

Resistant: hypertension, patient, or physician?

Zbigniew Gaciong

Department of Internal Medicine, Hypertension and Vascular Diseases, Medical University of Warsaw, Warsaw, Poland

Numerous treated hypertensive patients remain at a higher risk for adverse cardiovascular events because they do not reach the target blood pressure (BP) of less than 140/90 mmHg. In some patients with uncontrolled hypertension, resistant hypertension (RHT) can be diagnosed. In the recent guidelines, RHT has been arbitrarily defined as BP levels that remain above the goal despite the patient being prescribed 3 or more antihypertensive medications, or requiring 4 or more drugs to control their BP. The treatment should include a diuretic, all agents should be administered at optimal doses (ie, 50% or more of the maximum recommended antihypertensive dose), and the antihypertensive regimen should be given at an adequate time to be effective.¹

Why high blood pressure cannot be controlled?

A substantial number of patients present with uncontrolled hypertension that appears to be resistant to treatment but actually may be related to other factors. There are 5 most common causes of pseudoresistance, the first being an inaccurate measurement of blood pressure (ie, use of an inappropriately small blood pressure cuff in obese patients with a large arm circumference).

Another cause is poor adherence to antihypertensive therapy, which is very difficult to identify because the information provided by a patient may be misleading. Unfortunately, there are no reliable, easy-to-use, and economical methods to assess drug adherence in clinical practice. Specific self-report questionnaires (eg, the 8-item Morisky Medication Adherence Scale), pharmacy refill data, pill counts, and electronic monitoring are subject to many uncertainties and easy manipulation by patients.^{2,3} Even direct measurements of prescribed medications in plasma or urine may be affected by the so called white-coat adherence phenomenon wherein patients tend to improve their adherence before and after clinical visits. Also, many commonly used drugs have pharmacokinetics and pharmacodynamics that provide “therapeutic” levels after the ingestion of 1 to 2 doses.³ However, in 208 patients referred to a tertiary center for the diagnosis and treatment

of RHT when their urine was screened for antihypertensive drugs using liquid chromatography and mass spectrometry, 10% of them were found to be completely nonadherent and 15%—partially nonadherent.⁴ A similar analysis was done in 36 Polish patients with RHT, using a direct measurement of the plasma levels of prescribed medications. Nonadherence (complete or partial) was observed in 31 patients (86%).⁵

In the general population of hypertensive patients, the rate of nonadherence is also high. Data from electronic health records and pharmacy registries show that during the first year of treatment, about 50% of the patients stop taking medications (nonpersistence), while those who remain on therapy take around 75% of prescribed medications (noncompliance).³ However, the assessment based on the results of studies on adherence may be overestimated owing to a selection bias (nonenrollment of nonadherent subjects) and the observer effect (also known as the Hawthorne effect), which refers to better adherence in subjects who are aware of being observed.⁶

As it can be expected, patients with better adherence have better BP control and a lower risk of cardiovascular complications.⁷ However, it is difficult to conclude that this is exclusively due to high rates of medications taken. In the CHARM study,⁸ which included 7599 subjects with chronic heart failure treated with angiotensin receptor blocker (candesartan) or placebo, good adherence was associated with lower all-cause mortality independently of treatment assignment. The finding that adherence even to placebo was strongly related to outcome suggests the existence of “adherent personality”, which by itself is associated with better prognosis.⁸

The third common cause of pseudoresistance is ineffective nonpharmacological treatment. The lack of appropriate lifestyle modifications (reduction in sodium intake, body weight control, and increased physical activity) is common among hypertensive patients and is associated with a decreased response to BP-lowering drugs. It should be noted that it frequently occurs with nonadherence to medical therapy.⁹

Correspondence to:
 Prof. Zbigniew Gaciong, MD,
 PhD, Katedra i Klinika Chorób
 Wewnętrznych, Nadciśnienia
 Tętniczego i Angiologii, Warszawski
 Uniwersytet Medyczny,
 ul. Banacha 1a, 02-097 Warszawa,
 Poland, phone: +48-22-599-28-28,
 fax: +48-22-599-18-28, e-mail:
 zgaciong@hotmail.com
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The fourth cause is suboptimal antihypertensive therapy (therapeutic inertia). Physician inertia (ie, the lack of therapeutic action when the patient's BP is uncontrolled) is generated by several factors including doubts about the risk represented by high BP (particularly in elderly patients), fear of a reduction in vital organ perfusion when BP is reduced (the J-curve phenomenon), and concern about side effects. Several physicians also maintain a sceptical attitude towards guidelines because of their multiplicity and origin from different sources (international and national scientific societies, governmental agencies, local hospitals, etc.), which sometimes makes their recommendations inconsistent. Guidelines are frequently perceived as unrealistic when applied to the environment where physicians operate.

