

# Are We Doing Enough to Combat Poor Adherence to Pharmacotherapy in Atherosclerotic Cardiovascular Disease?

Sandeep Bansal<sup>1</sup>, Mohanan Padinhare<sup>2</sup>, Jagdish Chander Mohan<sup>3</sup>, Kimi Shetty<sup>4,\*</sup>, Jyoti Juneja<sup>5</sup>, Shreenath Hariharan<sup>6</sup>

<sup>1</sup>Department of Cardiology, Consultant and Head of Cardiology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, INDIA.

<sup>2</sup>Department of Cardiology, Westfort Hi-Tech hospital, Thrissur, Kerala, INDIA.

<sup>3</sup>Department of Cardiology, Chairman and Head of Cardiology, Jaipur Golden Hospital, Jaipur, INDIA.

<sup>4</sup>Department of Medical Affairs, Medical Lead, Novartis Healthcare Private Limited, INDIA.

<sup>5</sup>Department of Medical Affairs, Senior Medical Scientific Liaison, Novartis Healthcare Private Limited, INDIA.

<sup>6</sup>Department of Ex-employee at Medical affairs, Novartis Healthcare Private Limited, INDIA.

## ABSTRACT

Atherosclerotic Cardiovascular Disease (ASCVD) is a globally prevalent non-communicable disease contributing significantly to Cardiovascular (CV) morbidity and mortality. Approximately, 70% of Cardiovascular Disease (CVD) cases and deaths have been attributed to modifiable risk factors. To overcome the risk factors, therapeutic adherence plays a pivotal role in ASCVD management and is determined by multiple factors. This review highlights the effect of poor adherence on ASCVD events in India, ways to prevent non-adherence and ensure optimum outcomes for patients. Among the major risk factors that cause ASCVD, dyslipidemia is often neglected or inadequately treated. Studies from India have identified varying rates of adherence to lipid lowering therapies in ASCVD. Factors such as lower socioeconomic status, health literacy, asymptomatic nature of disease, forgetfulness and cost of medications contribute towards non-adherence. This has resulted in significantly higher hospitalizations for CVDs and an increased risk of mortality and indirect cost. Further, emphasis is warranted on patient education, enhanced physician-patient relationship and communication, increased access to health care, frequent use of fixed drug combinations, and affordability in improving therapeutic adherence in ASCVD. With innovation in therapeutics, the pharmaceutical sector can contribute significantly to improve adherence.

**Keywords:** Atherosclerotic cardiovascular disease, Adherence, Lipid lowering therapy.

## Correspondence:

**Dr. Kimi Shetty**

Medical Lead, Novartis Healthcare Private Limited, INDIA.

Email: kimi\_kishore.shetty@novartis.com

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## INTRODUCTION

### Atherosclerotic cardiovascular disease - epidemiology in the world and India

Cardiovascular Diseases (CVD) caused due to atherosclerotic origin are defined as Atherosclerotic Cardiovascular Disease (ASCVD).<sup>1</sup> An estimated 18 million people died due to CVD in 2019, representing 32% of the total deaths globally.<sup>2</sup> This makes CVD one of the leading causes of mortality worldwide, with more than 80% of these attributed to Ischemic Heart Disease (IHD) and stroke.<sup>2</sup> If we look at the Indian perspective, 54.5 million patients

with CVD contributed to 28% of total deaths in 2016, of which ~18% deaths were due to IHD.<sup>3</sup> It is also well known that CVD occurs a decade earlier in Indians than the European population, which could correlate to India contributing to one-fifth of all the cardiovascular (CV) deaths worldwide.<sup>4</sup>

### ASCVD risk factors and its management

Dyslipidemia, hypertension, diabetes mellitus (DM), smoking, and obesity are considered to be the conventional risk factors that are associated with the increased prevalence of ASCVD.<sup>5</sup> India, being a country of diabetics, we often find higher awareness on DM status and therapies, unlike dyslipidemia, which, is one of the cornerstones of ASCVD causation.<sup>6</sup> Abnormal lipids account for >50% of coronary artery disease (CAD) and cerebrovascular disease, and lipid-lowering therapy (LLT) with statins can reduce this risk by >50%.<sup>7,8</sup> ASCVD management focuses on control



