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Therapeutic concordance improves blood pressure control in patients with resistant hypertension

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Abstract

Introduction: An empathetic approach may be particularly useful in patients with therapy-resistant hypertension (TRH), defined as the failure to achieve target blood pressure (BP) despite a maximal doses of 3 antihypertensive drugs including a diuretic. However, the effects of therapeutic concordance have not been determined in hypertensive patients.

Methods: We designed a study to explore the impact of therapeutic concordance in patients with TRH, who were included in an intervention arm based on a protocol in which trained personnel periodically verified the pharmacological regimen of these patients.

Results: From a cohort of 5331 hypertensive patients followed-up for 77.64 ± 34.44 months, 886 subjects were found to have TRH; of these, 322 had apparent TRH (aTRH: uncontrolled office BP but optimal home BP) and 285 refused to participate in a second follow-up study,

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Conflict of interest

None.

CRediT authorship contribution statement

Valentina Trimarco: Conceptualization, Writing – original draft, Writing – review & editing. **Raffaele Izzo:** Data curation, Formal analysis. **Pasquale Mone:** Visualization, Methodology, Writing – original draft. **Maria Lembo:** Investigation, Visualization, Data curation. **Maria Virginia Manzi:** Investigation, Visualization, Data curation. **Daniela Pacella:** Formal analysis, Software, Data curation. **Angela Falco:** Investigation, Visualization. **Paola Gallo:** Investigation, Visualization. **Giovanni Esposito:** Visualization. **Carmine Morisco:** Visualization. **Gaetano Santulli:** Investigation, Visualization, Software, Writing – original draft, Writing – review & editing. **Bruno Trimarco:** Writing – original draft.

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yielding a population of 279 patients with true TRH (tTRH). These tTRH patients were followed according to the therapeutic concordance protocol for 91.91 ± 54.7 months, revealing that 210 patients (75.27%) remained with uncontrolled BP (uncontrolled tTRH, Group I) while 69 patients (24.73%) reached an optimal BP control (average BP <140/90 mmHg in at least 50% of follow-up visits, Group II). Strikingly, at the end of the second follow-up, the percentage of patients displaying a decline in kidney function was significantly smaller in Group II than in Group I (8.5% *vs* 23.4%, $p < 0.012$).

Conclusions: Taken together, our findings indicate for the first time that therapeutic concordance significantly improves the outcome of antihypertensive treatment in a population of patients with TRH.

Keywords

Adherence; Blood pressure; Concordance; EGFR; Hypertension; Pharmacologic resistance

1. Introduction

Although the process for the management of arterial hypertension appears overall simple (diagnosis, treatment, reduction of blood pressure (BP) leading to improved outcomes), in practice it is much more complex. To achieve a successful outcome, one key factor is represented by the patient's actual acceptance of the assigned treatment. This important aspect depends not only on the efficacy, side effects, and influences on quality of life of antihypertensive drugs, but also on other less well recognized, often overlooked factors. Recognition of and attention to these potential barriers to effective treatment should represent an integral part of the management of hypertension.

The factors that determine acceptance of treatment by the patient are multifaceted [1-3] and may not be fully reflected by the term "compliance," defined as acting in accordance with a desire or request, and implying that patients are simply acquiescing to their physician's instructions. The most recent terminology, *i.e.* "concordance," better describes the requirements for treatment acceptance and implies that all those involved are in agreement in trying to achieve treatment goals [1, 2,4-7].

Commonly perceived barriers to concordance include factors related to both the patient and the physician. Since hypertensive subjects often do not complain about specific symptoms, it is necessary for the patients to fully understand the relevance of the antihypertensive treatment which should be maintained life-long to improve cardiovascular (CV) prognosis [8-11]. Furthermore, side-effects, polypharmacy, lack of understanding of treatment targets, and limited patient involvement in treatment decisions represent other crucial issues that contribute to poor concordance [12-15]. Determinants of poor concordance also include poor clinic attendance records, erratic repeat prescription ordering, and complexity of treatment schedules [16,17].

