

# ECHOs of Medication Non-Adherence in Hypertensive Patients: A Systematic Review

Satish S<sup>1</sup>, Agnes Jain Rose<sup>2</sup>

<sup>1</sup>Associate Professor, Department of Pharmacy Practice, Srinivas College of Pharmacy, Mangalore, India

<sup>2</sup>Student, Pharm D, Srinivas College of Pharmacy, Mangalore, India

Corresponding Author: Agnes Jain Rose

## ABSTRACT

Globally, hypertension has been one of the most common diseases. Although there has been improvement in the blood pressure control with the use of antihypertensive drugs, poor adherence to medications is still a problem. This has caused economic, clinical and humanistic outcomes (ECHOs) resulting in severe health crisis. This includes worsening of present disease condition, increase in co morbid diseases, increase in health care costs and ultimately death.

This systematic review has broadened the scope of knowledge by providing valuable input into the development of clinical, economic and humanistic framework to standardize the consequences of medication non-adherence with the ECHOs. Literature documents the multiple adverse clinical consequences of medication non-adherence. It is also associated with a greater risk of cardiovascular events including vascular stiffness, left ventricular hypertrophy, micro albuminuria, acute coronary syndromes, stroke and transient ischemic attack and chronic heart failure ultimately leading to death. Humanistic outcomes were evaluated by measuring the symptomatic and functional status and quality of life. Economic outcomes were mainly affected by hospital related costs, productivity costs, social welfare costs, personal costs, cost to the family and friends and other associated costs.

**Keywords:** Hypertension, Medication non-adherence, Clinical outcomes, Economic outcomes, Humanistic outcomes

## INTRODUCTION

Essential hypertension, also known as primary hypertension is the most common type of hypertension. Secondary hypertension occurs due to the underlying co-morbidities. If the underlying co-morbidities are corrected, blood pressure could return to normal. [1] It is known as silent killer in developed and developing nations. [2] More than 26% of the adult populations worldwide have been diagnosed to have hypertension. [3] Unfortunately, the adherence rates of antihypertensive agents remain below optimum. It has been identified as one of the main causes of failure in achieving blood pressure control. [4] The various complications of hypertension were also clarified with arterial changes understood as fundamental reason to those adverse consequences [5]. These consequences may result in severe health crisis causing economic, clinical and humanistic outcomes (ECHOs). This includes worsening of present disease condition, increase in co morbid diseases, increase in health care costs and ultimately death.

However, non-adherence can cause higher risk in geriatric patients which could lead to poor disease control associated with multiple morbidities and poly pharmacy. [6] Medications play a major role in preventing and treating diseases. Therefore it is necessary to know the problems that arise due to low adherence to medications. [7]

Adherence to medications is the process by which patients take their

medications as prescribed by a registered physician. [8] Medication non-adherence or non-compliance can be defined as the failure to take medications as prescribed intentionally or unintentionally. [9] Adherence to long-term therapy for chronic illnesses like hypertension is very much essential to enhance the effectiveness of pharmacotherapy. Else it could cause

decline of health leading to increased emergency room visits and hospitalizations. It has also been found that the increasing number of drugs that are prescribed during hospital discharge has some association with non-adherence and majority of patients did not understand the purpose of their medication administration which is one of the major reasons for non-adherence. [10]

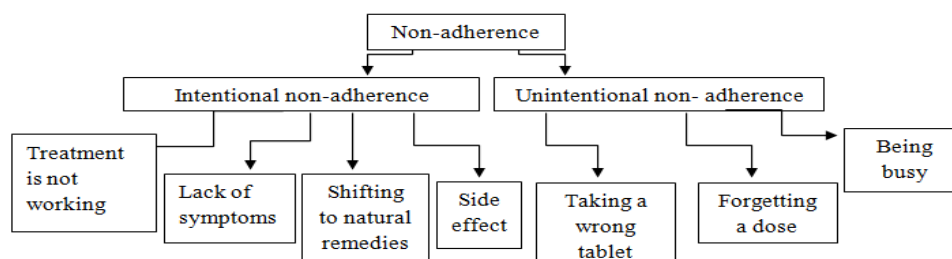


Figure 1: Common reasons for medication non – adherence

Simplifying drug regimens, reducing pill burdens and better explanations of the reason for medication administration should be targets for intervention. [11] Clinicians should counsel patients on how to improve adherence instead of changing prescriptions, increasing drug dosage or adding medications. [12]

## OUTCOMES OF MEDICATION NON-ADHERENCE

This systematic review broadens the scope of knowledge regarding clinical, economical and humanistic outcomes of medication non-adherence among hypertensive population groups. Medication non-adherence is generally associated with increased healthcare costs, poor clinical outcome and decreased quality of life. A large variety of outcomes can be used to measure the clinical, economic and humanistic impacts. They include total healthcare cost, pharmacy costs, in-patient costs, out-patient costs, emergency department costs, medical costs, hospitalization costs, increased rates of co morbidities, complications of hypertension as well as patient satisfaction.

