

Factors affecting adherence to antihypertensive medication in Greece: results from a qualitative study

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Introduction: Although hypertension constitutes a major risk factor for cardiovascular morbidity and mortality, research on adherence to antihypertensive treatment has shown that at least 75% of patients are not adherent because of the combined demographic, organizational, psychological, and disease- and medication-related factors. This study aimed to elicit hypertensive patients' beliefs on hypertension and antihypertensive treatment, and their role to adherence.

Methods: Transcripts from semistructured interviews and focus groups were content analyzed to extract participants' beliefs about hypertension and antihypertensive treatment, and attitudes toward patient–physician and patient–pharmacist relationships.

Results: Hypertension was considered a very serious disease, responsible for stroke and myocardial infarction. Participants expressed concerns regarding the use of medicines and the adverse drug reactions. Previous experience with hypertension, fear of complications, systematic disease management, acceptance of hypertension as a chronic disease, incorporation of the role of the patient and a more personal relationship with the doctor facilitated adherence to the treatment. On the other hand, some patients discontinued treatment when they believed that they had controlled their blood pressure.

Conclusion: Cognitive and communication factors affect medication adherence. Results could be used to develop intervention techniques to improve medication adherence.

Keywords: hypertension, medication adherence, patient compliance, doctor–patient communication, antihypertensive medicine

Introduction

Nonadherence to treatment medication, especially in chronic diseases, is a complicated issue affecting patients' health, health expenditure, and recourses' utilization.^{1,2} A number of studies, both qualitative and quantitative, examine the factors that are believed to explain variations in adherence in other chronic diseases.^{3–5} Based on such findings, interventions have been designed to improve patient compliance.⁶

Research on health behaviors, such as medication adherence, has resulted in the formulation of specific psychological theories addressing patients' beliefs and roles. Leventhal and colleagues' Self-Regulatory Model (SRM)⁷ suggests that when individuals face a health threat, they form both cognitive and emotional representations of the disease, which act in parallel to influence associated health behaviors. Cognitive representations comprise of beliefs on illness identity, antecedent causes, consequences, timeline, and cure-control,⁸ whereas the emotional representations comprise individual's emotional reaction to the disease. Furthermore, individual's beliefs about treatment have been proposed as another determinant to understand the way in which patients make

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decisions about their treatment.⁹ Finally, different aspects of doctor–patient communication have been examined as potential predictors of medication adherence.¹⁰

Hypertension is the medical condition where the systolic blood pressure is more than 140 mm Hg and the diastolic blood pressure is more than 90 mm Hg.¹¹ It is a chronic disease which is considered to be one of the major public health problems and a significant cardiovascular risk factor. According to the World Health Organization (WHO), each year, at least 7.1 million people die as a result of increased blood pressure.¹² For the treatment of hypertension, a broad range of antihypertensive medications are currently available, as well as Therapeutic Lifestyle Changes such as weight reduction, increased physical activity, and reduction of dietary salt intake, which have proven to be important in disease management.¹³ Although there is evidence that increased blood pressure can actually be controlled with the cardiovascular risk factor being thus reduced,¹⁴ 75% of patients diagnosed with hypertension cannot achieve full control of their blood pressure.¹³ Poor blood pressure control is associated with higher healthcare resource utilization and costs¹⁵ and increased risk of cardiovascular diseases. Nonadherence to antihypertensive medication is the main reason for failure to control blood pressure among those under treatment.¹⁶

In Greece, although there is no nationwide data available for the prevalence of hypertension, it is estimated that 25% of the adult population are suffering from it.¹¹ Moreover, it is estimated that 40% of hypertensive adults are unaware of their condition, and 25% of those receiving treatment do not succeed in controlling their blood pressure.¹¹ Other studies have shown that awareness and control of hypertension and blood pressure is lower in Greece compared with other countries.^{17,18}

In addition, few studies have been conducted in Greece investigating the issue of adherence to treatment. The aim of the present study was to investigate the factors affecting antihypertensive medication adherence in Greece.

