



The Open Hypertension Journal

Content list available at: www.benthamopen.com/TOHYPERJ/

DOI: 10.2174/1876526201810010041, 2018, 10, 41-45



EDITORIAL

Suboptimal Adherence to Antihypertensive Treatment: Causes and Management

Received: July 8, 2018

Revised: September 14, 2018

Accepted: October 5, 2018

Abstract: Suboptimal adherence to antihypertensive treatment is very common and is associated with poor control of blood pressure and increased risk for cardiovascular events. Therefore, frequent evaluation of compliance is essential in all hypertensive patients. Simplifying treatment regimens, using fixed-dose combinations and long-acting agents improves adherence, facilitates achievement of treatment targets and reduces cardiovascular morbidity and healthcare expenditures. Accordingly, physicians should be educated to implement these changes in hypertensive patients, particularly in those who require multiple antihypertensive agents to achieve blood pressure controls and in those who receive additional medications for comorbidities.

Keywords: Hypertension, Adherence, Compliance, Fixed-dose combination, Cost, Cardiovascular morbidity, Compliance indices.

Hypertension is accountable for 9.4 million deaths per year worldwide. Hypertension is a major modifiable risk factor for coronary heart disease, stroke, chronic kidney disease and heart failure [1]. The American Heart Association/American College of Cardiology recently recommended an aggressive approach in the management of hypertension, characterizing as stage I hypertension systolic blood pressure [BP] > 130 mmHg and/or diastolic BP > 80 mmHg [2]. On a more conservative approach, the European Society of Cardiology/European Society of Hypertension consider as stage I hypertension systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg [3].

The first step for the management of hypertension consists of adoption of a healthier lifestyle, *i.e.* regular exercise, reduction in sodium intake, weight loss decrease in alcohol consumption and smoking cessation. In blood pressure targets are not achieved with lifestyle changes, antihypertensive treatment should be initiated and continued for life [1 - 3]. Antihypertensive treatment has been consistently shown to reduce cardiovascular morbidity and mortality [4].

Despite the established benefits of antihypertensive treatment, a considerable proportion of patients with hypertension do not adhere to the prescribed antihypertensive therapy. It has been reported that only 30% of hypertensive patients continue to receive their antihypertensive treatment at 1 year after treatment initiation [5]. Moreover, most patients discontinue treatment within the first 3 months [5]. A recent study reported that one in every 8 patients filled-in only one prescription of antihypertensive agents [6]. These rates have remained unchanged during the last decade, despite the increasing rates of awareness and management of hypertension [7]. Of note, even patients with resistant hypertension who undergo renal denervation show poor adherence to treatment [8 - 11] Table 1. Interestingly, it has been reported that a substantial proportion of patients take higher doses of antihypertensive agents than those recommended, a practice which is also associated with higher risk for cardiovascular events [12].

Several factors contribute to the low rates of adherence to antihypertensive treatment. First, most patients require multiple agents to achieve BP targets and compliance declines with the increase in number of prescribed medications [13]. Accordingly, the use of fixed compositions has been consistently shown to improve compliance to antihypertensive therapy [14 - 17]. Fixed combinations also appear to reduce BP more than free combinations [16, 17]. Healthcare costs and cardiovascular morbidity also appear to be reduced by the use of fixed combinations [18, 19]. Reducing the complexity of the drug therapy by prescribing long-acting agents taken once daily also has favorable effects on adherence [18 - 21]. Among patients treated with 3 antihypertensive agents, reducing this number to 2 had a positive impact on adherence [22]. Moreover, combining antihypertensive agents with a statin and aspirin in a single pill also improves adherence [23]. In addition, initiation of antihypertensive treatment simultaneously with lipid-

lowering therapy also results in better compliance to both treatments, possibly because it enables patients to organize better medication refill [24]. A second important driver of low adherence is the cost of medications. Indeed, the use of generic medications is associated with better adherence [25]. Female gender, young age, low socioeconomic status and absence of comorbidities are also associated with suboptimal adherence [26]. In contrast, patients with established cardiovascular disease appear to be more compliant to antihypertensive treatment, possibly because they had better perception of their risk for a recurrent cardiovascular event [27]. Among antihypertensive classes, compliance appears to be better with angiotensin converting enzyme inhibitors and angiotensin receptor blockers [6, 15, 26]. Educating the patients about the benefits of antihypertensive treatment on cardiovascular morbidity and mortality, stressing the need for sustained adherence and addressing concerns about the safety of antihypertensive agents is also important in improving adherence. Having a schedule in medication intake and use of electronic reminders are also helpful. Regular evaluation of adherence and discussion of barriers to adherence are also important.

