Chapter

Medication Adherence in Cardiovascular Diseases

Suol Thanh Pham, Thi Anh Nguyen, Nghia Minh Tran, Hoang Thi Kim Cao, Khanh Kim Le, Chu Xuan Duong, Thao Huong Nguyen, Katja Taxis, Khanh Duy Dang and Thang Nguyen

Abstract

Cardiovascular disease is a significant cause of death globally. While effective long-term medications that reduce the risk of morbidity and mortality related to cardiovascular disease are readily available, nonadherence to prescribed medications remains a significant reason for suboptimal management. Consequently, this might lead to increased morbidity and mortality and healthcare costs. Medication nonadherence causes are myriad and complicated, with factors at the patient, healthcare provider, and health system levels. Many clinical trials have investigated interventions to target these factors for improving medication adherence, including improving patient education, testing behavioral interventions, implementing medication reminder tools, reducing medication costs, utilizing social support, utilizing healthcare team members, and simplifying medication dosing regimens. This book chapter describes factors influencing medication adherence and highlights the impact of varying levels of adherence on patients' clinical and economic outcomes. We also summarize interventions for improving medication adherence in cardiovascular disease.

Keywords: cardiovascular disease, medication adherence, factors, health outcomes, economic outcomes, interventions

1. Introduction

Cardiovascular disease (CVD) is illnesses affecting the heart and blood vessels, including coronary heart diseases, cerebrovascular diseases, peripheral arterial diseases, rheumatic and congenital heart diseases, and venous thromboembolism [1]. CVD is a leading cause of death and disability worldwide [2]. According to the Global Burden of Diseases in 2019, CVD accounts for 15.52% of disability-adjusted life years (DALYs) and 32.84% of deaths [3].

Given the adverse health outcomes of CVD, if left untreated, long-term prevention and/or treatment of this disease is recommended. Treatment for CVD depends on its type and severity and can be divided into three main categories: lifestyle changes,

medications, and surgical procedures. Overall, lifestyle changes and medications are often recommended for chronic CVD conditions, while surgical procedures are sometimes required to treat acute CVD events such as heart attack or stroke. In recognition of the vital role of medications in CVD management, this chapter is focused on medications for treating this disease.

Despite the availability of effective CVD medications, medication nonadherence remains pervasive globally [4]. A 27% nonadherence rate in patients with acute coronary syndrome (ACS) was reported only 1 week after discharge [5]. At 1 month following ACS, 34% of patients did not fill all prescriptions [6]. At 1–2 years following ACS, the nonadherence rate reaches 55–60% [7]. Medication adherence is how patients take medication(s) as prescribed by their healthcare providers [8]. Whereas nonadherence is defined as different behaviors: not initiating a new prescription, discontinuing medication(s) early, or not taking medication(s) as scheduled (e.g. less frequently) [9]. The rate of adherence for an individual patient is usually reported as the proportion of days covered (PDC) by the prescribed medication(s) over a specific time [10]. Methods for measuring adherence include direct and indirect methods, each of which has advantages and disadvantages. Direct methods, such as observed administration or measuring the concentration of medication in the blood, are more accurate but expensive and time-consuming. Indirect methods for measuring adherence, such as patient self-reporting or pill counting, are easier to conduct but less accurate. No measurement method is gold standard, and researchers should select a method based on their targeted nonadherence behavior(s) [11].

Past studies illustrated that nonadherence to cardiovascular medications negatively influences clinical and economic cardiovascular outcomes [12, 13]. Medication adherence in CVD is challenging to manage in routine practice due to multiple factors simultaneously affecting it [4]. These factors are classified into five interactive dimensions: patient, socioeconomic, healthcare system, therapy, and condition. Various interventions have been investigated to target these factors, and some appear promising. With accumulating studies on medication adherence in CVD in recent years, the chapter thus aims to update on common factors influencing medication adherence, clinical and economic outcomes of medications (non) adherence, and interventions targeting the identified factors to improve medication adherence in CVD.

