Medication Adherence Interventions for Cardiovascular Disease in Low- and Middle-Income Countries: A Systematic Review

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Purpose: The burden of cardiovascular diseases (CVD) is high in low- and middle-income countries (LMICs). Medications are integral to the management and control of CVD; however, suboptimal adherence impacts health outcomes. This systematic review aims to critically examine interventions targeted at improving medication adherence among persons with CVD in LMICs.

Methods: In this systematic review, we searched online databases PubMed, Embase, and CINAHL for studies that evaluated a medication adherence intervention for CVD, reported adherence as an outcome measure, were conducted in LMICs and reported the strategy or tool used to measure adherence. We included articles published in English, available in full text, peer-reviewed, and published between 2010 and 2020.

Results: We included 45 articles in this review. The majority of the studies implemented counseling and educational interventions led by nurses, pharmacists, or community health workers. Many of the studies delivered medication-taking reminders in the form of phone calls, text messages, short message services (SMS), and in-phone calendars. Multi-component interventions were more effective than unifocal interventions. Interventions involving technology, such as mobile phone calls, electronic pillboxes, and interactive phone SMS reminders, were more effective than generic reminders. The outcomes reported in the studies varied based on the complexity and combination of strategies. When interventions were implemented at both the patient level, such as reminders, and at the provider level, such as team-based care, the effect on medication adherence was larger.

Conclusion: In LMICs, medication adherence interventions among persons with CVD included a combination of patient education, reminders, fixed-dose combination therapy and team-based care approach were generally more effective than singular interventions. Among patients who had CVD, the medication adherence interventions were found to be moderately effective. Future studies focusing on improving medication adherence in LMICs should consider non-physician-led interventions and appropriately adapt the interventions to the local context.

Keywords: medication adherence, cardiovascular diseases, LMICs, systematic review

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally, accounting for about 17 million (30%) deaths annually.1 This number of CVD deaths is projected to increase to over 23.3 million by 2030.1 The population most affected are people living in regions where more than 80% of all CVD deaths occur.2 Although the CVD epidemic has begun to recede in some high-income countries (HICs), CVD mortality rates in low- and middle-income countries (LMICs) continue to rise to
about 300–600 CVD deaths per 100,000 population every year. Of note, in countries such as the United States, some of the gains achieved are being lost.\textsuperscript{1} Sub-optimal adherence to medications for the prevention and treatment and chronic conditions is considered a significant public health concern. It is also associated with poor control of CVD risk factors, CVD complications, worse health outcomes, and increased healthcare costs.\textsuperscript{3,4} In HICs, optimal adherence is only about 50% among patients who have CVD. Adherence to CVD medications is even lower in emerging economies where there are challenges of limited health resources, socioeconomic barriers, and inequities in access to healthcare.\textsuperscript{3,5}

Adherence is defined as the extent to which a person’s medication-taking behavior corresponds with an agreed recommendation from a healthcare provider.\textsuperscript{6} Achieving 80% or higher adherence to recommendations is considered “good”.\textsuperscript{7,8} The treatment of CVD usually involves long-term use of medications, and their full benefit is often undetected as only about 50% of patients take their medications as prescribed.\textsuperscript{9} Barriers to medication adherence include forgetfulness, cost, side effects, cultural beliefs, health insurance, depression, comorbidities, polypharmacy, lack of social support, patient-provider communications and relationships, and lack of health insurance.\textsuperscript{10,11}

There are several interventions for improving medication adherence: patient education, medication regimen management, fixed-dose combination medications, consultation with clinical pharmacists, and team-based care.\textsuperscript{12,13} Other strategies are cognitive-behavioral therapies, use of incentives, and medication-taking reminders such as electronic pill monitoring with text messages, automated refill tracking of in-patient electronic records, or email alerts to a provider for missed refills.\textsuperscript{12} While these strategies have been widely used in research and healthcare practice in high-income countries; they have not been sufficiently adapted for use in LMICs—where the burden of diseases is high, and challenges with medication utilization are higher.\textsuperscript{13,14} It has been suggested that increases in medication adherence interventions would likely have a more significant impact on the health of the population than other specific medication treatments.\textsuperscript{3} While studies have described medication adherence as being low in LMICs and focused on the barriers and factors influencing, research is scarce regarding the implementation of medication adherence strategies in these settings.\textsuperscript{14,15} Therefore, this study aimed to critically examine interventions targeted at improving medication adherence among persons with cardiovascular diseases in LMICs.