Methods

Study design

Semistructured interviews and focus groups were conducted in order to elicit data from people with hypertension. Semistructured interviews were preferred for those attending the Hypertension Centers (HCs) (Group A), allowing the investigators to approach them individually, as HC attendees were of older age. Older age is related to sensory loss that interferes with reception of the spoken message. People with sensory

loss thus frequently experience communication problems.¹⁹ One-to-one semistructured interviews could overcome this problem, which might otherwise influence older age participants' ability to participate effectively in focus groups. Focus groups were preferred for the group of younger participants (Group B), aged between 40 and 50 years, who were not or usually were not attending the HC, suffer from sensory loss. The age criterion was based on the available data regarding hypertension prevalence in Greece.²⁰ According to these data, diagnosed hypertensive patients younger than the age of 40 years represent less than 1.6% of the total number of hypertensive patients. Although it would be really hard for these patients to be identified, we decided to have this age criterion of hypertensive patients older than 30 years in case we could not find anyone between the ages of 30–40 years. In the case of focus groups, the lower limit was increased, from 30 to 40 years of age, because it was impossible for us to identify hypertensive patients between the ages of 30–40 years among the registered hypertensive patients. Fieldwork was conducted during the period May–July 2008.

Participants and settings

Group A participants were recruited from HC established in hospitals of the greater Athens area. Three HCs were purposively selected in order to reflect different geographic and socioeconomic regions. Two were established in public hospitals, and the third was established in an insurance fund hospital. In each center, the physician in charge assisted researchers to recruit patients.

Participants had to meet the following inclusion criteria in order to participate in the study: (a) being aged above 30 years, (b) receiving antihypertensive treatment for at least 1 year, and (c) speaking the Greek language fluently.

When patients who met the inclusion criteria attended the HC, on a specific day, an invitation letter was given to them by their physician explaining the purpose and the methodology of the study. In total, 25 patients accepted to be interviewed. Interviews were conducted, immediately after patients' medical examination in a private room in the HC, provided for the purposes of this study.

All interviews were facilitated by two researchers (psychologist [PP] and co-moderator [VT]). All interviews were anonymous and were audio taped, after participants' consent.

For Group B participants, the inclusion criteria were as follows: (a) being aged between 40 and 50 years, (b) receiving antihypertensive treatment for at least 1 year, (c) not consulting an HC, and (d) speaking the Greek language fluently.

Recruitment for Group B participants was made with convenience and purposive sampling. A telephone invitation survey among 200 registered hypertensive patients was conducted in order to identify those who met the inclusion criteria and were willing to attend the focus group sessions. In total, 18 patients (50% female) accepted to participate. Similar to semistructured interviews, participants were informed about the aims of the study, the methodology, and were assured of anonymity and confidentiality.

Two focus groups were organized, one comprising of 9 males and the other comprising of 9 females, in order to facilitate group dynamics and achieve higher homogeneity.²¹ Each group was moderated by an experienced psychologist and a co-moderator whose primary responsibility was to take notes during sessions. Both researchers met after each session in order to assess the procedure and identify crucial elements for the interpretation of the data.

Focus groups took place at the Department of Health Economics, National School of Public Health in Athens. The first session had a duration of 2 hours 8 minutes and the second 2 hours 22 minutes. Comfortable chairs, beverages, and snacks were offered in order to create a pleasant atmosphere and lighten the burden of the long duration of the focus group. Focus group sessions were tape-recorded, after participants' written consent.

Content and questions

According to standard methodology, open-ended questions and probes were predetermined for use during the semistructured interviews and the focus groups. These were based on the review of the relevant literature, taking into consideration the recommendations of the research team. Questions and probes fell within four research topics (see Table 1): perceptions and beliefs about hypertension, perceptions and beliefs toward antihypertensive treatment, patient—physician relationship, and patient—pharmacist relationship. Commencing questions in each research topic were general, capturing participants' beliefs in hypertension and treatment. Probes were more specific in order to elicit the opinion, experience, and behavior of the participant. Only demographic information was collected by a purpose-made short questionnaire.

Analysis

All interviews and focus group recordings, as well as notes kept by the focus group co-moderator, during the sessions were fully transcribed. Transcriptions were analyzed using content analysis,²² without using any qualitative data software. Each researcher (PP and VT) separately studied

Table 1 Topics and subtopics of the qualitative study

No	Main topics	Subtopics
1	Perceptions: beliefs about hypertension	<ul style="list-style-type: none"> • Risk factors • Complications • Sources of information • Symptoms and disease diagnosis
2	Perceptions: beliefs about antihypertensive treatment	<ul style="list-style-type: none"> • Attitudes and beliefs towards drugs in general • Adverse drug reactions • Factors influencing adherence to antihypertensive treatment • Adherent characteristics
3	Patient–physician relationship	
4	Patient–pharmacist relationship	<ul style="list-style-type: none"> • Dispensing/recommending medications

the transcriptions and the notes kept by the co-moderator, identified the emergent themes and keywords, and categorized the findings according to the four research topics. Then, the research team met in order to compare the findings, interpret results, and formulate conclusions. Demographic data were analyzed using MS Excel 2007.

