulatory BP monitoring (24-h BP \geq 130/80 mm Hg on three or more antihypertensive drug classes at optimal/maximal tolerated drug dosages)¹ seen during this time frame who signed the informed consent, were included in the analysis. Exclusion criteria were age < 18 years, estimated glomerular filtration (eGFR) < 30 ml/min/1.73 m² according to the CKD-EPI formula, body mass index (BMI) \geq 40 Kg/m² and suspicion or demonstration of secondary hypertension. All patients underwent detailed endocrine and vascular work-up for secondary hypertension, including an MR- or CT-angiography if indicated, as recommended in the guidelines.¹

Office and 24-h ambulatory BP values were measured using validated oscillometric devices (see below). For all recruited patients, a detailed clinical history and physical examination were available, and a urine sample of 10 ml was collected. Five validated questionnaires were administered to the patients, in order to assess different aspects of their psychological profile as well as past traumas and subsequent post-traumatic stress disorder (PTSD, see below). The duration of the whole procedure was about 60 min. Urines were collected on the day of signature of the written informed consent, in order to take into account the correct information of the patient and the necessity to avoid interfering in the medication-taking behaviour.^{12,13} This study was approved by the Comité d’Ethique hospitalo-facultaire des Cliniques Universitaires Saint-Luc (Brussels) as well as the Comitato Etico Interaziendale of the A.O.U. Città della Salute e della Scienza di Torino (Torino) and was performed according to the principles of the Declaration of Helsinki and its subsequent modifications.

2.2 | Assessment tools

2.2.1 | Physiological measures

Office BP

Blood pressure was measured according to the European guidelines from the European Society of Hypertension¹ using the validated oscillometric device Omron HEM 907 (Omron Health Care, Kyoto, Japan), after a 5-min silent rest in seated position following good practice recommendations.¹⁴ Three measurements were obtained at 1-min interval from each other and the mean value was considered in subsequent analyses.

24-h ambulatory BP monitoring

Twenty-four-hour ambulatory BP values were measured using an automated, noninvasive oscillometric device, the validated Mobil O Graph, I.E.M (Mobil O Graph, I.E.M GmbH, Stolberg, Germany), recording BP measurements at 30 min intervals throughout 24 h, with at least 20 valid measurements during day-time (between 6h00 and 23h00) and 7 at night-time (between 23h00 and 6h00).¹⁵ Assessment of the severity of hypertension was based on mean 24-h systolic BP, adjusted for the number of antihypertensive drugs and adherence level.

2.2.2 | Biochemical analysis (urine LC-MS/MS)

All patients provided a 10 ml urine sample, stored at a temperature of -20°C before analysis. Detection of antihypertensive drugs in the urine was performed using a liquid chromatography system coupled with a tandem mass spectrometer as detector (LC-MS/MS) at Institute of Legal Medicine, University Hospital Frankfurt, Goethe-University Frankfurt, Frankfurt/Main (Germany), as recommended⁷ and established in previous studies.^{8,13} Briefly, an ethyl acetate extraction (1 ml) of 200 μ l aliquots of urine was performed after adding internal standards. After mixing and centrifugation, the organic phase was evaporated. The dry residue was reconstituted with 100 μ l 0.1% formic acid/acetonitrile (80:20, v/v) and analyzed by LC-MS/MS. All prescribed antihypertensive drugs and metabolites were detectable. Full drug adherence, partial drug adherence and total non-adherence were defined as presence of all, part or none of prescribed drugs in the urine, respectively. Drug adherence was defined as the percentage of prescribed antihypertensive drugs which were effectively detected in the urine.