Mounting evidence indicates that patients' beliefs are also important determinants of these processes (*e.g.* lack of patient insight into the illness, and lack of a genuine belief in the

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merits of preventive treatment); indeed, patients balance their reservations about taking medicines against reasons for taking them [18,19].

An approach described as therapeutic concordance places greater emphasis on the patient's perspective within collaborative relationships between patients and health professionals [20,21]. However, relatively little is known on the hypertensive patients' perspectives in terms of the management of their illness and their views on concordance. Since an empathetic approach to hypertensive patients with multiple comorbidities and polypharmacy may be particularly useful in patients with therapy-resistant hypertension (TRH), defined as the failure to achieve target BP when a patient is treated with maximal doses of 3 antihypertensive drugs including a diuretic [22], we designed a study to explore the impact of therapeutic concordance in TRH patients.

2. Methods

2.1. Study design and participants

The Campania Salute Network (CSN) is an open electronic registry, networking community hospital-based hypertension clinics and general practitioners from the Campania region in Southern Italy to the Hypertension Research Center of "*Federico II*" University Hospital in Naples (ClinicalTrials.gov Identifier: NCT02211365) [23-32]. Recruited subjects are referred to the Hypertension Research Center for CV imaging and possible refinement of diagnosis and treatment. The registry currently includes > 15,000 patients with hypertension. Detailed characteristics of this population have been previously reported [23].

Patients with uncontrolled office BP (≥140/90 mmHg) and home BP (>135/85 mmHg) despite prescription of three antihypertensive drugs including a diuretic, free of prevalent coronary heart disease (history of myocardial infarction, or coronary revascularization), were included in the true TRH group (tTRH); those with uncontrolled office BP but with optimal home BP (white coat effect) were included in the apparent (aTRH).

The tTRH patients were included in an intervention arm in which a trained pharmacist had primary responsibility for assessing the medical pharmacological history. Dedicated personnel reviewed the medication regimen of tTRH patients. Based on the potential interactions, the specialists suggested changes in therapy accordingly. Furthermore, physicians tried to reach a concordance with the patients so that they became more involved in the decision-making process, were better satisfied with the service they received, better informed about their condition and more inclined to co-operate in their management. Concordance therapeutic approach was reiterated at each follow-up visit, scheduled at six-month intervals. The total follow-up time was defined as the time from enrollment until incident CV event or death, loss to follow-up, or end of follow-up.

We excluded hypertensive patients with ascertained secondary hypertension, and patients showing conditions that may reduce life expectancy such as cancer, dementia, peripheral vascular disease, abdominal aortic aneurysm, and venous thrombosis (deep vein thrombosis and pulmonary embolism).

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2.2. CV risk factor and disease assessment

Demographic characteristics and relevant risk factors were obtained at enrollment, including age, sex, race, self-reported heart attack and stroke history, diabetes, and smoking habit. Body weight and height were measured as well, and body mass index (BMI) was calculated.

Documented CV disease was defined at the first examination in the outpatient clinic and included previous myocardial infarction, angina pectoris, coronary or carotid revascularization procedures, stroke, transitory ischemic attack, atrial fibrillation, or congestive heart failure.

Systolic and diastolic BP were measured after 5 min resting in the sitting position, 3 times at 1–minute interval, according to current guidelines and standard procedures of CSN Registry [33]. Auscultatory or oscillometric semiautomatic sphygmomanometers attended by physicians were used and validated periodically according to standardized protocols [34], using cuffs of appropriate size [31,34]. The average of the 2 last measurements was taken as the office BP. Peripheral pulse pressure was calculated as systolic BP minus diastolic BP.

All patients were also invited to measure their BP at home (HBP) using validated device and according to current guidelines [33]. Patients were trained on BP measurement at home. All patients were invited to provide a validated device based on the list available at https://www.stridebp.org/. Written instructions and a self-recording sheet were provided to ensure adequate pressure monitoring. Data included 2 HBP measurements (approximately at 7 AM and 7 PM), over a period of 7 days before the scheduled visit, with a minimum interval of 1 min between measurements, and excluding the first measurement in each case. At each visit, HBP data were recorded if validated device was used.