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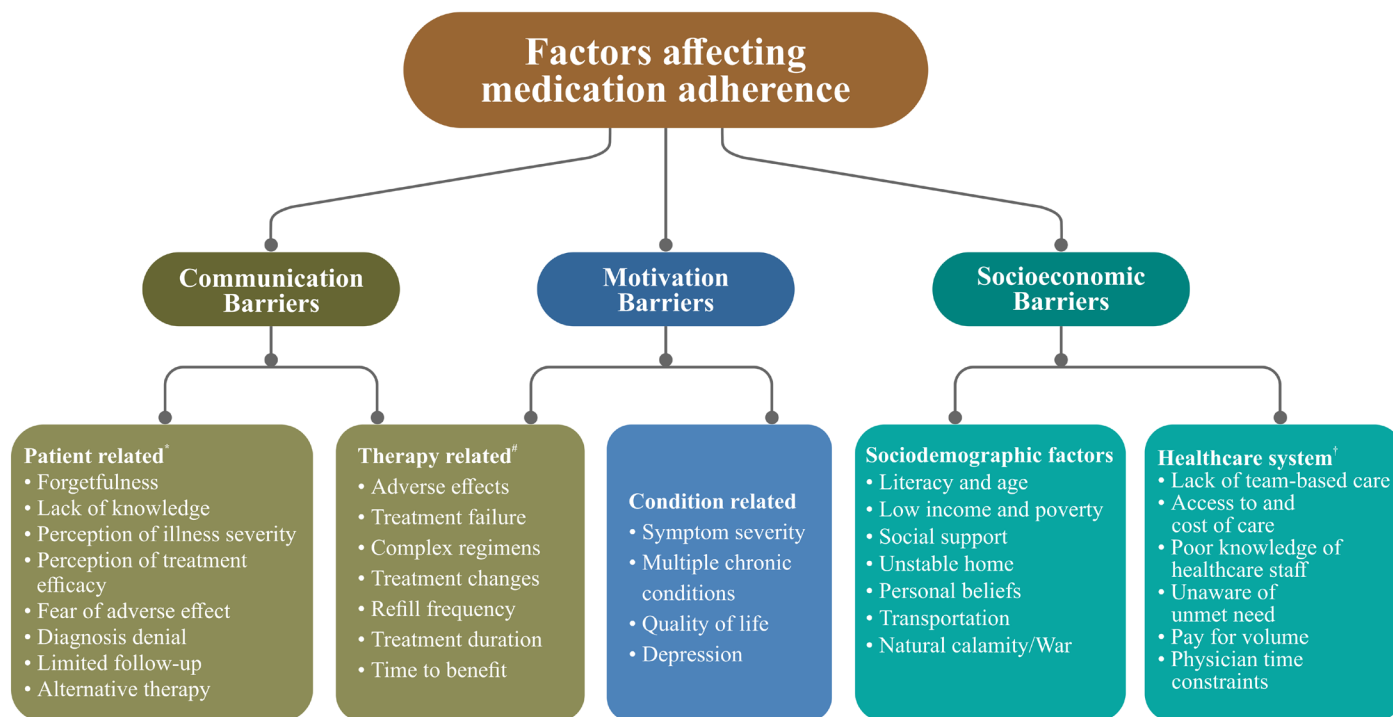
of risk factors and guideline directed treatment algorithms. International and national guidelines for ASCVD recommend multiple alternatives and algorithms for treatment based on severity of disease and number of risk factors.<sup>7-10</sup> However, treatment adherence is not considered as a factor in decision making while developing guidelines. This narrative review thus aims to highlight the impact of poor adherence in ASCVD

management, ways to reduce non-adherence and ensure optimum outcomes for patients.