2.2.3 | Psychological analysis

In order to evaluate the psychological profile of hypertensive patients, five validated questionnaires were used: the Emotion Regulation Questionnaire (ERQ)¹⁶⁻¹⁸; the Cognitive Emotion Regulation Questionnaire (CERQ)^{19,20}; The Toronto Alexithymia Scale (TAS-20)²¹; The Brief Symptom Inventory (BSI)²² and the Post Traumatic Diagnostic Scale

(PDS).²³ The CERQ was applied only in the Brussels cohort, because not available in Italian version. More details on the questionnaires and their interpretation are provided in references.^{12,13}

2.3 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, New York). Categorical variables are reported as percentages and continuous data as mean \pm standard deviation (SD) if normally distributed, or median (interquartile range [IQR]), if not-normally distributed. Independent t-tests and univariate ANOVA were used to highlight significant correlations involving continuous variables. Pearson's (for normally distributed variables) and Spearman's correlations (for those that were not) were used to determine the associations between adherence level and demographic, health-related and psychological variables. Correlations were also evaluated between demographic, health-related and psychological variables and the residuals of 24-h ambulatory systolic and diastolic BP, regressed on the number of antihypertensive drugs per day and adherence level, considered as reflecting the severity of hypertension. Finally, multivariate linear regression analyses were performed to investigate which demographic, health-related and/or psychological variables, among the significantly correlated, were independent predictors of adherence level and severity of hypertension. Collinearity was checked with a matrix of Pearson's correlations with $r \geq .8$ in at least one correlation as the criterion for multicollinearity and with exclusion of multicollinearity if all variance inflation factor < 10 .²⁴ The significance level for all the analysis was fixed at a 2-sided P -value $< .05$. All statistical analyses were performed both in the group including older patients and/or patients with a history of cardio- or cerebrovascular complication (OCRHTN), which is considered as the reference group, and in the group of younger patients with uncomplicated hypertension (YURHTN).

3 | RESULTS

3.1 | Characteristics of patients with OCRHTN versus YURHTN

Between October 2017 and June 2021, a total of 97 patients were enrolled. After taking into account age and medical history, 43 were assigned to the OCRHTN group, and 54 to the YURHTN group.

Compared to the OCRHTN group, younger patients without a history of cardiovascular disease, that is, belonging to the YURHTN group were almost 20 years younger ($P < .001$), were three-time more often smokers ($P = .038$), tended to be more overweight ($P = .074$), had a higher office and 24-h ambulatory diastolic BP ($P < .001$ for both) despite prescription of a higher number of drugs ($P = .026$) and were more frequently admitted to the emergency room ($P = .026$) (Table 1).

TABLE 1 Characteristics of the population

	OCRHTN N = 43	YURHTN N = 54	P-value
African origin (%)	2.3	13.0	.058
Age (years)	69 ± 7	48 ± 7	<.001
Women (%)	44.2	46.3	.873
BMI (Kg/m ²)	28.7 ± 4.5	30.6 ± 5.6	.074
Office SBP (mm Hg)	164 ± 23	171 ± 23	.139
Office DBP (mm Hg)	82 ± 17	102 ± 18	<.001
24h-ASBP (mm Hg)	146 ± 16	153 ± 20	.065
24h-ADBP (mm Hg)	82 ± 13	95 ± 16	<.001
N antiHTN drugs	4.1 ± 1.3	4.7 ± 1.3	.026
Adherence level (%)	83.5	59.3	.010
Complete adherence	66.7	37.0	.004
Partial adherence	26.2	38.9	.189
Non-adherence	7.1	24.1	.026
N years with treated HTN	20 ± 13	14 ± 9	.009
N total drugs	6.9 ± 4.1	6.8 ± 3.3	.894
N ED visits/year	.09 ± .51	.71 ± 1.74	.026
University degree (%)	28.6	24.1	.618
Living w/ partner (%)	69.8	66.0	.692
eGFR (ml/min/1.73 m ²)	71 ± 27	81 ± 21	.042
Statins (%)	25 (58%)	6 (11%)	<.0001
LDL-cholesterol (mg/dL)	109 ± 42	114 ± 58	.636
Type 2 Diabetes (%)	41.9	29.6	.209
Stroke history (%)	16.3	0	.002
Myocardial infarction (%)	20.9	0	<.001
Smokers (%)	9.3	25.9	.038

OCRHTN: patients with apparently treatment-resistant hypertension aged 60 or older and/or with a history of cardio- or cerebrovascular events. YURHTN: patients with apparently treatment-resistant hypertension without these characteristics.