Results

Group A comprised of 25 participants aged between 47 and 79 years (mean age, 63.7 years), whereas the 18 participants in Group B were aged between 40 and 50 years (mean age, 44.6 years; Table 2). Participants did not differ significantly in relation to gender. Group A participants were more likely (84%) to be under medication treatment for co-morbidities than their Group B counterparts (66.7%); however, this difference did not reach statistical significance.

Perceptions and beliefs about hypertension

Hypertension was considered a very serious disease responsible for even more dangerous medical conditions such

Table 2 Demographic characteristics of the participants

Characteristics	Semistructured interviews (Group A)	Focus groups (Group B)
	N = 25	N = 18
	Mean, N (%)	Mean, N (%)
Gender		
Male	12 (48%)	9 (50%)
Female	13 (52%)	9 (50%)
Age (mean)	63.7	44.6
No. of patients receiving additional medication for other conditions	21 (84%)	12 (66.7%)

as stroke and myocardial infarction. Stress, anxiety, limited physical activity, and unhealthy diet emerged as the perceived most important risk factors of hypertension.

- “Hypertension has very serious consequences, you can have a stroke ... it is very bad”. (Group A, female)
- “... Cardiovascular diseases and death. This is what I am thinking when I hear hypertension. If you don’t control it you will die”. (Group B, female)
- “I believe that stress is the major factor that makes all of us or at least most of us suffering from hypertension” (Group B, male)
- “It is not only stress, but the way of life in general”. (Group B, male)

Sources of information

The main sources of information were the physician or the pharmacist, the media, the Internet, and people who suffered from hypertension. However, participants admitted that their physician was the most trusted source. Participants were interested in further information for two reasons: to achieve a better understanding of their doctor’s advice and to check the validity of this advice.

- “My doctor gave me some information, but I search information through Internet too, so I can cross-check what he says”. (Group A, male)
- “... mainly my doctor and some books. But usually I talk with people who also suffer from hypertension, I feel more comfortable discussing with them” (Group A, female)
- “There are TV programs about health, but I always discuss everything I hear with my doctor” (Group B, male)

Symptoms and disease diagnosis

Although hypertension was associated with well-recognized symptoms, such as headaches and dizziness, participants often did not seek health care, at least until those symptoms became unbearable.

- “I knew that I had high blood pressure but I had never gone to a doctor, until I couldn’t bear the pain of the headaches” (Group A, male)
- “I was feeling a constant pressure in my head, so I decided to consult a doctor ...” (Group B, female)

When symptoms were mild, participants were usually referring to a pharmacist. If symptoms were more intense, they were looking for a specialist mainly an internist or a cardiologist.

- “I was not feeling well, so I went to a pharmacist to measure my blood pressure ...” (Group B, female)
- “One day, I felt very strange, like having a heart attack or stroke; I was so scared that I went to the hospital ...” (Group B, male)
- “I had strong headaches and because my father had also hypertension, I went to a cardiologist” (Group A, female)

Participants’ perceptions and beliefs toward antihypertensive treatment

Attitudes and beliefs towards drugs

Concerns and fear were expressed by the majority of participants regarding the use of medicines. Some of them expressed the opinion that the long-term use of medicines will have an impact on their immune system.

- “In general, I avoid taking medicines. If the decision is on me I will not take any drugs ...” (Group A, male)
- “... Some years ago I was suffering from spondylolisthesis and my doctor prescribed anti-inflammatory, and then my blood pressure was 18 to 19”. (Group A, female)
- “... I have taken so many drugs that I have destroyed my immune system ...” (Group A, female)
- “... I don’t like it (taking drugs) at all, because you try to fix one thing and something else goes wrong ...” (Group A, female)
- “Yes, but so many drugs? Don’t all of these end up in the liver? For how long can it (the liver) bear all these? ... and it is only one. I don’t know, I am a little afraid”. (Group B, female)

Adverse drug reactions

Adverse drug reactions were an issue of great concern for the majority of study participants. Some of them had stopped their treatment because they were afraid of the possible side effects. Avoidance of getting to know the possible side effects was also one of the reasons given for not reading the information leaflet of the drug.