According to our standard criterion, follow-up BP was considered optimally controlled when the average OBP values during follow-up visits was < 140/90 mmHg. Follow-up HBP was considered optimally controlled when the average HBP self-reported value was < 135/85 mmHg [33,35]. Isolated systolic hypertension was defined as systolic BP > 140 mmHg and diastolic BP < 90 mmHg; obesity was defined as a BMI ≥ 30 kg/m^2; fasting glucose and lipid profile were measured by standard methods; diabetes was defined as history of diabetes, use of any antidiabetic medication, or presence of a fasting blood glucose ≥ 126 mg/dL, confirmed on 2 different occasions [36-39]. Estimation of creatinine clearance (estimated glomerular filtration rate) was done using Chronic Kidney Disease Epidemiology Collaboration equation, as previously reported [40].

2.3. Cardiac and vascular ultrasound analysis

Echocardiograms were performed using commercially available phased-array machines following standardized protocols [30,31]. LV hypertrophy was identified by prognostically validated sex-specific cutoff values for LV mass/height: > 47 g/$m^{2.7}$ in women and > 50 g/$m^{2.7}$ in men. LV end-diastolic dimension was ratiometrically normalized by height. Relative wall thickness was calculated as the ratio between posterior wall thickness and LV internal radius at end diastole and considered increased if ≥ 0.43 [31,41].

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Carotid ultrasonography was performed using a commercially available ultrasound scanner equipped with a 7.5–MHz high-resolution transducer, following a previously published standardized protocol [31]. The maximal carotid intima-media thickness (IMT) was estimated offline in up to 12 arterial walls, including the right and the left, near and far distal common carotid (1 cm), bifurcation and proximal internal carotid artery. According to previous studies, increased IMT was defined as IMT > 0.9 mm and carotid plaque as a localized IMT ≥ 1.5 mm [30, 31,42],

2.4. Glomerular Filtration Rate (GFR)

GFR was measured by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [43]. GFR was measured both at baseline and at the time of the last available visit. GFR decline was defined, as recently suggested [44], by a ≥ 30% decrease in GFR from the initial value for patients in Stage III CKD at baseline or by a composite of achieved decrease ≥ 30% from baseline and a final value < 60 in patients with baseline GFR ≥ 60 ml/min/1.73 m^2.

2.5. Study endpoints

The primary endpoint was to evaluate whether by using a therapeutic concordance approach a satisfactory BP control could be obtained in TRH patients. Secondary endpoints were: the percentage of hypertensive “difficult-to-control” patients (achieving BP control with the administration of more than three drugs [45,46]); the time course of target organ damage, defined by reduction in LVMha, carotid IMT, and GFR decline [47]; the incidence of major adverse CV events (MACE). The null hypothesis was rejected at a two-tailed $p < 0.05$.

2.6. Ethical aspects

The ”*Federico II*“ University Hospital Ethics Committee approved the database generation of the CSN Registry. All participants signed a written informed consent.

2.7. Statistical analysis

Data were analyzed by SPSS (version 26.0; SPSS, IBM, Armonk, USA) and by the open software jamovi (version 2.3.16.0) and expressed as mean±SD or numbers and percentage, as appropriate. The χ^2 distribution was used to compare categorical variables, with Monte Carlo simulation to obtain exact p values. Binary logistic regression was applied to isolate independent predictors of incident GFR decline using backward stepwise selection of main potential confounders including age, gender and BP. The null hypothesis was rejected at a two-tailed $p < 0.05$.

3. Results

Starting from an initial cohort of 5331 hypertensive patients included in the CSN with ascertained home BP measurements, free of prevalent coronary heart disease (history of myocardial infarction, or coronary revascularization), we excluded hypertensive patients with a confirmed diagnosis of secondary hypertension and subjects with a follow-up < 12 months, and selected a population of 4943 patients who were monitored for 77.64 ± 34.44 months. At the end of this first followup period we found that 4057 patients did not have

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TRH, and 322 had aTRH (uncontrolled office BP but with optimal home BP, white coat effect).