Abbreviations: eGFR, estimated Glomerular Filtration Rate; BP, Blood Pressure; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; ED, Emergency Department.

3.2 | Drug adherence in patients with OCRHTN versus YURHTN

Mean drug adherence was significantly lower in patients with YURHTN versus OCRHTN, with a mirror distribution between fully and partly adherent patients, and completely non-adherent patients. In particular, the proportion of totally non adherent patients was three-fold higher in the YURHTN group ($P = .026$) (Table 1).

3.3 | Correlations between drug adherence and demographic, health-related and psychological variables

In the group of younger patients devoid of cardiovascular complication (YURHTN), drug adherence was correlated with male sex ($r =$

TABLE 2 Correlations between socio-demographic, health-related and psychological variables and adherence level

Variables	OCRHTN n = 43 r (P-value)	YURHTN n = 54 r (P-value)
Female gender	-	-.387 (.004)
Living with partner	-.331 (.035)	-
Family history of cardiovascular event	.369 (.019)	-
Family HTN	-	.356 (.008)
Number of ED visits/year	-.473 (.005)	-
ERQ - Suppressive expression	-	-.342 (.020)
TAS1 - Identifying feelings	-	-.290 (.043)
CERQ - Positive refocusing	-	.342 (.025)
CERQ - Planification	-	.459 (.002)
CERQ - Putting into perspective	-	.411 (.006)
CERQ - Adaptive strategies	-	.451 (.002)
BSI - Anxiety	-	-.344 (.021)
BSI - Somatization	-	-.543 (<.001)
BSI - Obsession/compulsion	-	-.397 (.007)
PDS - Number of traumatic events	-	-.336 (.031)
PDS - Neurovegetative symptoms	-	-.319 (.045)

r: Pearson r correlation coefficient.

OCRHTN: patients with apparently treatment-resistant hypertension aged 60 or older and/or with a history of cardio- or cerebrovascular events. YURHTN: patients with apparently treatment-resistant hypertension without these characteristics.

Abbreviations: HTN, hypertension; ED, Emergency Department; ERQ, Emotion Regulation Questionnaire; TAS-20, The Toronto Alexithymia Scale-20; CERQ, The Cognitive Emotion regulation Questionnaire; BSI, The Brief Symptom Inventory; PDS, Posttraumatic Diagnostic Scale.

.387; $P = .001$), family history of Hypertension (HTN) ($r = .356$; $P = .008$), and with distinct psychological characteristics. Poorly adherent patients were characterized by expressive suppression (ERQ $r = -.342$; $P = .020$), difficulty to identify feelings (TAS 1 $r = -.290$; $P = .043$), anxiety (BSI $r = -.344$; $P = .021$), somatization (BSI $r = -.543$; $P < .001$), obsession/compulsion (BSI $r = -.397$; $P = .007$), and, finally, a higher number of traumatic events and presence of neurovegetative symptoms related to them (PDS $r = -.336$, $P = .031$; $r = -.319$, $P = .045$, respectively). By contrast, a higher tendency to use adaptive coping strategies (CERQ $r = .451$, $P = .002$) such as positive refocusing (CERQ $r = .342$, $P = .025$), planification (CERQ $r = .459$, $P = .002$) and putting things into perspective (CERQ $r = .411$, $P = .006$) was associated with a better adherence to antihypertensive treatment in that group (Table 2).

In contrast, in the OCRHTN group, none of all psychological parameters analyzed were associated with drug adherence level, the latter being solely positively correlated with family history of cardiovascular events ($r = .369$; $P = .019$) and negatively correlated with the fact to live with a partner ($r = -.331$; $P = .035$) and the number of yearly admissions for hypertension to the emergency room ($r = -.473$; $P = .005$) (Table 2).