- “... If I read (in the leaflet) that the drug has adverse drug reactions and this or that can happen to me, I stop the treatment ...” (Group A, male)
- “If you read about side effects you should not take any medicine. However, I have prevented some reactions because I had read the information leaflet” (Group A, male)
- “I don’t read the side effects, because then I think that I suffer from all these reactions” (Group B, female)

- “I usually read the side effects, but I can’t understand everything ... I trust my doctor who prescribes it. If something goes wrong I believe that I will understand it” (Group B, male)

Factors influencing adherence to antihypertensive treatment

The level of adherence among participants ranged. Previous experiences regarding hypertension and the fear or knowledge that they could suffer from a complication if they did not control their blood pressure were important reasons for medication adherence.

- “I didn’t know what it means to have high blood pressure for years and what this can cause to you ...” (Group A, male)
- “... because I have read and I know what can happen to me if I do not follow the treatment” (Group A, female)
- “... I take the pill every day, because I am afraid” (Group B, female)
- “... my neighbor had a stroke 5 years ago and he hasn’t recovered yet. I see all these and I follow my treatment because I am afraid that this will happen to me too”. (Group B, male)
- “... I am afraid of what will happen to me because of the hypertension, there is also the heredity”. (Group B, male)

In addition, systematic disease management, especially in HC, was a significant factor influencing treatment adherence.

- “Here (in the HC) I have a program and I come regularly for my blood pressure ...” (Group A, male)
- “First of all, it is very important that I come here regularly and I have a program, an antihypertensive program, and since I’ve started taken my pills nothing has gone wrong ...” (Group A, male)

Another important factor affecting adherence was the acceptance of the disease and the adoption of the patient’s role. Most of the participants, especially the younger ones who participated in focus groups, were hesitant and negative to the idea of taking a medicine for their whole life. The sooner they perceived hypertension as a chronic disease, the more adherent they became.

- “... at first I was really stressed. I didn’t want to believe that I will receive an antihypertensive treatment, why me? I was feeling really sad, it was like killing me ...” (Group B, male)

- “I believe that it is tragic to take a medication for the whole of your life, I can’t stand it. I believe that it is the beginning of the end, the beginning of taking more drugs ...” (Group B, male)

Sometimes, acceptance of the disease led to the change of patient’s lifestyle.

- “... after this (the diagnosis of hypertension) the whole perspective about my diet changed ...” (Group B, male)

Adherence characteristics

Adherence to treatment was easier if the medication were received in the morning. In this case, the majority of participants had associated their medication with their breakfast or had invented different tricks in order to remember it.

- “I take it during breakfast, I am used to it now” (Group A, female)
- “I take it every morning, I set the alarm clock in order to remember it, you have to associate it with something, otherwise you forget it” (Group B, male)

Most of the participants admitted during weekends they received their medication some hours later than the appropriate, believing that this was an “innocent” tactic, although their doctor had warned them for the opposite.

- “At the weekends I take my pill 3 hours later ... I don’t believe it does any harm. On the contrary, three hours more sleep is good because our organism is calm when we are sleeping. When we wake up we need the pill ...” (Group B, female)

The drug substance also seemed to be an important factor affecting adherence when its effects interferes with patients’ activities.

- “I take one pill every morning. But, because it is diuretic, when I go out I do not take it ...” (Group A, male)

Finally, some of the participants mentioned that they stopped the treatment from time-to-time when they no longer suffered from symptoms or when they believed that they had controlled their blood pressure.

- “If my blood pressure is at good levels, I can’t see the reason to take it (the pill). I am afraid to take it because it might cause hypotension to me”. (Group A, female)
- “... When I have symptoms I follow my treatment, when I feel good I don’t ...” (Group B, female)
- “I stopped the treatment for a period, just to see what will happen, if I will get better ... but it didn’t work” (Group B, male)

Patient–physician relationship

The majority of participants considered the relationship with their physician of great importance. Good atmosphere during consultation and physician's time spent on giving advice and answering questions were mentioned as the most important characteristics of a "good" doctor. Distant and formal behavior of physician could be a reason for changing the doctor for some participants.