Therapeutic inertia may significantly contribute to the lack of hypertension control. In a large group of 468 877 patients from community-based practices, apparent RHT was detected in 44 684 subjects (9.5%); however, only half of them (22 189 patients) received optimal antihypertensive therapy.¹⁰

Therapeutic inertia may be also dangerous. A study by Xu et al.¹¹ suggested that waiting more than 1.4 months before intensifying antihypertensive therapy could increase the risk for a composite of cardiovascular events or death.

Finally, the fifth cause is so called white coat hypertension, a phenomenon wherein office BP levels may be substantially higher than BP during normal daily activities. In cross-sectional studies, the prevalence of white coat hypertension ranges from 10% to more than 20% and appears to be higher in children and elderly patients. Office BP measurements taken by a nurse or technician rather than a physician may minimize the white coat effect. To estimate the effect of the white coat reaction on office BP readings, out-of-office measurements (ambulatory or home monitoring) are necessary. In subjects with an office diastolic BP of 105 mmHg or higher, the probability of normal ambulatory BP is low (less than 5%) but such patients may still have the white coat effect that underestimates the efficacy of therapy. For example, in a study of 500 treated hypertensive patients (over 60% met the criteria for RHT), 37% had normal BP on ambulatory BP monitoring (ABPM).¹²

Apparent, true, pseudoresistant, or refractory hypertension? Patients with uncontrolled hypertension may have apparent resistance attributed to white coat hypertension, improper BP measurement, medication nonadherence, or suboptimal treatment regimens (therapeutic inertia). Therefore, they do not have true RHT but so called pseudoresistant hypertension, which can be excluded by ABPM, the evaluation of the therapeutic regimen, and confirmation of medication adherence.

True RHT can be diagnosed only in patients with an office BP level of more than 140/90

mmHg despite being compliant with an appropriate antihypertensive regimen and who also have uncontrolled BP confirmed by ABPM. The current European Society of Hypertension / European Society of Cardiology guidelines have introduced the definition of hypertension based on out-of-office BP measurement assessed by ABPM or home BP monitoring, which offers a more reliable assessment of actual BP than office BP.¹ Therefore, to confirm true resistance, a detailed clinical analysis is required with an obligatory BP measurement using ABPM.

Refractory hypertension can be diagnosed in patients with RHT, in whom BP cannot be controlled, even with maximal medical therapy under the care of a hypertension specialist. In a cohort of 304 patients referred to a specialized hypertension clinic for the management of RHT, refractory hypertension was diagnosed in 29 subjects. The authors suggested that sympathetic overactivity may explain treatment failure but they did not exclude other causes such as noncompliance.¹³

What can we tell from the results of the Pol-Fokus study?

The Pol-Fokus study¹⁴ is the largest multicenter study on the prevalence of RHT in Poland, in patients under the care of family physicians and specialists. A similar analysis from other countries included a substantially lower number of patients.¹⁵ The data from Pol-Fokus provide an important insight not only into epidemiology but also the risk factors for RHT. They confirm earlier prospective observations from the ASCOT-BPLA trial¹⁶ on the association between RHT and older age, obesity, diabetes, and impaired renal function. Patients with RHT typically have increased peripheral vascular resistance and volume expansion in the presence of normal cardiac output.^{17,18} In the Pol-Fokus study,¹⁴ RHT was also associated with increased pulse pressure (difference between systolic and diastolic BP), which suggests the role of diffuse stiffening of large arteries (arteriosclerosis). However, it should be noted that systolic hypertension is more difficult to control. In the ALLHAT trial of over 33 000 hypertensive patients treated with different antihypertensive drugs, only 67% of the participants reached a systolic BP below 140 mmHg, whereas 92% attained a diastolic BP below 90 mmHg.¹⁹

The ingestion of substances that can elevate BP or interfere with antihypertensive medications may be responsible for some cases of uncontrolled hypertension. In Pol-Fokus,¹⁴ the use of nonsteroidal anti-inflammatory drugs was associated with RHT.

