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The importance of medication adherence in hypertension: What clinicians should consider

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ABSTRACT

Non-adherence to antihypertensive medication is a major contributor to poor blood pressure control and represents a hidden cardiovascular risk factor. Several reasons account for this phenomenon and they include, at the physician level, communication skills, guideline knowledge, adequacy and complexity of the prescribed regimen, or therapeutic inertia. At the patient level, the asymptomatic condition of hypertension may generate an underestimation of treatment necessity, side effects, and the complexity of antihypertensive treatment. Several methods are available for measuring adherence, including self-report questionnaires or biochemical screening, although no gold-standard method routinely used in clinical practice exists. From the practitioner's perspective, the patient-practitioner relationship is a key element both in detecting adherence and in attempting to choose interventions tailored to the patient's profile. The use of single-pill combinations is a winner simplification of treatment scheme, as well as the implementation of a collaborative team-based approach and the development of electronic health tools also crucial tools for improving adherence, hopefully leading to an amelioration of cardiovascular outcomes.

 **Key-words:** non-adherence, hypertension, antihypertensive treatment, cardiovascular disease

INTRODUCTION

It is worldwide recognized that hypertension is the most important modifiable risk factor for cardiovascular diseases (CVD). It represents a global public health problem, being the principal cause of disability-adjusted life years. It is estimated that, by the year 2025, 1.6 billion of the world adult population will have hypertension, with an increase of about 60% compared to the year 2000. Nevertheless, despite availability of several classes of efficacious antihypertensive treatments, in a considerable number of patients worldwide, including Europe, blood pressure (BP) is still not satisfactorily controlled. A recent survey exploring data in 89 countries revealed that no more than 60% of treated patients had their BP controlled¹. Among multiple factors explaining such a disappointing control, poor adherence of patients is a major cause; a phenomenon amplified by the evidence that around 60% of hypertensive patients needs more than two anti-

hypertensive drugs to obtain a BP control². It is obvious that non-adherence to antihypertensive treatment leads to deleterious consequences in terms of CVD, as well documented by a large meta-analysis of 44 prospective studies evidencing that a good adherence to antihypertensive therapy significantly reduces the risk of CV outcomes³. This article will focus on the reasons for poor adherence, on how to detect adherence, and on the possible practical interventions to improve adherence.

DEFINITION OF TREATMENT ADHERENCE

According to WHO definition, adherence is “the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes – corresponds with agreed recommendations from a healthcare provider”⁴. While adherence to lifestyle changes plays an inescapable, fundamental role to obtain a well BP control, in the present article we will focus on adherence to medication. An

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arbitrary cut-off point of 80% of prescribed medications taken by the patient is used to distinguish adherence from non-adherence⁴. Briefly, adherence includes three components: initiation (i.e. taking the first dose of the prescribed medication), implementation (i.e. the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen) and discontinuation (i.e. when the patient stops taking the medication despite prescription being re-filled). These three phases are collectively called persistence. As documented by a longitudinal database study, the persistence declines over time and by the end of one year, almost half of the patients stop taking their medication⁵. Early discontinuation of treatment and suboptimal daily execution of the prescribed regimen are the most common causes of poor adherence. Additionally, there is a conspicuous proportion of patients (5%-20%) who never initiate intake of prescribed medication.

MEAN REASONS WHY HYPERTENSIVE PATIENTS ARE NON-ADHERENT

It is recognized that the phenomenon adherence is strongly influenced by a complex interplay between socioeconomic, healthcare system-related, medical condition-related, therapy-related and patient-related factors. At the physician level, communication skills, guideline knowledge, adequacy and complexity of the prescribed regimen, therapeutic inertia and time constraints can all impact adherence. At the patient level, several factors can adversely affect adherence and can differ from patient to patient (see Table 1 for details). The asymptomatic condition of hypertension may generate by patients an underestimation of treatment necessity or benefit, especially among younger and active individuals without comorbidities, who might also fear possible or experienced adverse effects. Adverse effects experienced by patients during therapy are one of the major reasons for non-adherence, possibly even more so if combined with lack of treatment benefit. Intensification of antihypertensive treatment, while giving greater protection against CVD, on the other side it may be accompanied by an increasing rate of treatment discontinuation because of adverse effects. In addition, regimen complexity (usually in terms of number of prescribed medications) could be a barrier to adherence, especially among older patients with co-morbidities. Adherence is inversely related

Table 1. Factors associated with poor adherence to antihypertensive therapy.

<i>Practitioner</i>
Physician inertia
Inadequate prescription / Regimen complexity
Lack of guideline knowledge / lack of training for hypertension treatment
Communication skills
Patient-provider relationship
Time constraints
<i>Patient</i>
They did not need antihypertensive medication because they had no symptoms
Denied the diagnosis and viewed it as a reaction to stressful events and not necessarily a chronic disease
Gaps in understanding risk factors and consequences of hypertension
Poor confidence in results
Concomitant comorbidities (mood, dementia, neoplasia)
Complex therapeutic scheme
Forgetting to take one's medication
Side effects

to the prescribed number of daily doses or number of medications⁶. This aspect of course involves also patients identified as resistant. Indeed, it was demonstrated that half of patients in whom it was initially diagnosed a condition of resistant hypertension were in fact found to be partially or completely non-adherent⁷.