Methods

Search Strategy and Selection Criteria

Using recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)\textsuperscript{16} and with the help of an information specialist, we conducted a literature review on medication adherence interventions for cardiovascular diseases in LMICs. We built a search strategy using relevant text words and their synonyms (Table S1); we also searched controlled vocabulary in the databases: Emtree in Embase, MeSH in PubMed, and subject headings Cumulative Index to Nursing & Allied Health Literature (CINAHL). Final searches were conducted on August 11, 2020, in PubMed, Embase, and CINAHL. The final search strategy can be found in the Supplemental Files (Table S1). We imported identified articles into Covidence\textsuperscript{17} and titles and abstracts were screened for eligibility based on the inclusion and exclusion criteria described below. We included studies that implemented or tested a medication adherence intervention for cardiovascular diseases, reported adherence as an outcome measure, were conducted in LMICs, and reported the strategy or tool used to measure adherence. The articles had to be published in English, available in full text, peer-reviewed, and published between 2010 and 2020. Studies that implemented medication adherence in conditions other than CVD were excluded. Systematic reviews, study protocols, editorials, and commentaries were excluded, including low-quality articles appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Tools (Table S2).\textsuperscript{18} Following the screening of titles and abstracts, full-text versions of screened articles were obtained. Two authors (B.O. and S.B.) independently reviewed the full text articles to determine the studies’ eligibility and subsequently extracted the data. During the full-text review process, discrepancies and disagreements were resolved through discussion and review by a third, independent author (A.A.). The PRISMA checklist and flowchart were also used to facilitate transparent reporting of the articles reviewed.\textsuperscript{16} The review protocol was registered in PROSPERO with registration number CRD42020211279.

Results

A total of 45 studies that met our inclusion criteria were included in this review (Figure 1). Four studies were conducted in Africa: two in Nigeria,\textsuperscript{19,20} one in Ghana,\textsuperscript{21} and one in South Africa.\textsuperscript{22} Eight of the studies were conducted in the Americas: Brazil,\textsuperscript{23–27} Argentina,\textsuperscript{28} Portugal,\textsuperscript{29} and Chile.\textsuperscript{30} Thirty-three of the studies were conducted in Asia:
Also, 35 of the studies were randomized clinical trials and nine articles were non-randomized studies; one study was a cohort study; others were quasi-experimental and pre-post studies. The sample size of the studies included in the review ranged from 30 to 5725. The total population in the intervention groups across all the studies was 25,493; the mean was 554 participants. For all the control groups, the total participants were 6315; the mean was 162 participants. The duration of interventions in the studies ranged from 4 weeks to 12 months.

In this review, many of the studies included multiple interventions that contributed to a more substantial effect on medication adherence. Almost three-fourths (72%, n=33) of the studies used a multi-component approach to the interventions. The complexity level of the interventions did not necessarily translate into a stronger effect. The dimensions of medication adherence determinants were provider, drug or therapy-level, and health system-level factors. Thus, medication adherence interventions were classified as patient, provider, drug/therapy, and health system-level interventions. Majority (91%, n=41) of the studies included in this review addressed medication adherence at the patient level. These interventions included fixed-dose combination therapy, patient education, lifestyle counseling, cognitive behavioral therapy, reminders, and incentives.