The results from Pol-Fokus¹⁴ demonstrate the potential role of therapeutic inertia in RHT. The authors did not provide information on average drug doses or modification of treatment in patients with uncontrolled hypertension but one should notice a high percentage of subjects still receiving thiazide diuretics despite an estimated glomerular filtration rate of less than 30 ml/min/1.73 m². The prevalence of RHT was

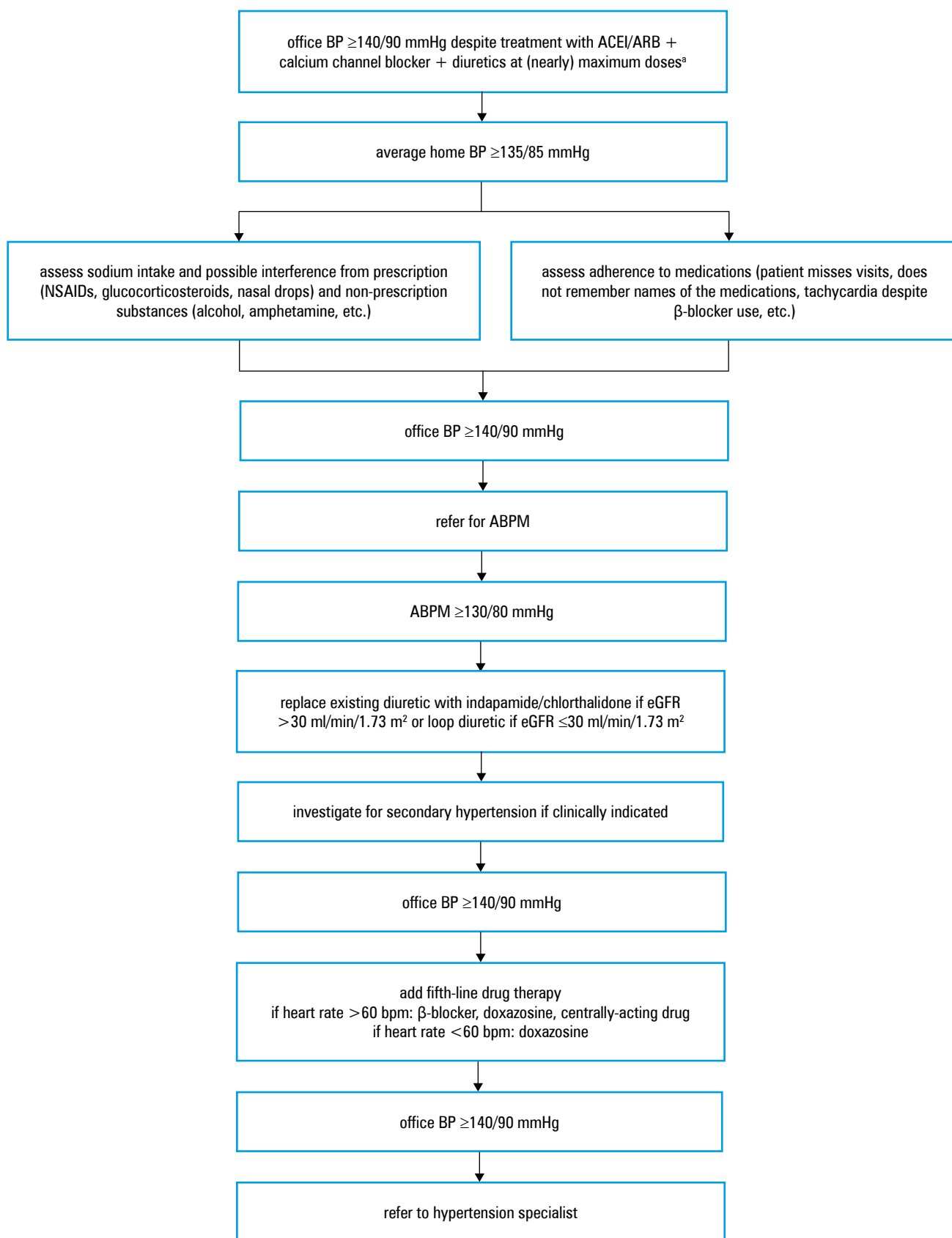


FIGURE Algorithm for the management of resistant hypertension²⁸

a indications for certain classes depend on concomitant diseases according to the European Society of Hypertension / European Society of Cardiology guidelines