2. Identification of nonadherence in clinical practice

The first and foremost issue for improving adherence is identifying nonadherence in all patients who do not respond to treatment. A simple and pragmatic solution for clinicians is to ask patients nonjudgmentally the frequency of their missed doses. Patients generally want to please their clinicians, thus avoiding declaring their missed doses. A few questions clinicians might ask their patients to feel more comfortable telling the truth were suggested: “I know it must be difficult to take all your medications regularly. How often do you miss taking them?” [8]. Other indirect questions should be asked to assess the likelihood of nonadherence, including how severe their disease is, what the benefits of taking medications are, whether they have any side effects from their medications and whether they have any troubles related to taking their medications (e.g. high medication costs or complex regimens).

3. Factors influencing adherence

After nonadherence is identified, there is a need to identify the underlying cause(s) to which intervention(s) might be tailored. According to World Health Organization (WHO), factors influencing medication adherence in CVD are classified into five different groups: patient-, socioeconomic-, healthcare system-, therapy-, and condition-related factors [14]. Based on the multidimensional nature of adherence, this classification accounts for all relevant factors influencing adherence. This corrects the traditional misconception that only patients are responsible for taking their medication(s) [14].

3.1 Patient-related factors

This aspect refers to the unique characteristics of each patient, not related to their illnesses or treatment, for example, age, gender, personal beliefs, education level, and understanding of their disease and treatment (see **Table 1** for details) [4, 15].

3.2 Socioeconomic-related factors

This aspect included influences originating from the patient's socioeconomic status (SES), not from the patient themselves nor the healthcare providers, for example, living conditions, financial situation, limited access to healthcare, and social support [4, 15]. Higher SES appeared to influence adherence positively, as detailed in **Table 2**.

3.3 Healthcare system-related factors

The relationship between patient and healthcare providers, or within the healthcare system itself, might influence medication adherence. This extended to communication problems and healthcare system requirements, making it difficult for patients to comprehend or follow treatment [4, 15].

The support from healthcare professionals played a vital role in improving patients' adherence, particularly during follow-ups. Inadequate communication between healthcare providers led to insufficient communication with patients, leading to nonadherence [4].

Insurance or other healthcare cost assistance was positively associated with medication adherence [29, 30]. Cost assistance helped patients to receive medications they would not afford otherwise. However, not all medications were covered [29, 30]. The ARTEMIS trial and the MI FREEE trial concluded that reducing the financial burden of treatment through full coverage prescription or copayment vouchers improved adherence [4]. One study reported increased adherence when providing a financial incentive to patients [31], while another reported that adherence only improved significantly when financial incentives were provided to both physicians and patients [4].

3.4 Therapy-related factors

This aspect included factors related to medication taking, such as medication class, side effects, dosing regimens, and polypharmacy [4]. The effects and complexity of the therapy might affect adherence.

Factor	Influence on medication adherence
Age	The correlation between age and medication adherence was controversial in the literature. While some found that increased age is positively correlated with adherence [16–20], and some found the inverse [16]. Patients aged 50–70 years had better adherence than those aged 18–50 years or over 70 years [15]. It was hypothesized that elderly patients had more comorbidities and, as such, were more concerned with their health and treatment [16].
Gender	The association between gender and adherence to cardiovascular medication remains inconsistent [15]. Some reported that the female gender was negatively correlated with adherence [19, 21–23]; one found that females have more adhered to medication than males [24]. In a systematic review, Bowry et al. found no association [25].
Ethnicity and linguistic proficiency	An American study reported Hispanic people have higher adherence rates than non-Hispanic people. Among native Spanish-speaking Hispanic people, those with better English skills showed lower adherence rates [26].
Forgetfulness	For more than one-third of all cases of nonadherence, forgetfulness was a common cause of nonadherence [4].
Education	Illiteracy or lower education level was associated with lower adherence [19, 27]. Understanding disease and treatment, especially the risk of nonadherence, increases the likelihood of adherence to treatment [15, 28].
Others	Alcohol use, stress, anxiety, impaired level of cognitive capabilities, and lack of time for medical appointments each separately had a negative impact on adherence [4, 15].

Table 1.
Patient-related factors that may influence medication adherence in CVD.