Table 1. Adherence to antihypertensive treatment in patients with resistant hypertension undergoing renal denervation.

References	Number of Patients	Adherence
8	83	71
9	106	75
10	168	82
11	85	49

Suboptimal adherence to antihypertensive treatments increases the risk for cardiovascular morbidity, adversely affects quality of life and increases healthcare costs [5, 15, 28]. In a recent meta-analysis of 18 studies (n = 1,356,188), a 20% increase in adherence to antihypertensive treatment was associated with a 9% lower risk of stroke [29]. In another meta-analysis of 44 prospective studies (n = 1,978,919), patients with good adherence to antihypertensive medication had 19% lower risk for cardiovascular events and 29% lower all-cause mortality than patients with poor adherence [< 80% adherence] [30]. Accordingly, monitoring the patients' compliance to treatment is essential. National healthcare databases are increasingly recognized as a useful and reliable source for evaluating the adherence to antihypertensive therapy [6, 31]. Moreover, recent consensus statements describe in detail the methods to assess adherence, which is important for obtaining consistent and comparable results from different healthcare systems [32]. Several different indices have been used to evaluate compliance to treatment [33]. A frequently used measure is the medication possession ratio (MPR), which represents the ratio of the patient's daily supply of all medications divided by a specific period of time [15, 33, 34]. Another commonly employed index is the proportion of days covered [PDC], which represents the amount of days a drug is accessible [35, 36]. The PDC is considered more reliable than the MPR for evaluating adherence because the latter cannot distinguish between drug discontinuation, substitution and addition [37]. Several other methods are used to evaluate adherence in everyday clinical practice including estimation of adherence by physicians, self-reported adherence using questionnaires, pill counting, electronic monitoring using an electronic pillbox, direct observation of intake of antihypertensive medications, measurement of biomarkers in the plasma or the urine and detection of antihypertensive drugs or their metabolites in the urine [38].