## CLINICAL OUTCOMES

Literature documents the multiple adverse clinical consequences of medication

non-adherence. It is also associated with a greater risk of cardiovascular events including vascular stiffness, left ventricular hypertrophy, micro albuminuria, acute coronary syndromes, stroke and transient ischemic attack and chronic heart failure ultimately leading to death. [13]

## Uncontrolled Hypertension and Progression to More Severe Hypertension

A cross-sectional survey conducted in Portugal in a hypertension outpatient clinic showed that the possible underlying cause of uncontrolled blood pressure is poor medication adherence. [14] Furthermore, a study conducted in Uzbekistan revealed that hypertension-controlled patients were significantly adherent to antihypertensive drugs than uncontrolled patients. [15] Another study was carried out on 88 patients with uncontrolled hypertension. It aimed the completion of Anxiety sensitivity index. During the interval between two primary care visits using an electronic pillbox, the adherence to BP medications was measured. The study showed that majority of patients with high anxiety sensitivity (low anxiety in actual) were found to be non-adherent to BP medications compared to patients with low index (high anxiety). [16]

**Vascular stiffness:** Hypertension causes an increase in the intra luminal pressure that

stimulates subsequent collagen production. [17] In a study of 42 geriatric hypertensive patients undergoing chronic antihypertensive therapy, the Ambulatory Arterial Stiffness Index (AASI) and its symmetric calculation were derived from 24 h-Ambulatory blood pressure monitoring (ABPM). The study showed that low adherence to antihypertensive therapy was found to be associated with increased standard AASI. [18] Other study findings demonstrate that both  $\beta$ -adrenergic blocker and angiotensin receptor blocker improve measures of vascular stiffness distinct mechanisms. Based on the observations made during the study, there may be a role for both  $\beta$ -blockers and ARBs in the treatment of vascular stiffness. [19]

**Left ventricular hypertrophy:** High blood pressure can increase the workload of the left ventricle. This could lead to the loss of elasticity of the heart muscles and eventually fail to meet the need. [20] In a study conducted in Nigeria, the Morisky Medication Adherence Scale (MMAS-4) was used to assess drug adherence among hypertensive patients. Patients with low adherence had higher rate of ECG LVH compared to patients with good adherence. [21] Differences in results among various antihypertensive drugs such as sympatholytics, ACE inhibitors and calcium channel blockers reflect the factors that affect left ventricular hypertrophy. [22]

**Microalbuminuria and Macroalbuminuria:** Microalbuminuria is found to be associated with increased cardiovascular risks in patients with hypertension. 55 patients with essential hypertension, 11–19 years old, receiving antihypertensive therapy were prospectively studied. Lowering of microalbuminuria lowering ceases the progression of LVH or induces turnabout. [23] A study was conducted in 155 patients and it revealed that with the increase in albuminuria, prevalence of arterial hypertension also increased. It included 48% of patients with

normoalbuminuria, 68% with microalbuminuria and 85% with macroalbuminuria respectively. [24]

**Acute Myocardial Infarction:** Patients with uncontrolled hypertension, hypertensive crisis and other risk factors such as cardiovascular disease; and also poorly adhere to medications, tend to experience adverse cardiovascular events. Some reports included very large numbers of patients who were newly treated for hypertension. Moreover, the components of composite cardiovascular disease such as myocardial infarction, stroke, and chronic heart failure are also associated with adherence. [25]

**Stroke:** Stroke causes functional or neurological deficits that often lead to death or permanent disability. High blood pressure is one of the modifiable risk factors but non-adherence to antihypertensive medication could lead to uncontrolled blood pressure. A study concluded that non-adherence to antihypertensive medication could increase the risk of stroke. Therefore, it is necessary for the healthcare providers to implement strategies that improve patients' adherence to medications. [26]

**Chronic kidney disease (CKD):** Kidney, which plays a major role in the elimination of body wastes, could be damaged due to hypertension, making elimination from the body difficult. The relationship between hypertension and CKD is linear. Studies carried out on hypertension and chronic kidney disease has shown that the rate of renal function impairment can be reduced by maintaining optimal blood pressure irrespective of the underlying renal disease. [27]

**Cognitive Function and Dementia:** Another well-known cause of poor adherence in elderly patients is cognitive dysfunction and dementia. Blood pressure control has a role to play in the prevention of cognitive dysfunction and dementia. [28]

Few studies have shown that improved adherence to medications in patients with cognitive dysfunction or dementia, but data demonstrating a clear impact is not available.