It is undoubtedly that adherence problem is amplified among older patients affected by cognitive decline, who are more prone to forgetfulness or confusion, leading to unintentional non-adherence. Changes in pill color and shape, exacerbated by the increasing use of different generics, often generate confusion in older patients, increasing odds of non-adherence. It is a precise duty by physician to identify the reasons for the patient's non-adherence, to instruct the patient or the caregiver on the drugs to be taken, in an attempt to optimize their effectiveness.

IS IT POSSIBLE TO IDENTIFY NON-ADHERENT PATIENTS?

Adherence screening is needed every time that BP control is not achieved, especially in patients taking many medications and in whom non-adherence is suspected. Detecting non-adherence requires methods that allow accurate and routine measurement. At present, there is no gold-standard method for adherence assessment and no free-of-charge valid avail-

able tools. Several self-report questionnaires can be used in hypertension, the most well-known being the Morisky Adherence Questionnaire⁸. Patient self-report measures are simple and inexpensive. However, patients might recall their adherence inaccurately or be tempted to over-report adherence in an attempt to conform to practitioner's expectations. Nevertheless, questionnaires might have value as complementary tools, as they can provide insights into barriers to adherence and patient beliefs that may influence adherence to medication. Adherence can also be put in evidence by objective methods, either indirectly, by using pharmacy refill records, pill counts or electronic monitoring devices or directly, by using directly observed therapy, digital pills or biochemical detection of medications in blood or urine⁹. Pharmacy refill records can thus provide information about medication discontinuation rates, although this method requires a closed pharmacy system whose efficacy is strongly dependent from the quality of the electronic data. Pill counting is a relatively simple method, but does not provide information on the timing of dose intake or real ingestion of medications. Finally, biochemical detection of medications in urine or serum (urine being preferred because of its noninvasive collection) by high performance liquid chromatography – tandem mass spectrometry (HPLC-MS/MS) provides accurate and objective measurement of adherence, albeit limited to a snapshot in time. Unfortunately, HPLC-MS/MS instrumentation is expensive and not widely available, but its use could help avoid expenses related to unnecessary treatment escalation, invasive procedures or clinical investigations for secondary causes of hypertension.

HOW TO AMELIORATE PATIENTS' ADHERENCE

The complexity and multifactorial barriers to adherence indicate the necessity to address the problem at several levels, and indeed multimodal interventions have generally been more successful than unimodal ones. This aspect has been well receipted by the 2018 European Society of Cardiology and European Society of Hypertension (ESC/ESH) guidelines¹⁰, which highlighted the concept that most useful interventions are those linking drug intake with habits, giving adherence feedback to patients, self-monitoring of BP using pill boxes and other special packaging, and motivational interviewing. What

could physicians do to improve adherence? As well described by Poulter et al.¹¹, the relationship of patient-practitioner has an important role to play in facilitating the detection of adherence problems and informing the choice of suitable solutions. The practitioner should ask patients about medication-taking behavior, raising questions phrased in a nonjudgmental way (Table 2). The importance of understanding the patients' perspective is being increasingly acknowledged. It is mandatory that the practitioner, beyond assessing the patients' understanding of the potential adverse effects, focuses his speech to the necessity of the treatment and the clinical benefits provided by the prescribed medications. Whenever possible, practitioners should tailor the pill-taking for patients. For instance, among working patients, it might be helpful to adapt the time of medication taking into account lifestyle constraints, for example, for a nightshift worker it might be impractical to take medication in the middle of the day. Different approaches might be needed for intentional and unintentional non-adherence. According to guidelines, it is important to conduct adherence assessment in a blame-free environment to identify specific barriers to adherence and suggest individualized solutions¹⁰. Good patient-practitioner communication is really crucial, as poor communication leads to higher risk of non-adherence. Nevertheless, it is important to remind that the amount of time spent by the provider with the patient was not ever associated with adherence, suggesting that quality of communication, rather than the absolute quantity of time, might be more important¹². A further step is to involve the patient in the medical decision. Shared decision-making is one of the strategies that

Table 2. Questions to ask patients with hypertension.

How long have you been taking your pills?
Are you aware of their benefit and of why you are taking them?
How do you take your tablets?
You are on 10 tablets - how do you manage?
During the last month, how many times have you not taken your tablets?
When is the most suitable time for you to take your pill?
When could you find time to take your medicine?
What could help you change or improve the way you take your medicine?

can be used for patient empowerment and adherence improvement. Indeed, a recent meta-analysis has shown that the improvement in hypertension control and patients' adherence promoted by use of home BP monitoring is largely explained by the combination of home BP monitoring with feedback to the patient, education and counseling¹³. Finally, prescription of single-pill combinations (SPCs) provides an extraordinary opportunity for physicians to simplify treatment and to reduce pill burden, thus addressing two factors with major impact on adherence: complexity of treatment regimen and polypharmacy.