Thus, we had a population of 564 tTRH patients with uncontrolled office BP (≥140/90 mmHg) and home BP (>135/85 mmHg) despite treatment with maximal dose of at least 3 antihypertensive drugs including a diuretic. Two hundred and eighty-five out of these 564 patients did not accept the proposal of new clinical approach; hence, the final population of the present study included 279 tTRH patients who had failed to show any statistically significant change in systolic (150.8 ± 18.0 *vs* 150.4 ± 20.0 mmHg, n.s.) and diastolic (82.0 ± 11.0 *vs* 83.4 ± 11.0 mmHg, n.s.) BP during the first follow-up period (Fig. 1). These tTRH patients were followed according to the therapeutic concordance protocol for a second follow-up period of 91.91 ± 54.7 months. The baseline clinical characteristics of this study population are shown in Table 1.

At the end of this second follow-up, 210 patients (75.27%) remained uncontrolled (uncontrolled tTRH, Group I) while 69 patients (24.73%) reached an optimal BP control (average BP <140/90 mmHg in at least 50% of follow-up visits, Group II). Of these patients, 27 (9.96%) obtained BP control with no more than 3 antihypertensive drugs, including diuretic at full doses. Forty-two (15.0%) patients who required more than 3 antihypertensive drugs to obtain a satisfactory BP control were considered subjects with difficult-to-control tTRH. Baseline characteristics of uncontrolled and controlled groups are reported in Table 2, which shows that the only statistically significant differences between the two groups were BP values, since systolic, diastolic, and pulse pressure were significantly higher in Group I (uncontrolled resistant hypertension) as compared to Group II (27 no longer tTRH and 42 difficult-to-control tTRH).

At the end of the second follow-up, Group I, despite the use of a larger number of antihypertensive drugs compared to Group II, did not show any reduction in systolic, diastolic, and pulse pressure, while in Group II we observed significant reductions in all these parameters.

No significant differences between our groups were detected in terms of changes in LVMha, carotid IMT, and prevalence of CV events. Nevertheless, at the end of follow-up the percentage of Group II patients displaying a GFR decline was significantly smaller than the one observed in Group I (8.5% *vs* 23.4%, $p < 0.012$). As a consequence, at the end of the follow-up there was a significant difference in GFR between the 2 groups (Group I: 73.39 ± 17.3 ml/min/1.73 m^2, Group II: 78.53 ± 13.71 ml/min/m^2, $p < 0.025$). A multivariable logistic regression analysis performed to define the determinants of GFR reduction revealed that the age of patients played a pivotal role but pulse pressure was also involved (Table 3). Specifically, we found an inverse correlation between GFR and pulse pressure (Fig. 2) which further corroborates the relevance of BP in improving kidney prognosis of hypertensive patients.

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4. Discussion

The main finding of our study is the observation that therapeutic concordance is particularly useful in improving the outcome of antihypertensive treatment in a general population of tTRH outpatients.

The objective of this clinical approach is to transform the patient from a mere passive receiver to an informed active participant who plays an unambiguous role in the entire treatment process [48]. A qualitative study conducted by Weiss and colleagues [49] examined the implementation of decision analysis to facilitate the involvement of patients in decisions about their healthcare, and reported that only a few newly diagnosed hypertensive patients felt they were able to discuss issues with their doctor, and that most felt the physician did not have enough time. Barriers in consultations and decision-making have been reported by both physicians and patients [50,51], albeit more recent findings suggest that health professionals should be aware of the potential impact of patients' feelings of guilt on consultations relating to the asymptomatic disease of hypertension [52,53].

TRH is defined as the failure to achieve target BP when a patient is treated with maximal doses of 3 antihypertensive drugs including a diuretic. TRH is not equivalent to uncontrolled hypertension, as patients with TRH might achieve target BP with full doses of 4 or more medications [22,54].