When educational interventions were customized, initiated early, and repeated at regular intervals, improvements in medication adherence were shown to be modest; 73% (n=33) of the interventions that included patient education were effective. The most substantial effect size
Table 1 Characteristics of Studies on Medication Adherence Interventions for Cardiovascular Disease in Low- and Middle-Income Countries (N=45)

| Author, Year | Country | Design | Disease | Sample | Interventions | HCP | Adherence Measure | Intervention Duration (mos) | Mean SBP Diff | Mean DBP Diff | MA Diff (%) |
|--------------|---------|--------|---------|--------|---------------|-----|------------------|-----------------------------|----------------|--------------|-------------|
| Adeyemo et al, (2013) | Nigeria | RCT | HTN | 280 Adults ≥40yrs | + | Nurse | Urine testing, Pill count | 6 | −34.7 (-38.8, -30.6)* | −18.1 (-20.3, -15.9)* | OR=0.84 |
| Sarfo et al (2018) | Ghana | Cluster-RCT | Stroke | 30 Stroke survivors | + | Nurse | MPR | 3 | NA | NA | 0.24 ±0.05 |
| Odusola et al (2015) | Nigeria | Pre/Post-test | CVD | 149 | NA | Nurse | MMAS-8 | 14wks | NA | NA | OR: 1.55 |
| Bobrow et al (2016) | South Africa | 3-arm RCT | HTN | Arm 1: 457 adults Arm 2: 458 adults | + | Research team | PMC | 12 | Arm 1: −1.6 (−3.7,0.62) Arm 2: −2.2 (−4.4,0.04) | NR | OR(Arm 1): 1.86 (1.39, 2.49)* OR(Arm 2): 1.60 (0.03, 0.76)* |
| Aguiar et al (2012) | Brazil | Pre/post-test | HTN | 35 Elderly patients, 60–75yrs | NA | + | Pharm | MMAS | 10 | −26.3 ±0.8* | −10.4 ±0.4* | 51.5%* |
| Bonetti et al (2018) | Brazil | RCT | CVD | 51 | 53 | + | Pharm | MedTake, ARMS, BMQ | 11 | NR | NR | MedTake: 92.1 (±9.9)* BMQ: 1.8 (±0.6) |
| Azevedo et al (2017) | Brazil | RCT | MetS | 35 adults | 30 adults | + | Pharm | BMQ | 6 | −11.4 ±4.5* | −3.9 ±0.7* | 18.2* |
| De Souza et al (2016) | Brazil | Quasi | HTN | 116 adults | NA | + | Nurse/PE Teachers | QATSH | 2 | −6.64 (−3.2,−10.1) | −1.94 (−0.03, 10.08) | −2.63* |
| Study ID | Country | Intervention | Study Design | Study Population | Outcomes | Adherence Measure | N | NR | OR | Notes |