**Diabetes:** Increased peripheral vascular resistance is considered the hallmark of hypertension in patients with both type I and type II diabetes. The pathogenesis of blood pressure in patients with diabetes is also associated with increase in the exchangeable. [29]

**Atherosclerosis:** Hypertension may induce shear-related injury to the vessel leading to atherosclerosis. Elevated lipids levels lead to endothelial dysfunction, smooth muscle cell proliferation, and lipid accumulation, foam cell formation that eventually leads to necrosis and plaque development. [30]

**Hypertensive retinopathy:** The retinal arterial consequences of mild hypertension comprise thickening and irregularity. Emboli may be seen occasionally in the retinal circulation. Data on the prevalence of hypertensive retinopathy signs have been found in recent studies carried out among the general population and it revealed that 3-14% of the population with hypertensive retinopathy is more than 40 years of age. These evidences were obtained from retinal photographs. [31]

**Sexual dysfunction:** Erectile or sexual dysfunction is likely in men with hypertension. This is because hypertension limits the blood flowing to the penis. Women could also experience sexual dysfunction due to increase in blood pressure. Reduction in the rate of blood flow to the vagina can lead to a decrease in sexual desire, difficulty achieving orgasm, arousal and vaginal dryness [32]

## HUMANISTIC OUTCOMES

The consequences of disease/treatment on a patient's functional status or quality of life (QoL) are called humanistic

outcomes; also referred to as health-related quality-of-life (HR-QoL). Humanistic outcomes in a patient include how a patient feels after treatment. If the patient is satisfied, the outcome is that he will adhere to the treatment and if unsatisfied, he would switch doctors/ pharmacies/medications whereas clinical outcomes are measures that refer to the occurrence of disease, symptom or sign or laboratory abnormality in clinical trials. Humanistic (or patient-oriented) outcomes are evaluated by the measurement of symptom status, functional status, and QoL. Symptom status is defined as a patient's perception of an abnormality in the physical, emotional, or cognitive state. Functional status is defined as the ability to perform the activities that people do in the normal course of their lives to meet their basic needs. Overall QoL is defined as subjective well-being or satisfaction with life. [33] It is measured using a 6-dimension or 8-, 12-, or 36-item Short-Form Health Surveys, 5-dimension EuroQol questionnaire or Health-Related QoL questionnaire. [34]

## Reduced Quality of life

When hypertension is controlled intensively to maintain the BP values below <140/<90, more serious adverse events occur. It could also lead to a very low pressure. There intensives therapies are always attributed to reduced quality of life. Yet, there are studies that indicate that with better control of hypertension and greater adherence to BP medications can provide higher quality of life. [35]

## Disability and Reduced Work Productivity

Uncontrolled HTN is a major contributor to serious events. Self-reported low adherence to anti-hypertensive medication was linked to higher levels of work impairment, that is individual present but less productive. A significant reduction in work productivity was reported by participants who were classified as low adherence with regard to their

antihypertensive treatment, primarily associated with productivity while at work. Stage 2 hypertensive respondents reported significantly more work productivity impairment than respondents with less severe stages of hypertension, and the number of co morbidities was also significantly associated with work productivity impairment. Initiatives targeting improved adherence to medications and improved BP control among patients with hypertension may present economic opportunities for employers by impacting work productivity. [36]

### ECONOMIC OUTCOMES

The economic impact of non-adherence and the benefit of adherence with appropriate interventions need to be understood. This would help in the estimation of the full cost on non adherence to medications. This includes:

#### Direct costs:

- **Hospital costs:** This includes medicine and health care costs that resulted due to increase in morbidity and hospital visits due to reduced adherence to the instructions and recommendations made by the medical practitioner.
- **Hospital associated costs:** These include costs outside the hospital setting that occur due to non-adherence.

#### Indirect costs:

- **Productivity costs:** The costs incurred by the patient and society because of lost or impaired ability to work or engage in leisure activities due to morbidity and lost economic productivity due to early death.
- **Social welfare costs:** costs liable to the social welfare system.
- **Personal costs:** costs to the patient due to loss of health and– subsequent loss of income as a result of non-adherence

#### Costs to the patient's family and friends:

costs to family members– and other

associates, such as time associated with caring for the patient.