3.4 | Correlations between severity of hypertension and demographic, health-related and psychological variables

In the group of younger patients with uncomplicated hypertension (YURHTN subset), the severity of hypertension defined as mean 24-h systolic BP adjusted for adherence level and the number of antihypertensive drugs prescribed, was correlated with male sex ($r = .463$, $P < .001$), family history of hypertension ($r = -.302$, $P = .026$), the total number of drugs prescribed per day ($r = .427$, $P < .001$) and with twelve psychological traits. In this group, the severity of hypertension was negatively correlated with the planification and adaptive strategies subscale of the *Cognitive Emotion Regulation Questionnaire* (CERQ $r = -.423$, $P = .005$ and $r = -.346$, $P = .023$, respectively) and positively correlated with higher anxiety (BSI $r = .344$, $P = .020$), interpersonal sensitivity (BSI $r = .299$, $P = .046$) somatization (BSI $r = .495$, $P = .001$), obsession and compulsion (BSI $r = .327$, $P = .028$) and paranoid ideation (BSI $r = .297$, $P = .048$) and five factors of the *Posttraumatic Diagnostic Scale*: the number of traumas ($r = .393$, $P = .011$), the total stress ($r = .380$, $P = .017$), the intrusions and reminiscences ($r = .388$, $P = .013$), the emotional blunting ($r = .354$, $P = .025$), and neurovegetative symptoms ($r = .426$, $P = .006$) (Table 3).

By contrast, as reported for drug adherence, in older patients / patients with a history of cardio- or cerebrovascular complication (OCRHTN group), none of all analyzed psychological parameters were associated with the severity of hypertension, but only the number of visits in emergency per year ($r = .560$, $P = .001$) and the total number of drugs prescribed per day ($r = .360$, $P = .023$) (Table 3).

3.5 | Predictive analyses

All demographic, health-related and psychological parameters significantly correlated with the variable of interest (drug adherence and severity of hypertension) were included in the models as potential predictors in predictive analyses.

3.6 | Regression analysis on the adherence level

In the subset of younger ATRH patients without a history of vascular complication (YURHTN), among the thirteen variables initially included in the model to predict adherence level, three of them remained as independent predictors: the “adaptive strategies” of the CERQ, sex and history of hypertension in the family. This final model accounted for 39.2% (adjusted R^2) of the variability in adherence level (Table 4).

In the OCRHTN group, three variables (those which were significantly correlated) were initially included in the model to predict adherence level. Two of them finally remained as predictors of drug adherence: the number of visits in emergency department per year as well as a history of cardiovascular events in the family, both accounting for 28.1% (adjusted R^2) of the variability in adherence level (Table 4).

TABLE 3 Correlation between socio-demographic, health-related and psychological variables and severity of hypertension

24h-SBP adj* Parameters	OCRHTN N = 43 r (P-value)	YURHTN N = 54 r (P-value)
Sex	-	.463 (<.001)
N of ED visits/year	.560 (.001)	-
Family HTN	-	-.302 (.026)
N of total drugs	.360 (.023)	.427 (.001)
CERQ - Planification	-	-.423 (.005)
CERQ - Adaptive strategies	-	-.346 (.023)
BSI - Anxiety	-	.344 (.020)
BSI - Interpersonal sensitivity	-	.299 (.046)
BSI - Somatization	-	.495 (.001)
BSI - Obsession /compulsion	-	.327 (.028)
BSI - Paranoid ideation	-	.297 (.048)
PDS - Number of trauma	-	.393 (.011)
PDS - Total stress	-	.380 (.017)
PDS - Intrusions	-	.388 (.013)
PDS - Emotional blunting	-	.354 (.025)
PDS - Neurovegetative symptoms	-	.426 (.006)

r: Pearson r correlation coefficient.