|---------|---------|--------------|--------------|------------------|----------|------------------|---|----|----|-------|
| Lourenco et al (2014) | Brazil | RCT | CAD | 59 adults, 56 adults | + | + | Nurses | MMAS | 2 | NR | NR | OR: 5.3*
| Mariani et al (2020) | Argentina | RCT | ACS | 52 adults, 48 adults | + | + | Clinical team | Pill count, MPR | 6 | 0.85 (−5.92, 7.61) | 0.97 (−2.44, 4.38) | RR: 1.05 (0.96, 1.14)
| Morgado et al (2011) | Portugal | RCT | HTN | 99 adults, 98 adults | + | + | Pharm | modified MMAS | 6 | −6.8 | −2.9 | MD: −16.9
| Verlaas et al (2017) | Chile | RCT | HTN | 163 adults, 151 adults | + | + | Clinical team | MMAS | 6 | −8.1 | −3.6 | −10.8
| Al-Qudah et al (2018) | Jordan | RCT | HTN | 48 adults, 49 adults | + | + | + | Pharm | MMAS | 6 | NR | NR | 26.7% (23.9, 29.4)
| Alhawari et al (2012) | Jordan | RCT | HTN | 68 adults, 68 adults | + | + | Nurse | ABMQ | 7wks | −23.1 (−25.9, −20.4) | −15.2 (−17.6, −12.8) | 26.7% (23.9, 29.4)
| Di et al (2019) | China | RCT | HTN | 103 <65 yrs, 107 <65 yrs | + | + | Health Educator | MPR | 6 | NA | NA | OR: 1.35* (0.77, 2.26)
| Farazian et al (2019) | Iran | RCT | HTN | 30 Adults 40-70yrs, 30 Adults 40-70yrs | + | + | Researcher | Validated Questionnaire | 4 wks | NA | NA | 16
| Golshahi et al (2015) | Iran | RCT | HTN | Group A: 45, Group B: 45, Group C: 45 | + | + | Cardiology residents | Single item question | 8 | −8.18 ± 18.3 | −3.89 ± 4.1 | 24.4
| Heidari et al (2017) | Iran | RCT | HTN | 32 Adults, 32 Adults | + | + | Research team | Validated Questionnaire | 1 | NA | NA | Mean: 370.3 ± 0.1
| Hosseinin- asab et al (2014) | Iran | RCT | HTN | 97 Adults, 97 Adults | + | + | Nurse, cardiologist, GP | Pill count, MMAS | 6 | −11.6 ± 8.6 | −8.1 ± 6.7 | 0.64 ± 2.0
| Kamal et al (2015) | Pakistan | RCT | CAD + CVA | 100 adults, 100 adults | + | + | researcher | MMAS-8 | 2 | NR | −2.6 (−5.5, 0.15) | MD: 0.54 (0.22, 0.85)
| Calano et al (2019) | Philippines | Pre/ postTest | HTN | 50 adults 40-59 years | NA | + | CHWs | HB-HBP | 2 | −8.6 ± 0.28 | −5.6 ± 1.64 | 3.5 ± 2.8