Factor	Influence on medication adherence
Living conditions	Living in areas with higher education rates or higher income positively impacted adherence [19].
Financial situation	One of eight patients with CVD had cost-related nonadherence [4]. People with higher income were inconsistently more likely to adhere to treatment, with some studies reporting correlation while others reporting none [15, 24]. The medication cost seemed to be inhibitive to adherence, and the unavailability of cheaper generic medications was also a factor in reducing adherence [29].
Access to healthcare	Geographical barriers preventing access to healthcare negatively affected adherence [27, 29]. The cost of travel to seek specific medications also impeded patients from following their treatment [29].
Social support	Culture inducing a distrust in medical treatment or problems with family relations may lead to nonadherence [27]. However, social support plays an important role in reinforcing adherence. Emotional support enabled people to voice their fears and ask for information as needed. Social support in the form of encouragement, prayers, and monetary aid helped keep patients motivated to follow treatment and maintain a healthy lifestyle [29].

Table 2.
Socioeconomic-related factors that may influence medication adherence in CVD.

Medication class consistently influenced adherence. Angiotensin II receptor blockers (ARBs) had the highest rate of adherence (~30–33% better than other classes), while diuretics showed the lowest rate [15]. Certain medications were reported to be hard to swallow [29]. Different packaging or brand names might cause some patients to dislike the medications, fearing fake medications [29]. Side effects might explain why different drug classes had different rates of adherence. At standard dose,

thiazides were more likely to cause a side effect compared with beta-blockers (BBs), calcium-channel blockers, and angiotensin-converting enzyme inhibitors (ACEIs), while ARBs were not associated with any side effects [15, 32].

Complex dosing regimens (e.g. a large number of daily doses) might negatively influence adherence [15]. The once-daily dosing regimen was associated with better adherence as opposed to twice-daily in patients with atrial fibrillation receiving oral anticoagulants [33]. Adherence was decreased in patients taking many medications to treat their comorbidities, contributing to the forgetfulness of taking medications [4]. Frequent changes in regimens also affected adherence negatively [29].

3.5 Condition-related factors

This aspect was related to the patient's illnesses and comorbidities [15]. Factors in this aspect influenced medication adherence differently; certain comorbidities increased adherence, while others decreased it [15]. Generally, comorbidities were associated with lower adherence [34].

Severe chronic illnesses with significant symptoms hampered adherence, as were chronic diseases with little to no symptoms [27]. Patients receiving primary prevention were less likely to adhere than patients receiving secondary prevention [15]. The impact of comorbidity on adherence varied. While diabetes was reported to improve adherence in CVD patients [15, 27], depression affected adherence negatively [15, 32, 35, 36]. Persistent depression decreased adherence more than remittent depression, and severe depression came with a 3.7 times higher risk of nonadherence than no depression [35].

4. Medication adherence-related outcomes

4.1 Clinical outcomes

Many observational studies have assessed the relationship between medication adherence and outcomes in CVD. Past evidence shows the broad impact of untreated or inadequately treated CVD ranging from major cardiovascular events (MACEs) to mortality. This might be caused by suboptimal adherence to effective medications. Nonadherence to statins in post-myocardial infarction (MI) patients was associated with up to 25% increased hazard of death [37]. In chronic coronary artery disease, nonadherence to cardioprotective medications (antihypertensive and antihypercholesterolemic medications) was associated with up to 40% increase in the risk of hospitalizations for cardiovascular events and up to 80% increase in the risk of death [38]. Conversely, optimal adherence was associated with significantly reducing cardiovascular events and mortality. A recent meta-analysis indicated that each incremental 20% increase in adherence level of cardiovascular medication reduced the risk of cardiovascular events by 9%, stroke by 16%, and all-cause mortality by 10% [39]. Several clinical studies highlighted the benefits of cardiovascular medications and the importance of adherence to prescribed medications to optimize health outcomes. This can raise awareness of the importance of medication adherence in CVD among clinicians, patients, healthcare insurers, and policymakers. The potential of overestimating the adverse outcomes of suboptimal adherence should be noted. Nonadherent patients are less likely to follow health recommendations (e.g. flu vaccination) and more likely to engage in harmful behaviors (e.g. smoking), impacting

health outcomes. Yet, these confounders can be minimized by (1) a well-designed study (i.e. using randomization, placebo, and double-blind) or (2) an appropriate statistical analysis. However, statistical analysis is less pronounced than study design, because a statistical analysis can be re-processed, but a poorly designed study can never be recovered. Medication adherence-related outcomes for specific diseases are detailed as follows:

4.1.1 Hypertension

Suboptimal adherence to antihypertensive drugs was associated with multiple adverse cardiovascular events from acute to chronic conditions (e.g. chronic heart failure) to death [32]. Suboptimal medication adherence was also associated with various organ disorders, including chronic kidney disease, cognitive dysfunction, and dementia [32]. A study including 155,597 patients with hypertension showed that highly adherent patients (≥80% PDC with antihypertensive medication) had less than half the risk of experiencing a cardiovascular event compared with lower adherent ones over a median duration of 5.8 years (adjusted hazard ratio [aHR] 0.44; 95% CI 0.42–0.45) [40].

In elderly diabetic patients having multiple comorbidities, a retrospective cohort study found that ≥80% adherence to ACEIs/ARBs was not associated with BP < 140/90 mmHg in those ≥85 years (risk ratio [RR] 1.01, 95% CI 0.96–1.07) or with multiple comorbid diseases (e.g. RR = 1.04, 95% CI 0.99–1.08) [41]. Reasons for uncontrolled BP despite optimal adherence might be (1) age-related physiological changes and (2) pathological changes by comorbidities (e.g. chronic kidney disease).

4.1.2 Myocardial infarction (MI)

Among post-MI patients, ≥80% adherence to both statins and ACEIs was associated with decreased risk of long-term MACEs (i.e. all-cause mortality, nonfatal MI hospitalization, stroke, or coronary revascularization) than <40% adherence (18.9% vs. 26.3%, HR 0.73, $P = 0.0004$) and 40–79% adherence (18.9% vs. 24.7%, HR 0.81; $P = 0.02$) at 2 years [42]. Another study across China in 4001 post-MI patients found that optimal adherence (≥90%) to cardiovascular medications was associated with a 39% reduction in the risk of 1-year cardiovascular events (aHR 0.61, 95% CI 0.49–0.77) [43].

4.1.3 Atherosclerotic cardiovascular disease (ASCVD)

In 12,976 patients with ASCVD from the American health insurance database, ≥80% adherence to both statins and ACEIs reduced the risk of long-term MACEs than <40% adherence (8.42% vs. 17.17%, HR 0.56, $P < 0.0001$) and 40–79% adherence (8.42% vs. 12.18%, HR 0.76, $P < 0.0001$) at 2 years [42]. Consistent with this finding, another study in 185,252 patients with ASCVD from the Taiwan National Health Insurance database found that ≥80% adherence to statins reduced the risk of ASCVD-related secondary rehospitalization (aHR 0.90, 95% CI 0.87–0.92, $P < 0.05$) and in-hospital death (aHR 0.59, 95% CI 0.53–0.65, $P < 0.05$) [44].

4.1.4 Heart failure (HF)

An analysis of 55,312 patients with HF indicated that each 10% increase in PDC by cardiovascular medications reduced all-cause mortality risk by 9% (odds ratio [OR]

0.91, 95% CI 0.90–0.92), emergency admissions by 11% (RR 0.89, 95% CI 0.89–0.89), hospital admissions by 6% (RR 0.94, 95% CI 0.94–0.94), and length of hospitalization by 1% (RR 0.99, 95% CI 0.99–1.00) (all $P < 0.0001$) [45].

4.1.5 Hypercholesterolaemia

Among 11,320 newly diagnosed patients with hypercholesterolemia initiated with statins, late statin initiation increased the risk of CVD events compared with early statin initiation (HR 1.24, 95% CI 1.02–2.51). Among early initiators, statin discontinuation was associated with increased risk for CVD (HR 1.71, 95% CI 1.10–2.67), but statin reinitiation was associated with decreased risk (HR 1.34, 95% CI 0.79–2.30) [46]. Another study in China with 99,655 adult patients indicated a 37% reduced risk of MACEs in those with ≥50% adherence with a statin (aHR 0.63, 95% CI, 0.41–0.98). Unlike primary prevention, no relationship between secondary prevention and statin adherence (PDC ≥ 50%) was detected in this study [47]. Previous studies, however, found statin adherence benefits in reducing the risk of adverse health outcomes for secondary prevention [48–51]. These discrepancies might be due to different baseline patient characteristics (CVD and its severity) and PDC cutoff points (50% in the Chinese study vs. 80% in others' studies). Secondary prevention seems to require ≥80% adherence to reduce cardiovascular risk.