An interesting meta-analysis documented a significant amelioration of adherence among patients taking SPCs compared with those on free combinations¹⁴. To further support the usefulness to adopt the SPCs regimen, it was demonstrated that hypertensive patients starting treatment on an SPC were 53% more likely to achieve BP control in the first year than those who started on monotherapy¹⁵, a regimen that led to fewer hospitalizations¹⁶ and a lower 5-year cardiovascular event rate¹⁷ as compared to those on free combinations.

Potential limits to SPC use include difficulty to identify the exact cause in case of adverse effect and a reduced prescription flexibility, although several available dosages allow individual treatment adaptation. The 2018 ESC/ESH hypertension guidelines highlighted the necessity of a simplifying treatment strategy to improve adherence and BP control, and recommend combination treatment as initial therapy for most patients with hypertension, with preferred use of SPCs¹⁰. Choice of the best therapeutic regimen and correct dosage of each component of the SPC is specific duty by physicians, in order to improve efficacy and encourage adherence to treatment.

In such scenario, the ESC/ESH Guidelines put in evidence the important role of nurses and pharmacists in the education, support, and follow-up of treated hypertensive patients. In particular, adherence improvement and better BP control can be achieved with nurses and pharmacist-led interventions, further enriched by taking advantage of telehealth technologies¹⁸⁻¹⁹.

CONCLUSION

Medication non-adherence is an underestimated, modifiable risk factor in the management of hypertension. Evaluation of medication adherence should

become an integral part of assessment of patients with hypertension. It is true that drugs do not work in patients who do not take them, but medication non-adherence is a much more complex problem than simply blaming the patient. There are patient-related factors as well as healthcare-related ones. It requires a significant effort to identify this problem in a chronic asymptomatic condition like hypertension due to its dynamic nature. While no single perfect method exists to assess medication adherence, a multi-complementary strategy can improve medication adherence by focusing on interventions to address immediate short-term barriers as well as maintaining long-term adherence, because medication adherence is a key preventive measure in the management of chronic diseases like hypertension. Winner approaches, such as simplifying treatment through SPC use, establishing a team-based care approach and eventually using e-health technologies as a supportive tool, provide opportunities to address the adherence problem.

REFERENCES

1. Beaney T, Burrell LM, Castillo RR, Charchar FJ, Cro S, Damasceno A, et al. May measurement Month 2018: a pragmatic global screening campaign to raise awareness of blood pressure by the International Society of Hypertension. *Eur Heart J* 2019; 40: 2006-17.
2. Thoenes M, Neuberger H-R, Volpe M, Khan BV, Kirch W, Bohm M. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. *J Hum Hypertens* 2010; 24: 336-44.
3. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013; 34: 2840-948.
4. Sabaté E, Sabaté E. Adherence to Long-Term Therapies: Evidence for Action. World Health Organization; 2003.
5. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *BMJ* 2008; 336(7653): 1114-7. doi:10.1136/bmj.39553.670231.2523
6. Gupta P, Patel P, Štrauch B, et al. Risk factors for non-adherence to antihypertensive treatment. *Hypertension* 2017; 69: 1113-20.
7. Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Nonadherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. *J Hum Hypertens* 2016; 30: 83-9.
8. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. *J Clin Hypertens (Greenwich)* 2008; 10: 348-54.
9. Gupta P, Patel P, Horne R, Buchanan H, Williams B, To-

- maszewski M. How to screen for non-adherence to antihypertensive therapy. *Curr Hypertens Rep* 2016; 18: 89.
10. Williams B, Mancia G, Spiering W, et al., Authors/Task Force Members. 2018 ESC/ESH Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36: 1953-2041.
 11. Poulter NR, Borghi C, Parati GF, et al. Medication adherence in hypertension. *J Hypertens* 2020; 38(4): 579-87.
 12. Fortuna RJ, Nagel AK, Rocco TA, Legette-Sobers S, Quigley DD. Patient experience with care and its association with adherence to hypertension medications. *Am J Hypertens* 2018; 31: 340-5.
 13. Tucker KL, Sheppard JP, Stevens R, et al. Self-monitoring of blood pressure in hypertension: a systematic review and individual patient data meta-analysis. *PLoS Med* 2017; 14:e1002389.
 14. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of healthcare costs and adherence. *J Clin Hypertens (Greenwich)* 2011; 13: 898-909.
 15. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. *Hypertension* 2012; 59: 1124-31.
 16. Yang W, Chang J, Kahler KH, et al. Evaluation of compliance and healthcare utilization in patients treated with single pill vs free combination antihypertensives. *Curr Med Res Opin* 2010; 26: 2065-76.
 17. Belsey JD. Optimizing adherence in hypertension: a comparison of outcomes and costs using single tablet regimens vs individual component regimens. *J Med Econ* 2012; 15: 897-905.
 18. Victor RG, Lynch K, Li N, et al. A cluster-randomized trial of blood-pressure reduction in black barbershops. *N Engl J Med* 2018; 378: 1291-301.
 19. Omboni S, Tenti M, Coronetti C. Physician-pharmacist collaborative practice and telehealth may transform hypertension management. *J Hum Hypertens* 2019; 33: 177-87.