- "I appreciate my doctor very much, he explains everything to me. He doesn't care only about prescribing. He practices real medicine. (Group A, male)
- "First of all they really seem to care about me. They listen to my questions and wishes and I understand it" (Group A, male)
- "I stopped consulting my first doctor because of his behavior. I don't know, this was probably because of his age, he was old, but the distance between me and the physician was big. I wanted to ask something and I hesitated, and when I did so his answers were yes or no, nothing more" (Group B, female)

Good communication and a rewarding behavior of the physician as well as a high level of confidence also seemed to facilitate adherence.

- "If I have good results, then my doctor congratulates me" (Group A, female)
- "I believe that the doctor should inspire you confidence, then you will follow the treatment and if the doctor is strict you will comply" (Group A, female)
- "I feel gratitude; the whole team here works for me". (Group A, male)

Patient–pharmacist relationship

Regarding patient–pharmacist relationship, participants trusted their pharmacist's advice on taking the appropriate medication when they concerned a minor health condition such as a sore throat or a cold. For more serious conditions such as hypertension, they trusted only their physician for prescribing a drug. Still, participants consult their pharmacist for additional information on treatment, such as whether they should take the drug before or after dinner.

- "... I don't want to take medicines if my doctor hasn't prescribed them ..." (Group A, female)
- "(I trust the pharmacist) ... for simple things like throat, nose and things like these. For more serious conditions I consult the doctor ..." (Group A, male)
- "I could trust my pharmacist for something simple like a sore throat. In that case I could consult the pharmacist instead of the physician" (Group B, male)

- "I will ask the pharmacist for additional information, for example if I should take my medication before or after dinner, things like that" (Group A, male)

- "... the pharmacist is not a doctor. The pharmacist sells drugs" (Group B, female)

Participants from the insurance fund HC referred to drug cost as another reason for not seeking pharmacist's advice on taking the appropriate medication.

- "... These are expensive (the antihypertensive drugs). How can I pay for these without a prescription? I am a pensioner and my pension is low" (Group A, female)
- "... my doctor has prescribed all the drugs I take ... I can't take it without a prescription, I am a pensioner and ... you understand ..." (Group A, female)

Discussion

Research on the adherence of antihypertensive treatment has shown that patient's nonadherence to medication is related with a mix of demographic, organizational, psychological, and disease- and medication-related variables.^{23,24} Thus, investigating patients' beliefs regarding hypertension itself and antihypertensive treatment, as well as communication factors that affect adherence, can have a great impact on designing effective interventions in order to improve treatment adherence.

The present study is the first in Greece, which examined hypertensive patients' beliefs about hypertension and antihypertensive medicines, as well as patients' behaviors concerning treatment adherence. It also examined patient–doctor relationship and its impact on adherence. Finally, the study examined patients' beliefs about the role of pharmacists. In general, results are consistent with findings from other qualitative studies on antihypertensive medication adherence.^{25,26}

The majority of participants considered hypertension as a very serious disease and were afraid and anxious about potential serious consequences on their health in case of failure to manage the disease. These negative feelings toward hypertension represent a finding that differs from those of other studies, where hypertension was found to be considered a less important disease with well-recognized symptoms.²³ Further research based on theoretical models like SRM is required so that Greek patients' beliefs about hypertension is further explored.

Stress emerged as one of the main risk factors of hypertension. Even though participants acknowledged the importance of this factor, stress was believed to be inevitable, and this situation was attributed to the modern way of living.

Participants were being informed about hypertension from a plethora of sources, but they trusted mainly their physician. Furthermore, they were feeling comfortable to discuss about hypertension with other hypertensive patients. This finding was also confirmed during the focus group sessions where participants were interested in sharing their experiences and discussing their health problem with each other.

Participants reported that they attend different health care facilities depending on the severity of symptoms. This behavior reflects the characteristics of the health care system in Greece and the way it is organized. In the absence of integrated primary care with a gate-keeping system, patients seek care and advice of the pharmacists when it concerns minor health conditions while they face limited or no barriers at all in accessing and choosing health care providers. This enables them to visit a specialist as often as they wish without referral from a general practitioner.