In the elderly, a study on 29,047 patients aged ≥65 receiving polypharmacy found that those who discontinued statins while maintaining other medications had an increased risk of hospital admissions for any cardiovascular outcome (HR 1.14, 95% CI 1.03–1.26), HF (HR 1.24, 95% CI, 1.07–1.43), all-cause mortality (HR 1.15, 95% CI 1.02–1.30), and emergency admissions (HR 1.12, 95% CI 1.05–1.19) (all $P < 0.05$) [52]. In diabetic patients aged ≥65 with comorbidities, those adhering optimally to statins (PDC ≥ 80) had a decreased LDLc (<100 mg/dl) across all age groups (e.g., ≥85: RR 1.13, 95% CI 1.09–1.16, $P < 0.05$) and in all comorbid levels (e.g. ≥4: RR 1.13, 95% CI 1.12–1.15, $P < 0.05$) [41]. The LDLc target of <100 mg/dl was associated with a lower risk of adverse cardiac outcomes [53].

4.1.6 Acute coronary syndrome (ACS)

A study in 7152 post-ACS patients showed that optimal adherents (PDC ≥ 75%) to any combination of antiplatelets, statins, BBs, and ACEIs/ARBs led to a significant reduction in cardiovascular risks (HR 0.80, 95% CI 0.73–0.88) than suboptimal adherents for all medications, except BBs alone [54]. Adherence to 2 or 1 drug significantly increased mortality risk compared with adherents to 4 or 3 (for two drugs: HR 1.2, 95% CI 1.0–1.3, $P < 0.05$; for 1 drug: HR 1.5, 95% CI 1.2–1.8, $P < 0.05$) [54].

4.1.7 Chronic coronary syndrome

Optimal adherence to guideline-directed medication therapy (i.e. a combination of antiplatelet drugs, ACEIs/ARBs, BBs, and statins) that reduced the risk of MACEs (HR 0.41, 95% CI 0.18–0.92, $P = 0.03$) was reported [55].

4.1.8 Symptomatic peripheral artery disease (PAD)

Patients with PAD being never on statins had a significantly higher mortality rate (31%) than those being continuous on statins (13%) or being new on statins (8%;

$P < 0.0001$) or on intensified statins (9%). Those who terminated statin medication or reduced statin dosage had higher mortality (34% and 20%, respectively; $P < 0.0001$) [56].

4.2 Economic outcomes

The cost-effectiveness of optimal adherence to the guidelines was commonly assessed by calculating the incremental cost-effectiveness ratio (ICER), representing the discrepancies in costs between the intervention and control groups divided by the discrepancies in effectiveness between both groups (Eq. (1)) [57]. Effectiveness is commonly expressed as quality-adjusted life years (QALY), combining quality and quantity of life. Whether optimal adherence can be considered cost-effective relies on a community's affordability for one QALY. The lower the ICER, the more the cost-effectiveness. To define the ICER cutoff point, the WHO proposed using the per capita gross domestic product (GDP) [58]. An intervention must cost less than once the national annual GDP per capita per QALY to be highly cost-effective. An intervention must cost less than three times the national annual GDP per capita per QALY to be considered cost-effective:

$$\text{ICER} = \frac{\text{Cost}_{\text{intervention}} - \text{Cost}_{\text{control}}}{\text{Effectiveness}_{\text{intervention}} - \text{Effectiveness}_{\text{control}}} \quad (1)$$