(Continued)
Table 1 (Continued).

| Author, Year | Country | Design | Disease | Sample | Interventions | HCP | Adherence Measure | Intervention Duration (mos) | Mean SBP Diff | Mean DBP Diff | MA Diff (%) |
|--------------|---------|--------|---------|--------|---------------|-----|------------------|--------------------------|---------------|---------------|-------------|
| Seng et al (2019) | Malaysia | Pre-post Quasi | HTN | 45 adults | NA + | Pharm | MALMAS, BMQ | 4 | $-6.5 \pm 0.4^*$ | $-1.6 \pm 2.6^*$ | 58.7%* |
| Fang et al (2015) | China | 3-arm RCT | CAD | 95 SMS, 92 SMS + ML | 93 Phone | Nurse/Physician | MMAS | 3 | NA | NA | OR (SMS + ML): 0.07 (0.03, 0.15). (SMS): 0.34 (0.18, 0.63) |
| Hsu et al (2015) | Taiwan | Cohort | HTN | 5725 ≥20yrs NHIRD database | 1623 ≥20yrs NHIRD database | + | Pharm/Physician | MPR | 6 | NA | NA | OR: 1.37 (1.22, 1.55) |
| Huang et al (2018) | China | Cluster RCT | HD | 46 Adults | 44 Adults | + | Nurse, Physician | MTBS | 5wks | $-3.3$ ($-9.7, 3.0$) | $-4.7 (-0.7, 1.1)^*$ | 8.9 ($-12.9, 30.2$) |
| Hsu et al (2019) | China | RCT | CAD/DM | 251 adults | 251 adults | + | Clinical team | Serum levels | 6 | 2.14 ($-0.8, 5.5$) | NR | -4 |
| Joshi et al (2018) | India | Cluster RCT | HTN | 1172 adults | 1140 adults | + | CHWs | PMC | 12 | $-2.76 \pm 0.6$ | NR | -13.5 |
| Kamal et al (2018) | Pakistan | RCT | CAD + CVA | 99 adults | 94 adults | + | Clinical team | MMAS-8 | 3 | NR | NR | MD=0.03 (0.13, -0.23, 0.29) |
| Kavita et al 2020 | India | Quasi | OVD | 250 adults | 250 adults | + | Nurses | MMAS | 6 | $-11.84$ ($-13.67, -10.01)^*$ | $-5.38$ ($-6.55, -4.09)^*$ | MD=1.63 |
| Maslakpaz et al (2016) | Iran | RCT | HTN | Arm 1: 41 adults (20-60 yrs) | 41 adults (20-60 yrs) | + | Research team | HB-HBP | 3 | NR | NR | Arm 1: $-6.24$ (2.33); Arm 2: $-4.76$ (2.58) |
| Study                          | Country | Design | Intervention | Baseline | Follow-up | Outcome | Comparator | Setting | Follow-up | Follow-up | Follow-up | Follow-up | Follow-up | Follow-up |
|-------------------------------|---------|--------|--------------|----------|-----------|---------|------------|---------|-----------|-----------|-----------|-----------|-----------|-----------|
| Najafi et al (2016)           | Iran    | RCT    | MI           | 50 adults | 50 adults | +       | Nurse      | MMAS    | 3         | NA        | NA        | −3.74     |           |           |
| Nguyen et al (2017)          | Vietnam | 2-arm  | CVD          | Arm 1: 80 adults (≥50yrs) | NR | +       | CHWs       | Validated Questionnaire | 3 | Arm 1: −3.2 (±0.1); Arm 2: −5.5 (±8.6) | 31.2% (11.4–15.1) |           |           |
| Nayeri et al (2014)          | Iran    | Post-test only | Stroke | 30 adults (patients and caregivers) | 30 adults | +       | Research team | ATR, AMR | 2 | NR | NR | −1.87 (±0.03) |           |           |
| Saleem et al (2015)          | Pakistan | RCT    | HTN          | 193 adults | 192 adults | +       | Pharm      | DAi-10  | 6 | −7 | −5.9 | 3.2 ±3* |           |           |
| Sundararajan et al (2020)    | India   | Quasi  | MI           | 77 adults | 77 adults | +       | Pharm      | MARS    | 6 | −6.7 ±1.65 | −2.64 ±0.21 | 21.3* |           |           |
| Sharma et al (2016)          | India   | RCT    | ACS          | 50 adults 40–59 years | 50 adults 40–59 years | +       | CHWs       | PIll count (CMAS) | 24 | −8.1 ±2.6 | −3.9 ±3.6 | 16* |           |           |
| Sheilini et al (2019)        | India   | RCT    | HTN          | 80 adults | 80 adults | +       | Nurse      | MMAS-10 | 6 | −0.38(2.51) | −1.32(0.12) | −2.41* |           |           |
| Tankumpuan et al (2019)      | Thailand | Quasi  | HTN          | 156 adults ≥60yrs | NA | +       | CHWs       | HB-HBP  | 6 | NA | NA | −1.45 (−2.42, 0.47)* |           |           |
| Xiao et al (2018)            | China   | RCT    | HTN/Stroke   | 87 adults | 87 adults | +       | Nurse      | HPLP II | 3 | −9.86 (1.18) | −0.59(9.56) | 3.91* |           |           |
| Woodham et al (2020)         | Thailand | Quasi  | HTN          | 100 adults, 60–79 years | 100 adults, 60–79 years | +       | Clinical team | PIll count | 3 | −13.24 ±2.43 | −17.25 ±2.84 | 7.02* |           |           |
| Xavier et al (2016)          | India   | RCT    | ACS          | 375 adults | 375 adults | +       | CHWs       | PIll count (CMAS) | 12 | −3.6 ±2.4 | −0.9 ±0.2 | OR: 2.62 (1.32, 5.19)* |           |           |

*(Continued)*
Table 1 (Continued).