In conclusion, suboptimal adherence to antihypertensive treatment is very common and is associated with poor control of blood pressure and increased risk for cardiovascular events. Therefore, frequent evaluation of compliance is essential in all hypertensive patients. Simplifying treatment regimens, using fixed-dose combinations and long-acting agents improves adherence, facilitates achievement of treatment targets and reduces cardiovascular morbidity and healthcare expenditures. Accordingly, physicians should be educated to implement these changes in hypertensive patients, particularly in those who require multiple antihypertensive agents to achieve blood pressure controls and in those who receive additional medications for comorbidities.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] WHO. A global brief on Hypertension, World Health Organization, WHO/DCO/WHO/ 2013.
- [2] Whelton PK, Carey RM, Aronow WS, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of cardiology/american heart association task force on clinical practice guidelines. *Hypertension* 2018; 71(6): 1269-324. [<http://dx.doi.org/10.1161/HYP.000000000000066>] [PMID: 29133354]
- [3] Mancia G, Fagard R, Narkiewicz K, *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2013; 31(7): 1281-357. [<http://dx.doi.org/10.1097/01.hjh.0000431740.32696.cc>] [PMID: 23817082]
- [4] Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338: b1665. [<http://dx.doi.org/10.1136/bmj.b1665>] [PMID: 19454737]
- [5] Chowdhury R, Khan H, Heydon E, *et al.* Adherence to cardiovascular therapy: A meta-analysis of prevalence and clinical consequences. *Eur Heart J* 2013; 34(38): 2940-8. [<http://dx.doi.org/10.1093/eurheartj/ehd295>] [PMID: 23907142]
- [6] Hasford J, Schröder-Bernhardi D, Rottenkolber M, Kostev K, Dietlein G. Persistence with antihypertensive treatments: Results of a 3-year follow-up cohort study. *Eur J Clin Pharmacol* 2007; 63(11): 1055-61. [<http://dx.doi.org/10.1007/s00228-007-0340-2>] [PMID: 17701032]
- [7] Kotseva K, Wood D, De Backer G, De Bacquer D, Pyörälä K, Keil U. Cardiovascular prevention guidelines in daily practice: A comparison of EUROASPIRE I, II, and III surveys in eight european countries. *Lancet* 2009; 373(9667): 929-40. [[http://dx.doi.org/10.1016/S0140-6736\(09\)60330-5](http://dx.doi.org/10.1016/S0140-6736(09)60330-5)] [PMID: 19286092]
- [8] Fadl Elmula FEM, Hoffmann P, Larstorp AC, *et al.* Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. *Hypertension* 2014; 63(5): 991-9. [<http://dx.doi.org/10.1161/HYPERTENSIONAHA.114.03246>] [PMID: 24591332]
- [9] Azizi M, Sapoval M, Gosse P, *et al.* Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): A multicentre, open-label, randomised controlled trial. *Lancet* 2015; 385(9981): 1957-65. [[http://dx.doi.org/10.1016/S0140-6736\(14\)61942-5](http://dx.doi.org/10.1016/S0140-6736(14)61942-5)] [PMID: 25631070]
- [10] Beaussier H, Boutouyrie P, Bobrie G, *et al.* True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence. *J Hypertens* 2015; 33(12): 2526-33. [<http://dx.doi.org/10.1097/HJH.0000000000000737>] [PMID: 26378683]
- [11] Azizi M, Pereira H, Hamdidouche I, *et al.* Adherence to antihypertensive treatment and the blood pressure lowering effects of renal Denervation in the Renal Denervation for Hypertension (DENERHTN) Trial. *Circulation* 2016; 134(12): 847-57. [<http://dx.doi.org/10.1161/CIRCULATIONAHA.116.022922>] [PMID: 27576780]
- [12] Stroupe KT, Teal EY, Tu W, Weiner M, Murray MD. Association of refill adherence and health care use among adults with hypertension in an urban health care system. *Pharmacotherapy* 2006; 26(6): 779-89. [<http://dx.doi.org/10.1592/phco.26.6.779>] [PMID: 16716131]
- [13] Gu Q, Burt VL, Dillon CF, Yoon S. Trends in antihypertensive medication use and blood pressure control among united states adults with hypertension: The national health and nutrition examination survey, 2001 to 2010. *Circulation* 2012; 126(17): 2105-14. [<http://dx.doi.org/10.1161/CIRCULATIONAHA.112.096156>] [PMID: 23091084]
- [14] Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. *Curr Med Res Opin* 2014; 30(12): 2415-22. [<http://dx.doi.org/10.1185/03007995.2014.964853>] [PMID: 25222764]
- [15] Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: Results from a population-based study in the elderly. *Am J Hypertens* 1997; 10(7 Pt 1): 697-704. [[http://dx.doi.org/10.1016/S0895-7061\(97\)00056-3](http://dx.doi.org/10.1016/S0895-7061(97)00056-3)] [PMID: 9234822]
- [16] Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: A meta-analysis of health care costs and adherence. *J Clin Hypertens (Greenwich)* 2011; 13(12): 898-909. [<http://dx.doi.org/10.1111/j.1751-7176.2011.00550.x>] [PMID: 22142349]
- [17] Zeng F, Patel BV, Andrews L, Frech-Tamas F, Rudolph AE. Adherence and persistence of single-pill ARB/CCB combination therapy compared to multiple-pill ARB/CCB regimens. *Curr Med Res Opin* 2010; 26(12): 2877-87. [<http://dx.doi.org/10.1185/03007995.2010.534129>] [PMID: 21067459]
- [18] 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(5): 897-905. [<http://dx.doi.org/10.3111/13696998.2012.689792>] [PMID: 22548677]
- [19] Brixner DI, Jackson KC II, Sheng X, Nelson RE, Keskinaslan A. Assessment of adherence, persistence, and costs among valsartan and hydrochlorothiazide retrospective cohorts in free-and fixed-dose combinations. *Curr Med Res Opin* 2008; 24(9): 2597-607.