The observations that tTRH is a common clinical condition among hypertensive outpatients without established atherothrombosis and that prevalence of tTRH increases with age and comorbidities [55] prompted us to explore the possibility that poor concordance with antihypertensive treatment, a well-recognized cause of inadequate BP control [56], could account for this phenomenon, at least partially. The results of our study support this hypothesis by showing a reduction in BP in 27 patients, who were no longer considered to be tTRH. Furthermore, by using this clinical approach we obtained a satisfactory BP control also in tTRH patients who had failed to satisfactorily respond to more than 3 antihypertensive drugs during the first follow-up, so therapeutic concordance allowed to reach a satisfactory BP control in 1 of 4 individuals previously defined as uncontrolled tTRH patients.

We further investigated the effects of this reduction in BP on the prognosis of these patients by assessing the prevalence of CV events and changes in target organ damage during the ~6-year follow-up. The lack of difference in CV events is not surprising considering the small number of events recorded in our high-risk population (31 CV events during more than 1500 patient-years of follow-up), which suggest an optimal control of other risk factors. Similarly, we did not observe any difference in the time course of cardiac and vascular target organ, while the control of BP was associated with a significant slowing in the progression of renal impairment. This phenomenon resulted to be associated with age, female sex, and pulse pressure. Pulse pressure is a surrogate marker of arterial stiffness and has been implicated in the early deterioration of renal function in diabetic patients [57,58]. Our results do not allow any inference on the pathophysiological mechanism underlying the association between pulse pressure and GFR decline. Still, a positive association between higher pulse

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pressure and worsening albuminuria was demonstrated in an earlier study in diabetic patients [59]. More recently, in a cohort of subjects with type 2 diabetes and preserved renal function at baseline, higher pulse pressure and pulse wave velocity in quartile distribution were shown to be positively associated with CKD progression regardless of demographic and clinical characteristics [60]. These Authors speculated that renal microvasculature renders the kidneys vulnerable to damage during pulse pressure elevation as glomerular capillaries are situated between the arterioles that bring blood to and from the glomerulus [61-63]. The renal adaptive mechanism, which is mediated by tubule-glomerular feedback and reactance to changes in BP in afferent arterioles [64], is disrupted by exposure to increased pulse pressure over prolonged periods [61-63]. Chronic elevation of pulse pressure might lead to transmission of pulsatile energy to the micro-vasculature [65]. This event in turn contributes to the remodeling of renal microvasculature and damage to the glomeruli [66,67]. The mediation analysis performed by Low and collaborators [60] suggested that increasing albuminuria, a well-established marker of renal damage [68], plays a central role in the direct correlation between increasing peripheral pulse pressure and CKD progression, since there is an earlier finding of pulse pressure > 60 mmHg being associated with deteriorating albuminuria [59]. A recent review by Butt and co-workers [69] explains the relationship between the force which compresses the capillary wall and injury to the glomerular filtration barrier, eventually leading to albuminuria. Furthermore, glomerular leakage of albumin triggers proinflammatory and pro-fibrotic responses, which in turn lead to tubulo-interstitial injury [70].

The major strength of our study is the availability of a prospectively recruited large population with an exceptionally detailed information on the individual clinical conditions derived by medical record reviews followed for many years. The main limitation of our study is the lack of a contemporary control group with a comparable duration of follow-up, which would have corroborated the conclusion that the improvement in BP control is entirely due to the concordance approach. However, as specified in the results section, our study population derives from a group of patients followed for more than 6 years with the traditional approach; in particular, the observation that 269 subjects had failed to obtain a satisfactory BP control in the first follow-up allows us to consider them as an ideal control group in a crossover study protocol.

In summary, our results demonstrate that an appropriate choice of antihypertensive agents and an active involvement of the patient in the treatment of hypertension is extremely useful in a population in which the achievement of normal BP levels is particularly tough, since it allows to reach a satisfactory BP control in ~25% of patients previously defined as uncontrolled tTRH hypertensives. Furthermore, this kind of hemodynamic response is able to significantly reduce the progression of hypertensive disease.