| Author, Year | Country | Design | Disease | Sample Intervention | Control Intervention | HCP | Adherence Measure | Intervention Duration (mos) | Mean SBP Diff | Mean DBP Diff | MA Diff (%) |
|--------------|---------|--------|---------|---------------------|----------------------|-----|--------------------|----------------------------|---------------|---------------|-------------|
| Yadzdn-parah et al (2019) | Iran | RCT | HTN | 30 Elderly pts ≥60yrs | + | Research team | MMAS-8 | 2 | NA | NA | −3.7 ± 0.7* |
| Yu et al (2015) | China | PCT | HF | 80 adults | + | Cardiologists, nurses.Pts | MMAS | 3 | −3.3 ± 0.8 | −1.9 ± 0.3 | 1.6 ± 0.3 |
| Zakeri et al (2020) | Iran | RCT | MI | 41 adults | + | Nurses | Validated Questionnaire | 3 | NA | NA | MD:1.31 ± 0.48 |
| Zhao et al (2015) | China | RCT | CHD | 45 adults | + | Pharm | single item question | 6 | NA | NA | 14.03 ± 8.9 |

Abbreviations:
- Edu: Education
- CBT: Cognitive Behavioral Therapy
- HCP: Healthcare Provider
- FDC: Fixed-Dose Combination
- SBP: Systolic Blood Pressure
- DBP: Diastolic Blood Pressure
- MA Diff: Medication Adherence Difference
- Months (Mos)
- Weeks (Wks)
- +: intervention present

Measurements:
- MMAS: Morisky Medication Adherence Scale
- MMPI: Medication Possession Ratio
- BMQ: Beliefs about Medicine Questionnaire
- MALMAS: Malaysian Medication Adherence
- HB-HBP: Hill-Bone-Compliance to High Blood Pressure Scale
- QATSH: Questionnaire on Adherence to Systemic Hypertension Treatment
- MAT: Treatment Adherence Measure
- ATR: Allocation to Treatment Ratio
- DAI-10: Drug Attitude Inventory
- CMAS: Composite Medication Adherence Score
- ARMS: Adherence to Refills and Medications Scale
- MTBS: Medication Taking Behavior Scale
- MARS: Medication Adherence Rating Scale
- HPLP II: Health Promoting Lifestyle Profile II

HealthCare Providers:
- CHWs: Community Health Workers
- Pharm: Pharmacists
- NPHW: Non-Physician Health Worker

Diseases:
- HTN: Hypertension
- MetS: Metabolic Syndrome
- HD: Hemodialysis Patients
- CAD: Coronary Artery Disease
- CHD: Coronary Heart Disease
- CVA: Cerebrovascular Disease

Note: *Statistically significant (based on p-value and/or confidence intervals).
was observed in Lourenco et al., a nurse-led intervention of in-person visits and made plans on medication-taking behavior with phone reinforcements. Medication adherence was more improved in the intervention group than in the control group after two months of follow-up (OR: 5.23, 95% CI: 2.03–13.49; p=0.001). The smallest effect size was observed in Kamal et al., where the intervention group received daily interactive voice calls regarding their medications for stroke and myocardial infarction (MI), daily tailored medication reminders, and weekly lifestyle modifications for three months. At the end of follow-up, the mean medication adherence was increased in the intervention group compared with the usual care group with a mean difference of 0.03 (±0.13), (95% C.I: −0.23–0.29; p = 0.40). Nurses provided education in 41% (n=19) of the studies, including as part of the clinical team; physicians provided education in 27% (n=12) of the studies, pharmacists provided education in 22% (n=10) of the studies, community health workers provided education in 13% (n=6) of the studies. The duration of the education was brief in some cases and delivered in a single session, while in other instances, education was delivered multiple times. Interventions in which patient education was delivered in-person, face-to-face were more likely to have a higher effect on medication adherence.