### Rationale for adherence in ASCVD

#### Defining adherence to medications

World health organization defines adherence as ‘the degree to which a person complies with the agreed suggestions as received



\*The PALM registry surveyed 5693 adults who were recommended statins for CVD. Patient-related factors were highlighted in this study. Fear of side effects and perceived side effects were the most common reasons cited for declining or discontinuing a statin.<sup>20</sup>

#A study highlighted the therapy related factors. In this study, patients with ASCVD were prescribed statins. Approximately 61% did not fill a new prescription, skipped statins, or stopped refilling statins. The most commonly reported factor for not taking the prescribed statin were preferring to lower cholesterol with lifestyle changes (66%), disliking medications in general (59%), and liver or kidney problems (31%); having trouble remembering (forgetfulness, 9%) to take statins.<sup>21</sup>

†A large scale survey on patients with ASCVD reported reasons for barriers to medication. 59% of patients reported cost<sup>†</sup> as main barrier to medications, while 45% reported alternate therapy<sup>\*</sup>, and 59% reported side effects<sup>#</sup> as main reasons for barriers to medication. The findings of the study highlighted that even after a CV event, patients were not aware of the risk of elevated LDL-C.<sup>22</sup>

**Figure 1:** Common factors affecting medication adherence.<sup>20-23</sup>

ASCVD: Atherosclerotic Cardiovascular Disease, CVD: Cardiovascular Disease.

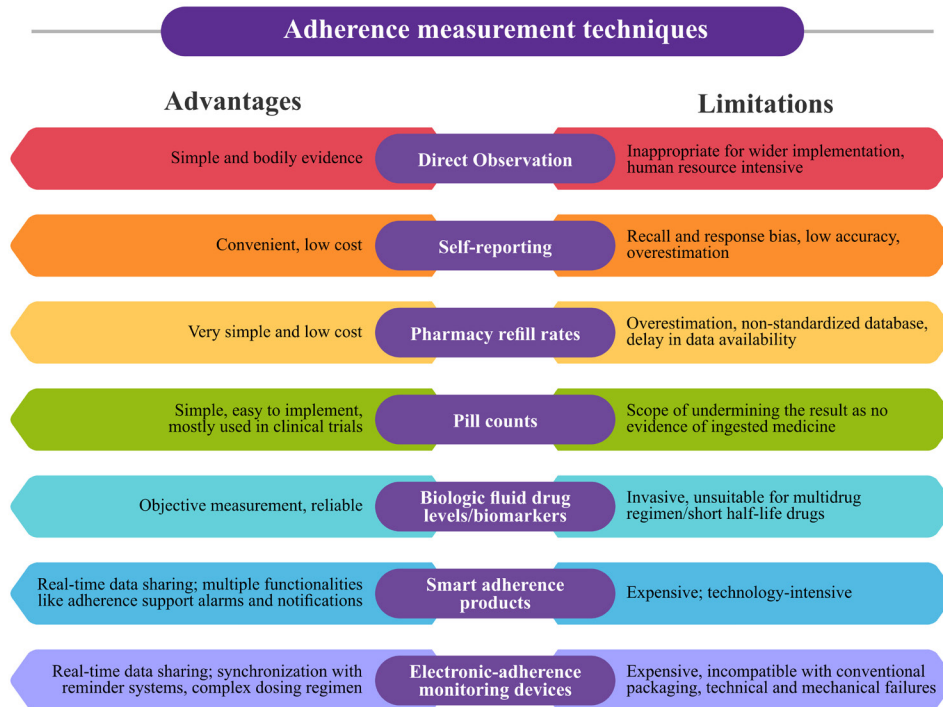
**Table 1:** Definition of adherence per the new taxonomy.