- [http://dx.doi.org/10.1185/03007990802319364] [PMID: 18812017]
- [20] Bramlage P, Ketelhut R, Fronk EM, *et al.* Clinical impact of patient adherence to a fixed-dose combination of olmesartan, amlodipine and hydrochlorothiazide. *Clin Drug Investig* 2014; 34(6): 403-11.
[http://dx.doi.org/10.1007/s40261-014-0188-z] [PMID: 24719291]
- [21] Jackson KC II, Sheng X, Nelson RE, Keskinaslan A, Brixner DI. Adherence with multiple-combination antihypertensive pharmacotherapies in a US managed care database. *Clin Ther* 2008; 30(8): 1558-63.
[http://dx.doi.org/10.1016/j.clinthera.2008.08.010] [PMID: 18803997]
- [22] Panjabi S, Lacey M, Bancroft T, Cao F. Treatment adherence, clinical outcomes, and economics of triple-drug therapy in hypertensive patients. *J Am Soc Hypertens* 2013; 7(1): 46-60.
[http://dx.doi.org/10.1016/j.jash.2012.11.001] [PMID: 23321404]
- [23] Thom S, Poulter N, Field J, *et al.* Effects of a fixed-dose combination strategy on adherence and risk factors in patients with or at high risk of CVD: The UMPIRE randomized clinical trial. *JAMA* 2013; 310(9): 918-29.
[http://dx.doi.org/10.1001/jama.2013.277064] [PMID: 24002278]
- [24] Agarwal S, Tang SS, Rosenberg N, *et al.* Does synchronizing initiation of therapy affect adherence to concomitant use of antihypertensive and lipid-lowering therapy? *Am J Ther* 2009; 16(2): 119-26.
[http://dx.doi.org/10.1097/MJT.0b013e31816b69bc] [PMID: 19114872]
- [25] Hong SH, Wang J, Tang J. Dynamic view on affordability of fixed-dose combination antihypertensive drug therapy. *Am J Hypertens* 2013; 26(7): 879-87.
[http://dx.doi.org/10.1093/ajh/hpt035] [PMID: 23512697]
- [26] Wong MC, Tam WW, Cheung CS, *et al.* Medication adherence to first-line antihypertensive drug class in a large Chinese population. *Int J Cardiol* 2013; 167(4): 1438-42.
[http://dx.doi.org/10.1016/j.ijcard.2012.04.060] [PMID: 22560948]
- [27] Citarella A, Linder M, Kieler H, *et al.* Influence of baseline low-density lipoprotein cholesterol values on statin therapy persistence. *Eur J Clin Pharmacol* 2016; 72(3): 349-57.
[http://dx.doi.org/10.1007/s00228-015-1996-7] [PMID: 26671240]
- [28] Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *Am J Manag Care* 2010; 16(8): 568-76.
[PMID: 20712390]
- [29] Xu T, Yu X, Ou S, *et al.* Adherence to antihypertensive medications and stroke risk: A dose-response meta-analysis. *J Am Heart Assoc* 2017; 6(7): e006371.
[http://dx.doi.org/10.1161/JAHA.117.006371] [PMID: 28743788]
- [30] Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Drug adherence in hypertension: From methodological issues to cardiovascular outcomes. *J Hypertens* 2017; 35(6): 1133-44.
[http://dx.doi.org/10.1097/HJH.0000000000001299] [PMID: 28306634]
- [31] Ferrajolo C, Arcoraci V, Sullo MG, *et al.* Pattern of statin use in southern italian primary care: Can prescription databases be used for monitoring long-term adherence to the treatment? *PLoS One* 2014; 9(7): e102146.
[http://dx.doi.org/10.1371/journal.pone.0102146] [PMID: 25072244]
- [32] Arnet I, Kooij MJ, Messerli M, Hersberger KE, Heerdink ER, Bouvy M. Proposal of standardization to assess adherence with medication records: Methodology matters. *Ann Pharmacother* 2016; 50(5): 360-8.
[http://dx.doi.org/10.1177/1060028016634106] [PMID: 26917817]
- [33] Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006; 15(8): 565-74.
[http://dx.doi.org/10.1002/pds.1230] [PMID: 16514590]
- [34] Sikka R, Xia F, Aubert RE. Estimating medication persistency using administrative claims data. *Am J Manag Care* 2005; 11(7): 449-57.
[PMID: 16044982]
- [35] Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002; 288(4): 455-61.
[http://dx.doi.org/10.1001/jama.288.4.455] [PMID: 12132975]
- [36] Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 2007; 10(1): 3-12.
[http://dx.doi.org/10.1111/j.1524-4733.2006.00139.x] [PMID: 17261111]
- [37] Malo S, Aguilar-Palacio I, Feja C, *et al.* Different approaches to the assessment of adherence and persistence with cardiovascular-disease preventive medications. *Curr Med Res Opin* 2017; 33(7): 1329-36.
[http://dx.doi.org/10.1080/03007995.2017.1321534] [PMID: 28422521]
- [38] Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Drug adherence in hypertension: From methodological issues to cardiovascular outcomes. *J Hypertens* 2017; 35(6): 1133-44.
[http://dx.doi.org/10.1097/HJH.0000000000001299] [PMID: 28306634]

Stelina Alkagiet

First Propedeutic Department of Internal Medicine
Medical School
Aristotle University of Thessaloniki
AHEPA Hospital
Thessaloniki, Greece

Konstantinos Tziomalos

First Propedeutic Department of Internal Medicine
AHEPA Hospital
1 Stilponos Kyriakidi Street
Thessaloniki, 54636, Greece
Tel: +30-2310-994621
Fax: +30-2310-994773
E-mail: ktziomalos@yahoo.com

© 2018 Alkagiet and Tziomalos.

This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 International Public License (CC-BY 4.0), a copy of which is available at: (<https://creativecommons.org/licenses/by/4.0/legalcode>). This license permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.