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Data Availability

Data will be made available upon reasonable request to the First Author(s).

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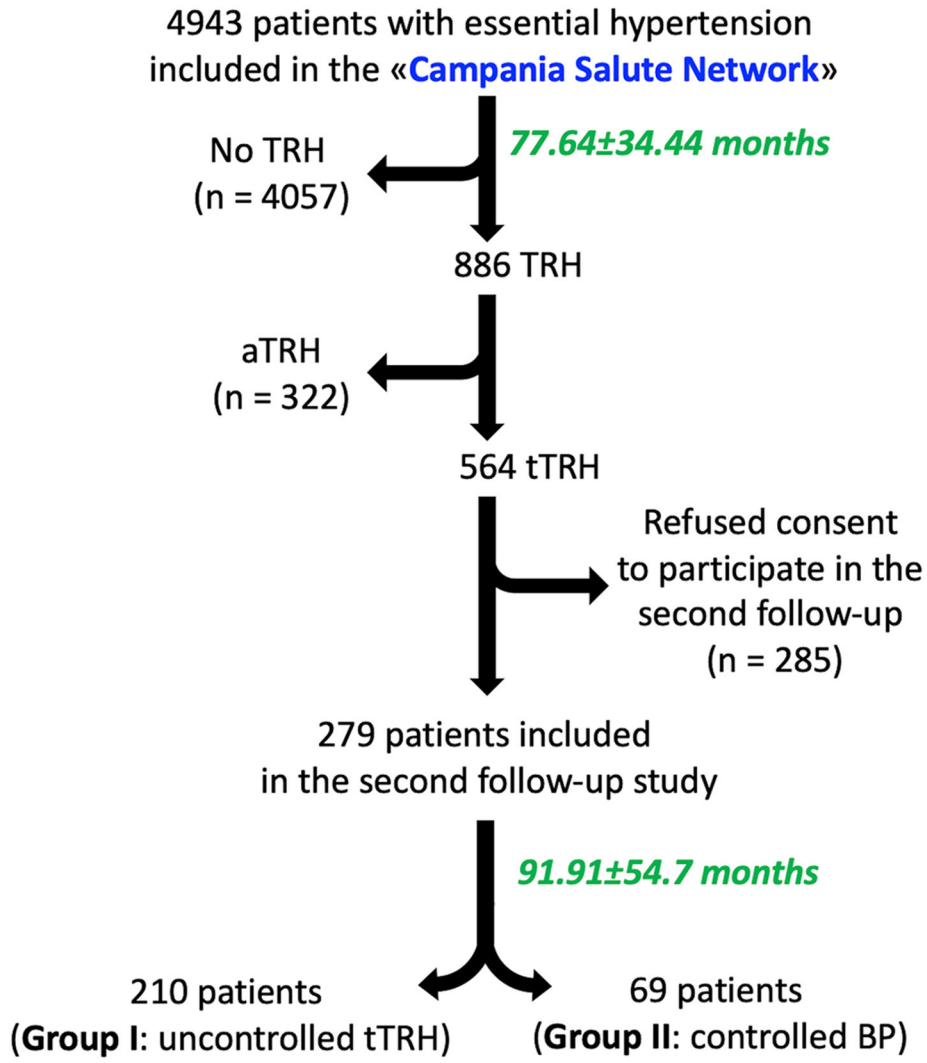

Fig. 1.

Flowchart of the study. TRH: therapy-resistant hypertension; aTRH: apparent therapy-resistant hypertension; BP: blood pressure; tTRH: true therapy-resistant hypertension.