Medication-taking reminders of phone calls, text messages, Short Message Services (SMS), or in-phone calendars were some of the most common medication adherence interventions. Reminders were more effective when they were personalized or interactive rather than generic. Many (48%, n=22) of the interventions included in this review were conducted by phone calls or by SMSs, including customized and interactive messages and electronic pillboxes. Only one study implemented incentives as a strategy to improve adherence in the form of free antihypertensive medication and transportation funds to attend clinic appointments. In the management of chronic diseases, a team-based approach, or team-based care, was identified as a strategy that may improve adherence. In this review, the interventions incorporated a team-based approach to CVD management and medication adherence. These interventions were nurse-led, community health worker-led, and clinical/community pharmacist-led. In Kavita et al., a team-based approach was used to deliver a medication adherence intervention; a group of experts from cardiology, nursing, community medicine, and fine arts developed and validated an intervention package that consisted of a booklet for nurses, a patient education booklet and flashcards for patient education. After one year of follow-up, the mean adherence scores were significantly higher in the intervention group (p <0.001); effect size (Cohen’s d) was 1.1.

Fixed-dose combination therapy or single-dose therapy has been recommended for use in the initial treatment of CVD and CVD risk factors rather than monotherapy because they may facilitate long-term adherence. Mariani et al. investigated whether a multi-cap containing four secondary prevention drugs would increase the adherence to treatment at six months following MI hospitalization and found that 98% of those who received the multi-cap were adherent to treatment six months after the intervention compared to 93.5% in the control group (RR: 1.05; 95% CI: 0.96–1.14; p = 0.347); however, there were no significant improvements in medication adherence between the groups.

Indirect adherence measurement methods were the most common methods used in the articles reviewed. These included the use of measurement scales, pharmacy chart records, self-report, pill counts, and calculating the medication possession ratio. Urine and blood testing were among the direct methods of assessment used in some of the studies. The measurement scales of medication adherence were among the most common and cost-effective ways of measuring medication adherence. These are validated scales, with acceptable reliability commonly used in research and clinical settings.

Discussion
This systematic review critically examined interventions targeted at improving medication adherence among patients with CVD in LMICs. Hypertension was the most common cardiovascular condition addressed across the studies. Interventions that were more effective at improving medication adherence included changing from multi-dose medications to fixed-dose combinations, team-based healthcare, and patient education combined with reminders. We also observed that studies that combined multiple medication adherence strategies in the interventions reported significant improvements in medication adherence. Our review builds on existing literature regarding medication adherence and highlights the medication adherence interventions conducted in LMIC.

Several factors contributed to non-adherence to CVD medications in LMICs. The extent of medication adherence was expected to be lower in LMIC due to a weaker health infrastructure and inequality in access to health care. These factors were outlined in the WHO report on adherence to long-term...
therapy and were also highlighted in a recent review of medication adherence in LMICs.\(^3\) Socioeconomic factors were significant contributors to medication non-adherence in LMICs, including long distances from treatment settings, high cost of medicines and limited drug supply, lower health literacy, family size, local beliefs about the origin of illnesses, and concerns about medical cost.\(^3,12\) Health care and system-related factors contributed significantly to non-adherence in LMICs, including inadequate or non-existent reimbursement by health insurance plans, irregular and insufficient drug supply, lack of medical supplies, poorly developed healthcare services, lack of knowledge and training for healthcare providers regarding managing CVD and other chronic diseases, lack of clear instructions from healthcare professionals including poor implementation of educational interventions.\(^12\)

Healthcare resources are scarce in low- and middle-income countries, and the feasibility of interventions is hinged on their cost-effectiveness and focus on quality improvement. Medication adherence is considered multi-dimensional, and interventions that address patient-related factors alone have not shown long-term evidence of medication adherence improvements.\(^66,67\) Medication adherence interventions that are multifaceted are encouraged in LMICs because they present an opportunity to improve cardiovascular outcomes while reducing healthcare spending and maximizing the use of already limited healthcare resources.\(^68\) To address the socioeconomic factors that affect adherence, recommendations include family preparedness, patient health insurance, an uninterrupted supply of medicines, sustainable financing, and reliable medication supply systems.\(^3\)