For primary prevention, adherence was predicted to be more cost-effective in patients with a higher 10-year risk for a cardiovascular event in a study across 13 European countries. The risk was calculated from a risk score tool and included males, age >65 years, smoking, HTN, diabetes, hypercholesterolemia, and history of CVD. Adherence to the European guidelines on CVD prevention (e.g. smoking cessation medication, BP-lowering medication, and cholesterol-lowering medication) was used as an intervention. A base case ICER of 52,968€/QALY over 10 years was estimated for patients with an average baseline risk of 20%. Considering high-risk patients (≥20%), the ICER was reduced to 29,093€/QALY with decreasing ICERs in higher-risk patients. Patients with higher-risk reductions (≥0.5%) were also associated with lower ICERs [59]. Another study evaluating the cost-effectiveness of enhancing adherence to antihypertension medications indicated that enhancing adherence from 52% (the baseline) to 70% and 80% resulted in a reduced ICER from €76,484 (95% CI €74,807–€78,152) to €75,055 (95% CI €73,490–€76,623) and €73,605 (95% CI €72,180–€75,157), respectively, for each hospitalization for a MACE prevented. This aligns with the previous findings based on a large database (n = 625,620). Mean annual healthcare costs were estimated to be lower for patients with 80–100% adherence to antihypertensive medications ($7182) than for those with 60–79% adherence ($7560) and <60% adherence ($7995) ($P < 0.001$ for both) [57].

For secondary prevention, in the post-MI population, optimal adherence (≥80%) had lower per-patient annual medical costs for hospitalizations of $369 and $440 compared with suboptimal adherence (≥40–≤79%), and nonadherence (<40%), respectively. In the ASCVD subgroup, optimal adherence had lower per-patient annual medical costs for hospitalizations of $371 and $907 than suboptimal adherence and nonadherence [42]. Another study in India found positive findings that adherence (80% or lower) to aspirin and BBs was highly cost-effective. The additional

ACEIs were cost-effective, based on Indian gross domestic product per capita [60]. In patients discharged with ACS, those adhering to medications, outpatient controls, and rehabilitation had lower costs for medications (€199 per year) and higher costs for outpatient controls and rehabilitation (€292 and €1024) compared with those who did not [61]. An Australian secondary prevention program for CVD (i.e. optimizing medication use and lifestyle modification) was found to produce an ICER of AUD 8081 per disability-adjusted life year (DALY) prevented, which is well below the acceptable benchmark of AUD 50,000 per DALY within the Australian healthcare system [13].

In chronic vascular diseases, enhancing medication adherence increased medication costs but produced medical savings by reducing hospitalization. An American study in 224,231 patients with risk for CVD indicated that adherents' average annual medication costs were $1058 more for those with congestive HF, $429 more for HTN, $656 more for diabetes, and $601 more for hypercholesterolemia as compared with non-adherents. In contrast, adherence lowered mean annual medical costs by $8881 in congestive HF, $4337 in HTN, $4413 in diabetes, and $1860 in hypercholesterolemia [62].

In sum, higher adherence to medications to treat CVD was associated with higher medication costs but lower nonmedication medical costs, reducing overall healthcare costs. Health economic models were estimates based on available evidence and several assumptions. Interpreting the results thus needs to be cautious when applying these models in the health policy decision-making process.

5. Interventions to improve adherence and clinical outcomes

Given multiple factors influencing medication adherence in CVD, interventions addressing these factors to improve adherence have received rising interest (**Table 3**). They were classified partly or wholly into several categories of intervention: patient education, behavioral interventions, using reminder tools, cost reduction, and financial aid, using a healthcare team, and using fixed-dose therapy (polypill). Multifaceted interventions appeared more effective than single ones [63, 64]. This can partly be explained by the multifaceted nature of factors influencing medication adherence. Due to differences in healthcare resources and patient characteristics between high- and middle- or low-income countries, the interventions should be appropriately adapted to the local context. As most effective interventions on adherence improvement demand greater resources, the healthcare system needs to be supported. In waiting for support, some simple strategies for improving adherence to CVD medication were proposed (**Table 4**) [8]. An initial intervention might not be effective when applied in other settings. Thus, the healthcare team should continuously assess the effectiveness and feasibility of the intervention.