Based on the results of our study, the factors that influence medication adherence concern the management of the disease, the treatment characteristics, and the patient–physician relationship. The systematic disease management includes regular appointments with the physician and intense counseling in order for the patient to be aware of the complications of uncontrolled blood pressure. Treatment characteristics, such as the time of receiving the medicine, the number of doses, and the drug substance, were reported as influential factors. These characteristics, which may be considered minor, are really important for patient compliance and have been identified in other studies as well.^{23,25–27}

Although an association between adherence and demographic characteristics such as age and gender could not be established due to the nature of the study, it seems that younger adults in Greece face greater difficulty in the acceptance of the disease and consequently in adhering to treatment. Age-related illness perception, with the elderly being more adherent, has also been reported in other studies.²⁷ Building on the results of the present study, a longitudinal quantitative survey would be useful in order to further explore – confirm or reject – the aforementioned finding.

Results suggest that the major factor affecting positive medication adherence is a good doctor–patient relationship. A physician who encourages and rewards patients, and most importantly, spends quality time with them in giving information and providing explanations about the disease and treatment contributes significantly in patients' compliance.

This finding is consistent with a number of previous studies that have established the importance of this relationship.^{23,25,26}

In contrast, pharmacist–patient relationship seems that it did not affect medication adherence among study participants. However, a finding worthwhile to be further researched is the role of cost of drugs in adherence because this was a matter of great concern for a number of participants, especially those attending insurance funds HC. Cost and particularly level of co-payment has been identified as an important factor associated with adherence to pharmaceutical treatment.²⁸

Perceptions of personal risk and outcome expectancies, as well as redefinition of self concept or social role, have been proven to create a “teachable moment” for risk-reducing health behaviors.^{29,30} In our study, participants do create a “teachable moment” about hypertension, by cognitively escalating the severity of their symptoms. Previous experiences regarding hypertension, either personal or those of friends and family, and knowledge about the complications of the disease were major determinants of a teachable moment. Nevertheless, due to organizational factors, participants seem to adopt a risk-reducing health behavior (ie, visit an HC) only at a very late stage. A primary intervention stage should be identified, and early prevention strategies should be adopted so that hypertensive patients benefit at an earlier prohypertension stage rather than waiting until they are diagnosed with hypertension.

Limitations

All participants of the present study reported adherence to treatment at the time of the study, a finding initially indicating high levels of adherence in Greek hypertensive patients compared with previous studies conducted in Greece.²⁰ Nevertheless, participants mentioned that they did not take medication at the right time, or skipped if they felt well, indicating a rather nonadherent than adherent pattern of behavior. This inconsistency perhaps shows a cognitive bias, which underline causes worth further investigation. Psychological factors like patients' frustration due to inefficient antihypertensive treatment or the meaning of monitoring blood pressure at home or telemonitoring might have some effects on adherence. Furthermore, the detected inconsistency could represent a time-related reference: participants referred to all these behaviors regarding their pharmaceutical treatment, considering them as past behaviors and not things that they usually do in the present. In addition, this result may only be due to a volunteer effect and can be considered a methodological limitation given that, according to literature,

adherence to antihypertensive treatment ranges between 50% and 70%.¹³ Unanimous adherence allowed the identification of the factors contributing to adherence but prevented us from exploring the factors that inhibit it (although it could well be assumed that the opposite factors can be responsible for nonadherence).

From a methodological point of view, the smaller number of participants interviewed in HC, three compared to the number of participants in the other two HCs, could be considered another limitation of the study. However, due to the qualitative methodology adopted and the fact that direct comparisons among HCs were not an objective of the study, this sample difference has a limited effect on results.

Finally, the long duration of the focus groups may be considered another limitation of the study. Although we took care to achieve a comfortable environment for participants, it is not quite sure whether they were fully engaging in the end of the discussion.

Conclusion

In conclusion, the present study confirmed that cognitive and communication factors—patients who were better informed, had previous experiences of the disease, and a good relationship and communication with their physician—were important determinants for adherence. These results could form the basis for designing effective interventions adjusted to the Greek reality aiming at both enhancing doctor–patient communication and empowering the patient himself. Such interventions have the potential to improve the adherence of hypertensive patients' medication and can consequently reduce hypertension-related costs.

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Disclosure

The authors report no conflicts of interest in this work.

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