	Initiation	Implementation	Discontinuation
Definition	Intake of the first dose of prescribed medication. <sup>12</sup> Approximately 2% of patients never start their treatment, despite being enrolled in a study. <sup>13</sup> In real practice, >20% in patients treated for HTN or DM or dyslipidemia do not start their treatment. <sup>14</sup>	Represents the extent of taking actual dosing by a patient as per the prescribed dosing regimen. <sup>12</sup> May define the quantifiable adherence to a specific treatment if complete dosing history is provided. <sup>12</sup> Occasional forgetfulness or negligence or short period treatment interruptions can cause poor implementation. <sup>12</sup>	Marks the end of therapy, when the next dose to be taken is omitted and the treatment is interrupted thereafter. <sup>12</sup>

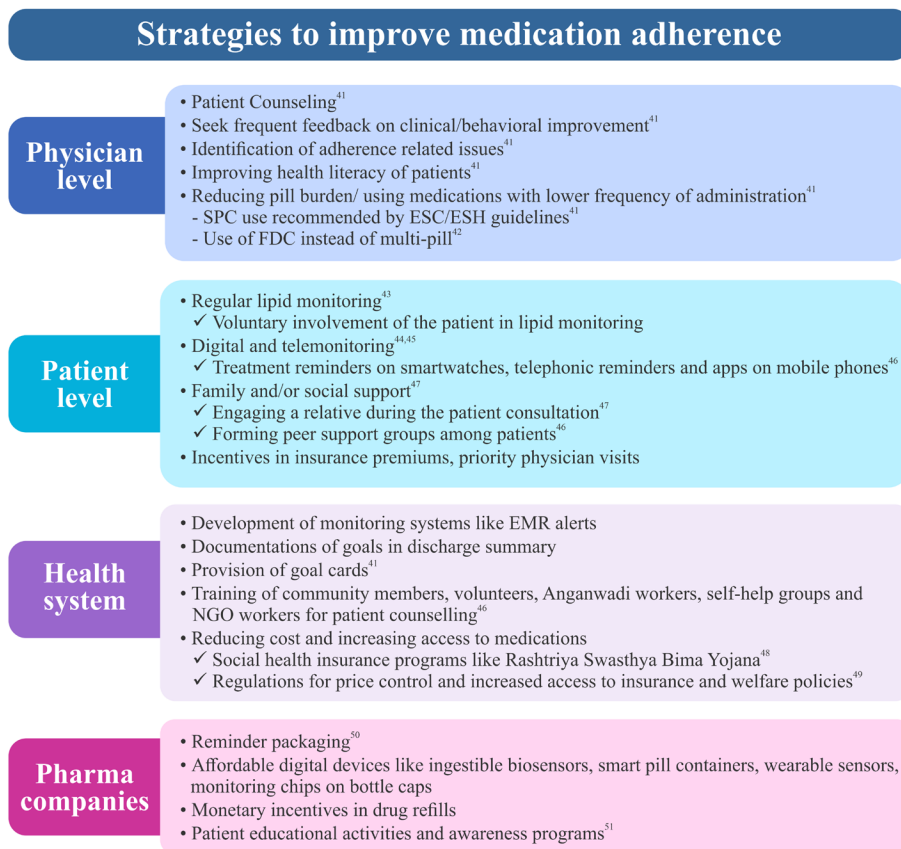
**Table 2: Literature evidence for ASCVD medication adherence from India.**