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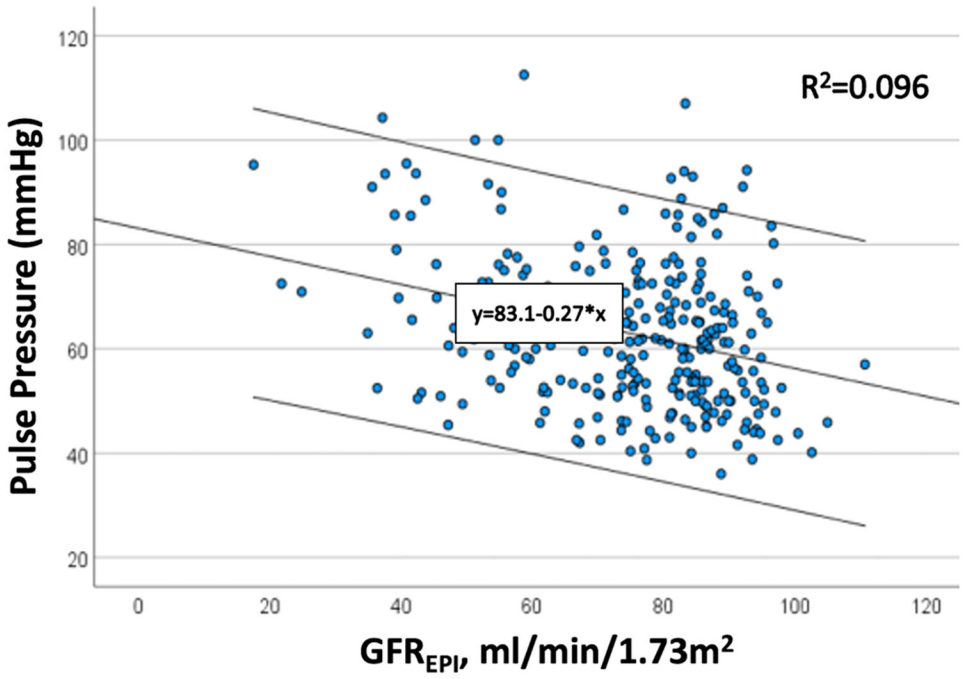

Fig. 2. Inverse correlation between pulse pressure and kidney function.

GFR_{EPI}: glomerular filtration rate measured by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

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Table 1

Main characteristics of our population.

Variable	value
N	279
Age, year, mean, SD	55.02 ± 10.29
Female sex, n (%)	112 (39.9)
Current smoker, n (%)	138 (49.1)
Diabetes, n (%)	65 (23.1)
SBP, mmHg, mean, SD	150.81 ± 18.02
DBP, mmHg, mean, SD	81.99 ± 10.64
HR, bpm, mean, SD	71.28 ± 11.91
Pulse pressure, mmHg, mean, SD	68.82 ± 16.67
IMT MAX, mm, mean, SD	1.72 ± 0.75
LVMha, $g/m^{2.7}$, mean, SD	52.76 ± 9.50
Glycemia, mg/dl, mean, SD	103.27 ± 24.14
Creatinine, mg/dl, mean, SD	0.98 ± 0.20
GFR_{EPI}, ml/min/1.73 m^2, mean, SD	87.20 ± 13.95
Uric acid, mg/dl, mean, SD	5.50 ± 1.48
Triglycerides, mg/dl, mean, SD	142.90 ± 75.37
Total cholesterol, mg/dl, mean, SD	207.55 ± 40.30
HDL cholesterol, mg/dl, mean, SD	49.27 ± 12.64
Serum potassium, mg/dl, mean, SD	4.30 ± 0.44
Year of hypertension, mean, SD	8.68 ± 7.91
Number of hypertension drugs, mean, SD	4.16 ± 1.04
Follow-up, year, mean, SD	6.47 ± 2.87

SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; GFR_{EPI}= glomerular filtration rate measured by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation; HR= Heart Rate; IMT= Intima media Thickness; LVMha= Left Ventricular Mass height-adjusted

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Table 2

Main characteristics of our two groups of patients.