**Other associated costs:** all other negative externalities not covered– above. For example, non-adherence with infectious diseases may cause public health problems if other patients are infected.

Medication non-adherence is estimated to cost €125 billion annually according to the European government and the cost arising due to this poor adherence is 14% of total healthcare in the UK. In the US, the relationship between non-adherence and associated costs is a continuous cycle. The costs associated with hypertension and the economic outcomes when adherence to antihypertensive therapy is increased have been investigated in five European countries namely Italy, Germany, France, Spain, and England over a period of 10 years. This study revealed that around €332 million can be achieved by increasing adherence to 70%. Such studies such can help inform decision makers and aid understanding of the importance of adherence. [37]

No much data on broader economic implications such as negotiable costs that come from higher disease prevalence is available. This fails to quantify the costs separately into direct and indirect costs probably due to coding or confidentialities in healthcare claim databases. Most of the studies have taken the perspective of the patient or healthcare provider to estimate the additional costs associated with non-adherence and it is compared with adherence costs. Current literature identifies and quantifies the economic burden of non-adherence, but no research has attempted to synthesize costs across disease states within major healthcare systems. Further exploration of the costs associated with non-adherence behavior is required to adequately quantify the overall cost of non-adherence to healthcare systems because the available data has considerable uncertainty.

## CONCLUSION

The economic, clinical and humanistic outcomes (ECHOs) of medication non-adherence will continue to grow as the burden of chronic diseases such as hypertension grows worldwide. Achieving satisfactory adherence may have far greater impact to improve antihypertensive treatments, and healthcare systems must evolve to meet this challenge. Improving medication adherence provides an opportunity to prevent hypertensive complications, major cost savings to healthcare systems as well as increase the quality of life of the patient. Predictions of population health outcomes by using the efficacy data of treatment need to be used in conjunction with adherence rates for planning and project evaluation. The correlation between increased non-adherence and higher disease prevalence should be used to circumvent avoidable costs and increase the therapeutic outcomes.

**Acknowledgement:** None

**Conflict of Interest:** None

**Source of Funding:** None

## REFERENCES

1. Salvi P. Hypertension and Spurious Systolic Hypertension in Youth. *High Blood Pressure & Cardiovascular Prevention*. 2007;14(3):145-196
2. Khan MU, Shah S, Hameed T. Barriers to and determinants of medication adherence among hypertensive patients attended National Health Service Hospital, Sunderland. *Journal of pharmacy & bioallied sciences*. 2014; 6(2):104.
3. Lee GK, Wang HH, Liu KQ et al. Determinants of medication adherence to antihypertensive medications among a Chinese population using Morisky Medication Adherence Scale. *PloS one*. 2013; 8(4):e62775.
4. Gosmanova EO, Molnar MZ, Alrifai A et al. Impact of non-adherence on renal and cardiovascular outcomes in US veterans. *American journal of nephrology*. 2015; 42(2):151-157.
5. D. Gareth Beevers, S. Robertson J. Chapter 1 A short history of hypertension. *Comprehensive Hypertension*. Elsevier. 2007:3-20
6. Hughes, C.M. Medication Non-Adherence in the Elderly. *Drugs Aging* 21.2004: 793–811
7. Wilhelmsen NC, Eriksson T. Medication adherence interventions and outcomes: an overview of systematic reviews. *European Journal of Hospital Pharmacy*. 2019; 26(4):187-192.
8. Vrijens B, De Geest S, Hughes DA et al. A new taxonomy for describing and defining adherence to medications. *British journal of clinical pharmacology*. 2012; 73(5):691-705.
9. Guthrie J. Consequences of Medication Non-Adherence. *Imedicare*. 2014
10. Pasina L., Brucato A.L., Falcone C. et al. Medication Non-Adherence among Elderly Patients Newly Discharged and Receiving Polypharmacy. *Drugs Aging* 31. 2014:283–289
11. Chisholm-Burns MA, Spivey CA. The 'cost' of medication non adherence: consequences we cannot afford to accept. *Journal of the American Pharmacists Association*. 2012; 52(6):823-826.
12. Cutler RL, Fernandez-Llimos F, Frommer M et al. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ open*. 2018; 8(1):e016982.
13. Burnier M, Egan B. Adherence in Hypertension. *Circulation Research*. 2019; 124(7):1124-1140.
14. Morgado M, Rolo S, Macedo AF et al. Predictors of uncontrolled hypertension and antihypertensive medication non adherence. *Journal of cardiovascular disease research*. 2010; 1(4):196.
15. Malik A, Yoshida Y, Erkin T et al. Hypertension-related knowledge, practice and drug adherence among inpatients of a hospital in Samarkand, Uzbekistan. *Nagoya journal of medical science*. 2014; 76(3-4):255.
16. Alcantara C, Edmondson D, Moise N et al. Anxiety sensitivity and medication non-adherence in patients with uncontrolled hypertension. *Journal of psychosomatic research*. 2014; 77(4):283-286.