Study reference	Patient population	Sample size	Adherence techniques	Adherence report	Factors for non-adherence
Grover <i>et al.</i> <sup>25</sup>	Adult patients with dyslipidemia or with comorbidities like HTN, DM or IHD on statins.	200	MMAS score Pill count.	MMAS score Low (<6): 58.5% Medium (6 to<8): 32.5% High (8): 9%. Pill count (<80%) Low (<6): 96.6% Medium (6 to<8): 13.8%. High (8): 0%.	Complexity of treatment regimen. Forgetfulness.
Thom <i>et al.</i> <sup>26</sup>	Adults with high CV risk, established CVD (history of CHD, ischemic cerebrovascular disease, or PAD).	2004	Self-report.	Intervention arm- FDC: 86.3% Usual care: 64.7%.	Adverse effect. Patient choice.
Fathima <i>et al.</i> <sup>27</sup>	Patients at a CVD clinic. >50% patients were with dual morbidity (HTN, DM, IHD).	162	4-item MMAS.	Completely adherent: 40.1% Partially adherent 58.6% Completely non-adherent: 1.3% Mean MMAS score: 3.2.	Young age. Medication cost.
Umarje <i>et al.</i> <sup>28</sup>	Patients prescribed with statins for any CVD (ASCVD, HTN).	130	Systematically developed and validated questionnaire.	For ASCVD Good: 36.85% Moderate: 21.05% Low: 42.1%.	Forgetfulness. Medication cost.
Ponnusankar <i>et al.</i> <sup>29</sup>	Patients with chronic conditions like HTN, DM and CV conditions and had an established prescription.	90	Pill count Self-assessment form.	Pill count score Counselled group: 92.24±4.5 Usual care group: 84.71±11.8. Self-assessment Completely compliant- Counselled group: 75% Usual care group: 66.6%.	Lack of knowledge, Medication cost, Re-fill issues. Adverse effects.
Hegde <i>et al.</i> <sup>30</sup>	Elderly residents of the area where study was conducted and known to have at least one of the four chronic illness namely, CVD (HTN, CHD, CAD, angina, MI), cancer, chronic lung disease (COPD and asthma) and DM.	184	Structured pre-tested interview.	Fully-adherent- 63.6% Partially-adherent-27.7% Non-adherent- 8.7%.	Availability of medication and re-fill issues. Lack of knowledge of patients. Lack of knowledge of healthcare provider. Self-alteration of medicine dosage. Fear of adverse effects and dependency. Difficulty in swallowing.

ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CHD, chronic heart disease; COPD, Chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus, FDC, fixed dose combination; HTN, hypertension; MMAS, Morisky medication adherence scale, MI, myocardial infarction; IHD, ischemic heart disease; LLT, lipid-lowering therapy; PAD, peripheral artery disease.



**Figure 2:** Advantages and limitations of commonly used adherence measurement techniques.<sup>31-39</sup>



**Figure 3:** Strategies to improve medication adherence in ASCVD.<sup>42-51</sup>

ASCVD: Atherosclerotic Cardiovascular Disease, ESC: European Society of Cardiology, ESH: European Society of Hypertension, FDC: Fixed Dose Combination, LLT: Lipid-Lowering Therapy, MI: Myocardial Infarction, NGO: Non-Government Organization, SPC: Single Pill Combination.

from a healthcare professional in terms of taking medication, following a diet, and executing lifestyle changes.<sup>11</sup> In 2012, Vrijens B *et al.* proposed a new taxonomy for adherence.<sup>12</sup> Based on this, adherence to medications is a process characterized by 3 major components: the initiation, the implementation, and the discontinuation (Table 1).<sup>12-14</sup>

### **Impact of non-adherence to medications for ASCVD**

Non-adherence is complex, unpredictable and a powerful dependent and independent variable of evidence-based practice that can affect patient management.<sup>15</sup> Recent reviews have shown that as many as 40% of patients do not adhere to their treatment regimens.<sup>16</sup> Non-adherence to medications have caused 125000 deaths annually and accounts for 10% to 25% of hospital and nursing home admissions; resulting in non-adherence to medications being one of the largest and most expensive risk factors.<sup>16</sup> Non-adherence to prescribed medications can increase risk of hospitalization for patients with CVD (mainly CAD), mortality and indirect costs.<sup>17,18</sup> Furthermore, evidence also suggests that intra-individual visit-to-visit variability of Low-density lipoprotein cholesterol (LDL-C) levels can be harmful. The Treating to New Targets trial demonstrated that for each 1-standard deviation increase in LDL-C variability, the risk of any CV event increased by 11%, death by 23%, myocardial infarction by 10% and stroke by 17%.<sup>19</sup>

### **Factors affecting adherence in ASCVD**

Adherence is a multidimensional phenomenon determined by the interplay of five sets of factors, here termed 'dimensions', of which patient-related factors are just one determinant (Figure 1).<sup>20-23</sup>