Abbreviations: ABPM, ambulatory blood pressure monitoring; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate

lower in primary care, which may be explained by the fact that difficult-to-treat patients with concomitant diseases were typically referred to specialists. However, the presence of cardiovascular complications or diabetes increases the probability of therapeutic inertia (lack of therapeutic action) during a visit.²⁰ This association was also confirmed in the analysis of data from the Pol-Fokus study,¹⁴ which may reflect the resistance of Pol-Fokus physicians to intensify treatment in high-risk groups. The underuse of certain classes of medications such as aldosterone antagonists (14.7%), α -adrenergic antagonists (4.8%), and calcium channel blockers (53.6%) may be another symptom of therapeutic inertia.

What cannot we tell from the results of the Pol-Fokus study?

Prejbisz et al.¹⁴ detected a relatively high rate of subjects with resistant hypertension (24.7%) but because the office measurements were not verified with ABPM all these subjects should be labelled as “apparent resistant”. A similar study²¹ (BP-CARE, Blood Pressure Control rate and Cardiovascular Risk Profile), including 1312 subjects from Central and Eastern Europe (Poland excluded) found 423 patients (32.2%) with apparent RHT, of whom 255 (19.4%) had true RHT based on the definition in ABPM (>130/80 mmHg). These rates are higher than those reported by others using electronic health records²² or pooling data from different sources.²³ Data from the NATPOL 2011 study,²⁴ which comprised a representative sample of 2400 Polish residents aged from 18 to 79 years, showed that 10% of hypertensive patients had uncontrolled BP despite the use of at least 3 antihypertensive medications (a diuretic included). The resistance was not confirmed with ABPM but BP values were derived from office measurements taken on 2 separate visits (Zdrojewski T, personal communication).

Interestingly, data from Pol-Fokus¹⁴ presented substantial regional variations (from 17.3% up to 30%) in BP control in Poland, which seems unexpected in a country with public health care system. It is difficult to identify a common cause for these differences, but one may suggest the role of financial disparities. However, the mean prevalence of RHT does not differ significantly between the provinces with a per capita income above and below the country median (22.8% and 23.7%, respectively; data available on request). It should be noted that from the initial group of 2000 physicians, only 1265 (63.2%) agreed to participate in the study, and numerous physicians did not provide all requested data. The recruitment protocol of patients into the study may also introduce a certain selection bias because it included only subjects treated for at least 1 year, which prefers patients with higher BP values.

Also, Prejbisz et al.¹⁴ did not mention whether the proportion of specialists to family physicians was similar in each part of the country, which might explain regional variations.

How should we manage patients with resistant hypertension?

RHT is not a separate disease entity but represents an advanced stage in the natural history of hypertension. BP control from the beginning of treatment not only reduces the risk of future complications but also inhibits progression of hypertension, probably by preventing the development of subclinical lesions sustaining increased BP. This was directly demonstrated in the TROPHY trial,²⁵ in which pharmacological treatment of prehypertension prevented the development of stage 1 hypertension. The benefits of good BP control are far-reaching (legacy effect), which was documented during a remote observation of the original cohort of patients who participated in the SHEP trial.²⁶ Subjects who were receiving active treatment during 4.5 years of the study had longer life expectancy, as compared with patients initially randomized to placebo. This difference remained significant after 22 years since the end of the trial, when all participants were advised to receive active therapy.²⁶

RHT is not synonymous with uncontrolled hypertension since RHT is not the only cause of uncontrolled hypertension. Other causes include inadequate BP assessment (white coat effect) or suboptimal treatment regimens (resistant physician) and pseudoresistance due to nonadherence (resistant patient). Despite improvements in BP control, hypertension-related mortality continues to increase.²⁷ The detection of removable causes of RHT, accurate measurement of BP, and an optimal treatment strategy with good patients' adherence should allow to control BP in more than 90% of primary care patients (FIGURE).²⁸ In case of failure, one should consider referral to a hypertension specialist.

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