17. Ecobici m, stoicescu c. Arterial Stiffness and Hypertension–Which Comes First? *Maedica*. 2017; 12(3):184.
18. Berni A, Ciani E, Cecioni I et al. Adherence to antihypertensive therapy affects ambulatory arterial stiffness index. *European journal of internal medicine*. 2011; 22(1):93-98.
19. Barbaro NR, Fontana V, Modolo R et al. Increased arterial stiffness in resistant hypertension is associated with inflammatory biomarkers. *Blood pressure*. 2015; 24(1):7-13.
20. Agarwal R. Prevalence of Left Ventricular Hypertrophy: Some Alternate Thoughts. *American Journal of Kidney Diseases*. 2005; 46(6):1148.
21. Ajayi EA, Adeoti AO, Ajayi IA et al. Adherence to antihypertensive medications and some of its clinical implications in patients seen at a tertiary hospital in Nigeria. *IOSR J Dent Med Sci*. 2013; 8(4):36-40.
22. Fouad-Tarazi FM, Liebson PR. Echocardiography studies of regression of left ventricular hypertrophy in hypertension. *Hypertension*. 198;II65.
23. Gall MA, Rossing P, Skøtt P et al. Prevalence of micro-and macroalbuminuria, arterial hypertension, retinopathy and large vessel disease in European type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 1991; 34(9):655-661.
24. Schmitz A. Microalbuminuria, Blood Pressure, Metabolic Control, and Renal Involvement: Longitudinal Studies in White Non-Insulin-Dependent Diabetic Patients. *American journal of hypertension*. 1997; 10(S6):189S-97S.
25. Dunn FG. Hypertension and myocardial infarction. *Journal of the American College of Cardiology*. 1983; 1(2 Part 1):528-532.
26. Lee HJ, Jang SI, Park EC. Effect of adherence to antihypertensive medication on stroke incidence in patients with hypertension: a population-based retrospective cohort study. *BMJ open*. 2017; 7(6):e014486.
27. Eskridge MS. Hypertension and chronic kidney disease: the role of lifestyle modification and medication management. *Nephrology Nursing Journal*. 2010; 37(1):55.
28. Ladekola C, Yaffe K, Biller J et al. Impact of Hypertension on Cognitive Function: A Scientific Statement from the American Heart Association. *Hypertension*. 2016; 68(6):e67–e94.
29. Epstein M, Sowers JR. Diabetes mellitus and hypertension. *Hypertension*. 1992; 19(5):403-418.
30. Dzau VJ. Atherosclerosis and hypertension: mechanisms and interrelationships. *Journal of Cardiovascular Pharmacology*. 1990; 15Suppl 5:S59-64.
31. Tien Yin Wong, Rachel McIntosh. Hypertensive retinopathy signs as risk indicators of cardiovascular morbidity and mortality. *British Medical Bulletin*. 2005; 73-74(1): 57–70
32. Volpe M. High Blood Pressure & Cardiovascular Prevention. *High Blood Pressure & Cardiovascular Prevention*. 2007; 14(1):1-3.
33. Ropka ME. Symptom status and functional status outcomes: humanistic outcomes in obesity disease management. *Obesity*. 2002; 10(s11):42S.
34. Freeman C, Giles L, Field P et al. Humanistic burden and economic impact of chronic kidney disease: a systematic literature review. *F1000Research*. 2019; 8(2142):2142.
35. Wagner, S. & Lau, H. & Frech et al. Impact of medication adherence on work productivity in hypertension. *American Journal of Pharmacy Benefits*. 2012; 4. e88-e96
36. Desai A, Mahajan N, Sewlikar S et al. Medication adherence: the critical step towards better patient outcome. *Int J Basic ClinPharmacol* 2014; 3:748-54.
37. Vrijens B, Antoniou S, Burnier M et al. Current situation of medication adherence in hypertension. *Frontiers in pharmacology*. 2017; 8:100.

How to cite this article: Satish S, Rose AG. ECHOs of medication non-adherence in hypertensive patients: a systematic review. *International Journal of Research and Review*. 2021; 8(7): 446-452. DOI: <https://doi.org/10.52403/ijrr.20210762>

\*\*\*\*\*