A similar review suggested that successes achieved from more intensive intervention can be further supported through investments in healthcare systems.\(^12\) Specifically, healthcare teams or health system-related interventions should include the following: training in the education of patients on the use of medicines, continuous monitoring and re-assessment of treatment—particularly monitoring of adherence—uninterrupted ready availability of information, good patient-provider relationships, monitoring adherence, training in communication skills, and evidence-based selection of medications.\(^12,13\) In our review, at each intervention level, studies that incorporated multiple means of delivery reported better outcomes.\(^19,20,22-24\) Thus, to achieve better outcomes, it is essential that future interventions consider multiple intervention delivery methods, including training of healthcare providers.

In this review, fixed-dose therapy interventions were found to be most effective for improving CVD medication adherence. To simplify regimen management, combination or fixed-dose therapy maximizes the number of medicines required while significantly reducing the number of pills a person has to take per time. Providers have a crucial role in optimizing and individualizing the medication regimen, including changing prescriptions from multiple medicines to single-pill, fixed-dose combinations when available.

Team-based care as an intervention to improve medication adherence was found to be particularly effective in our review.\(^19,24,36\) Physician density is low in most LMICs, further highlighting the need for a team-based care approach to expand access to CVD management. Nurses who work in community health centers or outpatient clinics have considerable access to patients with CVD, among whom they can perform risk assessments. In our review, the nurse-led interventions included patient education and counseling, reminders in the form of nurse-initiated phone interactions and SMS with patients, and a team-based healthcare approach. Similarly, pharmacists delivered efficacious interventions through education, a team-based healthcare approach, and reminders.\(^23,25,29,43,49,54,61\) It is essential that nurses and pharmacists play a more active role in the development and implementation of medication adherence interventions, particularly at the community level, where they are seen as critical resources.

For interventions that focused on reminders through phone calls and SMS, we found variations in the effectiveness. SMS reminders that were bi-directional and interactive\(^24,34\) yielded a higher level of adherence and blood pressure control than studies in which the SMS interventions were generic, passive, and one-way.\(^22,69\) Therefore, in designing an SMS or reminder-based intervention, it is essential to consider personalized, bi-directional, and interactive messages. The messages should be tailored to each patient’s needs and timed to coincide with each patient’s scheduled medication doses. In this review, many of the reminder-based interventions included using technology in the form of phone call reminders, interactive and informational SMS, and videos. These interventions also have the potential to improve health literacy. There are opportunities for technology-driven interventions in LMIC, for improving the quality of CVD care, medication adherence, and self-care management.\(^68\)
Overall, we found a modest body of evidence on the effectiveness of CVD medication adherence interventions in LMICs, as corroborated in similar systematic reviews on medication adherence in LMICs. However, the effects were inconsistent and varied by study design and country, which has also been found in a similar review. Many interventions in this review relied on existing healthcare interventions and resources while targeting local factors that affected medication adherence. These interventions can be adapted or adopted to other LMICs according to resource availability.

This review has some limitations. Medication adherence interventions in the studies reviewed were diverse, with different levels of complexity, delivery, and outcome assessments. Hence, we could not substantially categorize the interventions based on the level of intervention complexity nor undertake meta-analysis. Also, as with any systematic review, we acknowledge that some studies may have been missed despite thorough search strategies. Nonetheless, a major strength of this review is that the studies included were distinct in design, and included randomized controlled trials, non-randomized/quasi-experimental studies, and cohort studies. This provides an opportunity to evaluate the external validity of the studies and the extent to which the interventions may be conducted in real-world settings.

Non-adherence to medication is a significant factor in CVD management and control associated with increased risk of poor CVD outcomes and complications. This review shows that comprehensive medication adherence interventions that simultaneously incorporate multiple strategies are effective, especially when the local nuances and contexts such as cost of medicines, availability of infrastructure for technology-dependent interventions, health literacy, and beliefs are properly integrated into the delivery of the intervention. This is particularly important for future studies on improving the delivery of medication adherence interventions in LMICs.

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