*24-h Systolic Blood Pressure adjusted for the level of adherence and the number of antihypertensive drugs. 24h-SBP: 24-h Systolic Blood Pressure; OCRHTN: patients with apparently treatment-resistant hypertension aged 60 or older and/or with a history of cardio- or cerebrovascular events. YURHTN: patients with apparently treatment-resistant hypertension without these characteristics.

Abbreviations: ED, Emergency Department; HTN, hypertension; CERQ, The Cognitive Emotion regulation Questionnaire; BSI, The Brief Symptom Inventory; PDS, Posttraumatic Diagnostic Scale.

3.7 | Regression analyses on severity of hypertension (based on 24-h systolic ABPM)

In the subset of younger ATRH patients without a history of vascular complication (YURHTN), among the fifteen variables initially included in the model to predict the severity of hypertension, two of them remained as independent predictors: the “planification” of the CERQ and the somatization subscale of the BSI. This final model accounted for 39.0% (adjusted R^2) of the variability in severity of hypertension (Table 4).

In the OCRHTN group, two variables (those which were significantly correlated) were initially included in the model and remained as predictors of severity of hypertension: the yearly number of admissions to the emergency department as well as the total number of drugs prescribed, jointly accounting for 35.0% (adjusted R^2) of the variability in severity of hypertension (Table 4).

Similar results were obtained when evaluation of severity of hypertension was based on 24-h diastolic BP, with the exception of the

TABLE 4 Multivariable regression with stepwise backward selection for prediction of the level of adherence and the severity of hypertension

OCRHTN N = 43	B	E.S.B.	β
Adherence			
1 st predictor – Number of visits in ED/year	–.259	.090	–.433 (.008)
2 nd predictor – CV event in the family	.199	.095	.316 (.045)
→ Explained 28.1 % of variability			
24h-SBP adjusted*			
1st predictor - Number of visits in ED/year	8.012	2.254	.529 (.001)
2nd predictor – Total number of drugs	.515	.266	.282 (.043)
→ Explained 35.0 % of variability			
24h-DBP adjusted*			
Predictor – Number of visits in ED/year	5.918	1.577	.565 (.001)
→ Explained 29.7% of variability			
YURHTN N = 54	B	E.S.B.	β
Adherence			
1 st predictor – CERQ Adaptive strategies	.013	.005	.371 (.014)
2 nd predictor – Female gender	–.319	.114	–.368 (.009)
3 rd predictor – HTN in the family	.264	.135	.278 (.049)
→ Explained 39.2 % of variability			
24h-SBP adjusted*			
1st predictor – CERQ Planification	–1.473	.457	–.434 (.003)
2nd predictor – BSI Somatization	4.039	1.406	.387 (.007)
→ Explained 39.0 % of variability			
24h-DBP adjusted*			
1st predictor – CERQ Planification	–1.032	.308	–.442 (.002)
2nd predictor – BSI Somatization	2.885	.946	.402 (.004)
→ Explained 41.6% of variability			

OCRHTN: patients with apparently treatment-resistant hypertension aged 60 or older and/or with a history of cardio- or cerebrovascular events. YURHTN: patients with apparently treatment-resistant hypertension without these characteristics; B: unstandardized beta coefficient; β : standardized beta coefficient (B value in standard deviation unit); ED: Emergency Department; CV: Cardiovascular; 24h-SBP: 24-h Systolic Blood Pressure; 24h-DBP: 24-h Diastolic Blood Pressure; CERQ: The Cognitive Emotion Regulation Questionnaire; HTN: Hypertension; BSI: The Brief Symptom Inventory.

*Blood pressure values adjusted for the level of adherence and the number of antihypertensive drugs.

number of drugs which was not an independent predictor of severity of hypertension in the OCRHTN group (Table 4).