Variables	GROUP I - Uncontrolled resistant hypertension (N = 210)	GROUP II - Controlled resistant hypertension (N = 69)	p value
Age, year, mean, SD	55.01 ± 9.96	55.08 ± 11.38	0.962
Female, n (%)	91 (42.9)	21 (30.4)	0.066
Current smoker, n (%)	105 (49.5)	33 (47.8)	0.806
Diabetes, n(%)	49 (23.1)	16 (23.2)	0.990
BMI, kg/cm^2, mean, SD	28.50 ± 3.98	27.93 ± 3.82	0.311
Glycemia, mg/dl, mean, SD	103.86 ± 24.7	101.51 ± 22.51	0.503
Creatinine, mg/dl, mean, SD	0.98 ± 0.20	0.98 ± 0.21	0.985
GFR_{EPI}, ml/min/1.73 m^2, mean, SD	86.73 ± 13.92	88.60 ± 14.08	0.376
Uric acid, mg/dl, mean, SD	5.52 ± 1.53	5.46 ± 1.29	0.840
Triglycerides, mg/dl, mean, SD	144.25 ± 70.18	138.62 ± 90.49	0.621
Total cholesterol, mg/dl, mean, SD	208.71 ± 39.86	203.85 ± 41.79	0.420
HDL cholesterol, mg/dl, mean, SD	49.05 ± 13.14	49.91 ± 11.15	0.705
Serum potassium, mEq/L, mean, SD	4.33 ± 0.44	4.24 ± 0.43	0.207
SBP at first visit, mmHg, mean, SD	152.79 ± 17.91	144.29 ± 16.70	0.001
DBP at first visit, mmHg, mean, SD	82.81 ± 10.35	78.93 ± 10.22	0.007
HR, bpm, mean, SD	71.90 ± 11.73	69.23 ± 12.35	0.110
SBP at last visit, mmHg, mean, SD	151.59 ± 15.19	130.06 ± 6.58	< 0.0001
DBP at last visit, mmHg, mean, SD	85.16 ± 9.33	77.41 ± 6.79	< 0.0001
Pulse pressure at first visit, mmHg, mean, SD	69.98 ± 17.16	65.36 ± 14.74	0.046
Pulse pressure at last visit, mmHg, mean, SD	66.42 ± 14.54	52.64 ± 7.38	< 0.0001
Year of hypertension, mean, SD	8.90 ± 7.99	8.06 ± 7.69	0.463
Number of visits, mean, SD	20.54 ± 10.63	19.75 ± 9.15	0.592
Total therapy, number of drugs, mean, SD	3.56 ± 0.67	3.61 ± 0.60	0.601
Number of antihypertensive drugs at last visit, mean, SD	4.25 ± 1.04	2.90 ± 1.00	0.016
Follow-up years, mean, SD	6.47 ± 2.78	6.44 ± 3.15	0.932
CV events, n (%)	24 (11.3)	9 (13)	0.699
LVMha at first visit, g/m$^{2.7}$, mean, SD	53.15 ± 9.67	51.12 ± 8.12	0.117
LVMha at last visit, g/m$^{2.7}$, mean, SD	52.99 ± 13.31	49.58 ± 9.17	0.049
IMT max at first visit, mm, mean, SD	1.74 ± 0.75	1.66 ± 0.74	0.453
IMT max at last visit, mm, mean, SD	2.22 ± 0.83	2.12 ± 0.85	0.405
Creatinine at last visit, mg/dl, mean, SD	1.09 ± 0.46	0.98 ± 0.25	0.050
Delta GFR_{EPI}	−15.67 ± 20.83	−9.16 ± 15.36	0.028
Delta Pulse Pressure	−3.56 ± 14.20	−12.72 ± 14.28	< 0.0001

BMI= Body Mass Index; SBP= Systolic Blood Pressure; DBP= Diastolic Blood Pressure; GFREPI= glomerular filtration rate measured by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation; HR= Heart Rate; IMT= Intima media Thickness; LVMha= Left Ventricular Mass height-adjusted

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Table 3

Determinants of GFR_{EPI} reduction of at least 30%.

Variables	OR (C.I.)	p value
Age (years)	1.04 (1.00–1.08)	0.052
Female sex	0.39 (0.19–0.82)	0.013
Pulse pressure (x 5 mmHg)	1.25 (1.10–1.39)	0.001