5.1 Patient education

The mode and frequency of the delivery of educational material may impact its effectiveness. Providing a few episodes of educational mails and/or phone calls did not improve adherence to secondary prevention medications in patients with MI (OR 1.03, 95% CI 0.77–1.36) [65] or with obstructive coronary artery disease (mail only vs. usual care, OR 0.98, 95% CI 0.81–1.19; mail and phone call vs. routine care, OR 0.99, 95% CI 0.82–1.20) [80]. However, tailored and interactive educational programs

Intervention	Population description	Outcome	Reference
Educational reminders	Myocardial infarction	Improved medication adherence	[65]
Physician-led intensive follow-ups	Unstable angina	1. Improved medication adherence 2. Lower MACEs: recurrence of angina, recurrence of myocardial ischemia, cardiac death, all-cause death, and revascularization	[66]
Physician-led education during hospitalization and telephone follow-ups	ACS	1. Lower all-cause death, cardiac death, and MACEs 2. Increased survival, cardiac death-free survival, and MACE-free survival	[67]
Nurse-led counseling	Statin user for primary or secondary prevention	1. Improved statin adherence 2. Lower LDLc	[68]
Live and web-based counseling	Risk for CVD	Reduced 10-year Framingham Risk Score at both 4 and 12-month follow-up for both formats	[69]
Motivational interviewing	New coronary stent	Improved medication adherence	[70]
Short message service (SMS) and structured telephone support (STS)	Chronic HF	1. Improved medication adherence 2. Lower 180-day all-cause mortality or readmission	[71]
Phone calls	Post-ACS	Improved adherence to aspirin and clopidogrel	[72]
Phone calls and reminder letters	New statins users	Improved statin adherence	[73]
Phone calls, reminder letters	≥40 years with diabetes or ASCVD	1. Improved adherence to statin and ACEIs/ARBs 2. Reduced LDLc	[74]
Smartphone apps	Elderly patients with atrial fibrillation	Improved medication adherence	[75]
Social support	Heart failure	Improved medication adherence	[76]
Pharmacist-led intervention	New users of cardiovascular medications	Improved medication adherence	[77]
Multifacet (education and regular follow-up)	CVD	1. Improved medication adherence	[63]
Multifacet (patient's pill count, family support, and education)	≥50 years and hypertension with 10-year cardiovascular risk >30%	1. Improved medication adherence at 6 months 2. Decreased SBP at 6 months 3. Reduced cardiovascular events at 5 years	[78]

Intervention	Population description	Outcome	Reference
Multifacet	ASCVD	1. Improved medication adherence for all interventions 2. Improved both adherence and BP and LDLc control for SMS, community health worker-led intervention, and polypills	[79]

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BP, blood pressure; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LDLc, low-density lipoprotein cholesterol; NA, not available; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio; SBP, systolic blood pressure; SMS, short message service; STS, structured telephone support.

Table 3.
Interventions that may improve medication adherence and clinical outcomes in CVD.

Identify nonadherence
• Assess predictors of nonadherence: nonresponse to medication missed appointments.
• Ask nonjudgmentally about missed doses and barriers to adherence
Emphasize the benefits of the regimen and the outcomes of adherence
Simplify the regimen as much as possible and provide simple, clear instructions
Assess patient's readiness to follow the regimen and provide advice on how to do it when needed
Involve multidisciplinary healthcare team members (e.g. nurse, pharmacist, and primary care staff)
Customize the regimen according to the patient's wishes
Obtain support from family, friends, and social services when needed
Follow up on the patient's progress at every appointment

Table 4.
Strategies for improving medication adherence in CVD.

with reinforcements improved CVD medication adherence. Earlier and more regular health checks with clinicians have improved adherence to cardiovascular medications [43, 81]. Intensive follow-up phone calls and regular consultations with cardiologists for patients with ACS were associated with higher adherence (58% intervention vs. 40% control, $P < 0.001$) and lower MACEs (19% intervention vs. 29% control, $P < 0.001$) at 36 months follow-up [67]. Face-to-face education by a nurse also significantly improved adherence to statin therapy ($P < 0.01$) and significantly lowered LDLc levels for primary prevention (2.66 vs. 3.00 mmol/l, $P = 0.024$) [68].

Regular educational information formats besides in-person also indicated an improvement in medication adherence. Both web-based and counselor-delivered formats improved adherence to medications in moderate-to-high risk patients with coronary heart disease (18% improvement in the web-based group and 21% improvement in the counselor group) [69]. Structured text messages and phone calls regularly made by a nurse positively affected medication adherence (78.9% message vs. 81.4% call vs. 69.5% control, $P = 0.011$) and reduced mortality or readmission (50.4% message vs. 41.3% call vs. 36.5% control, both $P < 0.05$) in patients hospitalized for acute HF [48]. A series of educational phone calls from nurses over 9 months improved

12-month medication adherence to dual antiplatelet therapy among patients with recent drug-eluting stent placement (87.2% call vs. 43.1% control ($P < 0.001$)) [72].