Studies reporting adherence for ASCVD medications are scarce in India. A recent RWE study on 575 Indian patients followed up for a year after an acute coronary syndrome event showed, that even though all patients were prescribed statins on discharge (96.6% on high intensity statins), only 20.8% of these patients were on guideline directed LDL-c goals at the end of 1 year. The reasons for this could range from lack of treatment escalation to poor adherence.<sup>24</sup> Prescription combinations are sometimes poorly understood across specialties, leading to unintentional discontinuation of drugs.<sup>24</sup> Reasons for non-adherence in India are highlighted in Table 2.<sup>25-30</sup> Fathima *et al.* reported age and medication cost as the main factor for non-adherence among the Indian patients with CVD. A significantly higher proportion of individuals 60 years of age or older were fully adherent to the prescribed medications as compared to those under the age of 60 years. Similarly, a significantly higher proportion of those individuals who perceived that their medicines were non-expensive were fully adherent as compared to those who perceived that their medicines were expensive.<sup>27</sup> An Indian

study highlighting the benefits of patient counselling reported most patients rated forgetfulness (57.14% in the counseled and 36.84% in the usual care group), and cost of medications (28.57% in the counseled and 15.78% in the usual care group) as the main reason for non-adherence. While, 11.1% of patients in the counseled group and 47.36% in the usual care group stated side effects and lack of access as reasons for their non-adherence.<sup>29</sup> A cross-sectional study measuring the impact of adherence of statin therapy on patients with ASCVD reported lack of knowledge, cost, re-fill issues, and adverse effects as the main factors for non-adherence.<sup>28</sup>

### **Detecting poor medication adherence**

There are two broad methods for detecting poor adherence i) direct ii) indirect. Direct methods include monitoring of the patient taking the medication through direct observation or smart adherence products or the detection of the drug or its metabolite in the patient's biological fluid. While, indirect methods include self-reporting, electronic adherence monitoring tools, pharmacy refill rates, and pill counts (Figure 2).<sup>31-39</sup>

### **Combating poor adherence in ASCVD: The neglected unmet need**

Multiple strategies such as increased patient counselling, continuous involvement by health care professionals such as specialized nurses, and a new awareness of the impact of media-directed educational messages on patient behavior are needed to improve adherence to medication in order to reduce the risk of CV events, especially in an outpatient setting.<sup>40,41</sup>

### **Strategies to improve drug adherence in ASCVD**

Strategies to improve drug adherence in ASCVD have been summarized in Figure 3.

## **CONCLUSION**

ASCVD awareness, treatment accessibility/affordability and control are significant challenges in the Indian setting. Therapeutic adherence is a crucial factor in achieving ASCVD control, and it may get neglected in routine clinical practice. As multiple factors underlie poor adherence in patients with ASCVD, a universal approach is necessary to identify and address the same. Strategies involving patients, physicians, and health systems are needed. In the Indian setting, increased ASCVD awareness, increased access to health care, and medications affordability are the need of the hour to improve treatment adherence.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTION

Idea for the article was designed by Kimi Shetty, Jyoti Juneja, and Shreenath Hariharan. Literature search and data analysis was performed by Kimi Shetty, Jyoti Juneja, and Shreenath Hariharan. The manuscript was drafted and/or critically revised by Sandeep Bansal, PP Mohanan, JC Mohan, Kimi Shetty, Jyoti Juneja, Shreenath Hariharan.

## ABBREVIATIONS

**ASCVD:** Atherosclerotic Cardiovascular Disease; **CAD:** coronary artery disease; **CHD:** chronic heart disease; **COPD:** Chronic obstructive pulmonary disease; **CV:** cardiovascular; **CVD:** cardiovascular disease; **DM:** diabetes mellitus; **ESC:** European Society of Cardiology; **ESH:** European Society of Hypertension; **FDC:** Fixed Dose Combination; **HTN:** hypertension; **IHD:** Ischemic Heart Disease; **MMAS:** Morisky medication adherence scale; **LDL-C:** low-density lipoprotein cholesterol; **LLT:** Lipid-Lowering Therapy; **MI:** Myocardial Infarction; **NGO:** Non-Government Organization; **PAD:** peripheral artery disease; **SPC:** Single Pill Combination.

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