4 | DISCUSSION

Compared to older and/or vascular patients with ATRH (OCRHTN): (i) younger patients without a history of vascular complication (YURHTN) were strikingly more often non-adherent; (ii) in this subset, both drug adherence and the severity of hypertension were correlated with previous trauma, PTSD as well as psychological factors such as anxiety, depression, obsessive-compulsive traits, somatization and altered expression of emotions, while none of these factors appeared to be involved in OCRHTN; (iii) in particular, poor adaptive strategies, lack of

planification in difficult life situations and tendency to somatize were strong, independent predictors of both poor drug adherence and the severity of hypertension only in the YURHTN subgroup (Figure 1). These results are in agreement with our previous findings in less selected groups of patients with ATRH, and their interpretation has been discussed elsewhere.^{12,13}

In contrast, in older patients or patients with a history of vascular complications, independent predictors of drug adherence and severity of hypertension were limited to the number of yearly admissions to the emergency room for hypertension, the number of prescribed drugs and, for drug adherence, a family history of cardiovascular events, the latter probably responsible for a better awareness of risk and thus an improved adherence to drug treatment (Figure 1).

Profiling of Patients with Apparently Treatment-Resistant Hypertension

<p>< 60 year-old with uncomplicated hypertension</p> <p>High probability of poor drug adherence</p> <p><i>Main predictor of poor drug adherence:</i> Poor ability to use adaptive strategies</p> <p><i>Main predictor of severity of hypertension:</i> Poor ability to planify Tendency to somatize</p> <p>Prioritize direct evaluation of drug adherence and psychological evaluation</p> <p>In addition to drug treatment, consider psychological interventions aiming at improving drug adherence, psychological well-being and blood pressure control*</p>	<p>≥ 60-year-old OR with a history of cardiovascular complication</p> <p>Usually satisfactory drug adherence</p> <p>No or little influence of psychological factors on degree of drug adherence or severity of hypertension. Few relevant predictors of either drug adherence or severity of hypertension</p> <p>Prioritize interventions aiming at decreasing arterial stiffness and vascular damage, likely to break the vicious circle of resistant hypertension*</p>
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* Not demonstrated by the current study, requires further investigation

FIGURE 1 Summary of the main findings of the study and tentative consequences for evaluation and management of patients with Apparently Treatment-Resistant Hypertension according to patient profile (younger patients with uncomplicated hypertension versus older patients / patients with a history of cardio- or cerebrovascular complication).

In view of these results, it would appear that poor drug adherence and psychological factors associated with both poor drug adherence and severity of hypertension are mostly involved in younger ATRH patients without a history of cardiovascular disease. In contrast, in older patients or in patients with a history of cardiovascular disease we hypothesize that drug resistance, at least at the time of inclusion was mostly related to increased arterial stiffness and vascular damage. Nevertheless, due to the cross-sectional nature of the study, we cannot exclude that a proportion of these patients were previously not adherent and became so only with time or after a cardiovascular complication occurred, often in association with adoption of a healthier lifestyle including losing weight and/or quitting smoking. It is also possible that psychological disorders secondary or not to an ancient trauma and subsequent PTSD played a role in the pathogenesis of hypertension and subsequent accumulation of vascular damage, eventually leading to drug resistance, but that these hidden features cannot easily resurface using simple auto-questionnaires. Besides its cross-sectional character, other limitations of our study include lack of direct assessment of arterial damage and relatively small sample size, limiting the ability to perform subgroup analysis.

Still, our results highlight the fact that young ATRH patients without cardiovascular complications should be prioritized for assessment of drug adherence as well as for psychological evaluation, irrespective of the degree of drug adherence. In these patients, a comprehensive management including adoption of healthier lifestyle, improvement of drug adherence and adequate psychological care may prevent transition to irreversible vascular damage and truly refractory hypertension (Figure 1).

The complex interrelation between trauma/PTSD, altered psychological profiles, unhealthy lifestyle, poor drug adherence and progressive arterial damage in the multistep process leading to ATRH, their temporal sequence and relative contribution in patients with different clinical presentations deserve to be further investigated in a larger, multicenter, longitudinal study incorporating direct measurement of drug adherence, regular assessment of target organ damage and arterial stiffness and psychological testing.

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CONFLICT OF INTEREST

None.

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