Patient education might improve medication adherence in CVD patients who do not fully understand the severity of their disease and the benefits of cardiovascular medication(s). The educational programs with reinforcements have improved adherence in most studies.

5.2 Behavioral interventions

A meta-analysis evaluating the impact of motivational interviewing over a year demonstrated a modest increase in medication adherence in patients with stroke (pooled RR 1.13, 95% CI 1.01–1.28) [70]. Promising results were again demonstrated in another RCT in which motivational interviewing improved both adherence (OR 1.91, 95% CI 1.19–3.05) and reduced rates of uncontrolled SBP (OR 0.62, 95% CI 0.50–0.78) compared with the control group [78]. Other counseling techniques such as providing patient feedback regarding medication adherence and enhancing family involvement showed a beneficial but negligible effect on medication adherence [82, 83].

Improving patient motivation and behaviors has not shown significant improvements in adherence outcomes. These interventions should be tailored to patients who are less motivated to take medication.

5.3 Reminder tools

Mobile phone-delivered interventions seemed to increase adherence to medication prescribed for the primary prevention of CVD, according to a Cochrane review of 14 trials with 25,633 randomized participants. Trials of BP self-monitoring with mobile phone telemedicine support modest benefits. One trial reported modest reductions in LDLc but no benefits for BP [84]. In a randomized trial of 5216 initiators of statin, those who received automated phone calls had significantly increased adherence (42.3% intervention vs. 26.0% control; absolute difference = 16.3%, $P < 0.001$; RR 1.63, 95% CI 1.50–1.76) [73]. Utilizing text message reminders also improved medication adherence in CVD in recent meta-analyses [85, 86].

Smartphone apps providing reminder alerts, adherence reports, and optional peer support significantly improved medication adherence (between-group difference 0.4; 95% CI 0.1–0.7, $P = 0.01$). However, this difference in adherence did not produce a significant difference in BP control between the groups (between-group difference −0.5, 95% CI −3.7–2.7, $P = 0.78$) [87]. A smartphone app integrating education, automatic reminder, and patient engagement strategies improved medication adherence among elderly patients with atrial fibrillation. Approximately 78% (14/18) of the patients in the high-adherence group at baseline remained in the same state, 45% (24/53) of the patients in the medium-adherence group at baseline moved to the high-adherence group, and 72% (18/25) of the patients in the low-adherence group moved to either the medium- or high-adherence group [75]. A meta-analysis of nineRCTs evaluating the impact of apps on medication adherence showed an improvement in SBP, DBP, total cholesterol, and LDLc levels in the intervention arm. Apps have an acceptable degree of usability, yet the app characteristics conferring usability and effectiveness are ill defined [88].

Mobile phone calls, text messages, and applications can improve adherence and clinical outcomes. Patients who often forget to take medications and use technology can try these techniques.

5.4 Social support

Frequent seeing friends and relatives in a structural manner were modestly associated with greater adherence in 17,113 patients with CVD or CVD risk factors [89]. In hypertensive patients, structural social support improved adherence in two prior meta-analyses [90, 91]. In patients with severe mental diseases (e.g. schizophrenia and bipolar disorder), perceived social support improved adherence to CVD medication. There was a 4.2% increase in medication adherence for each 1% increase in social support (OR 1.04, 95% CI 1.02–1.07, $P = 0.002$) [92]. In an HF setting, a prospective cohort study in Taiwan showed an intimate relationship with a spouse or caregiver was associated with a lower risk of 18-month all-cause readmission and cardiac readmission. The intimate partners will likely enhance HF patients' profound physical and psychological well-being [93]. In a Japanese study, poor adherence to medication in super-aged patients with HF is associated with poor clinical outcomes. Multivariable analysis revealed that not receiving assisted living at least once a week was independently associated with hospitalization, mainly due to poor medication adherence. The analysis also revealed that assisted living was particularly effective for patients affected by dementia [76].

Social support can significantly facilitate medication adherence in CVD, especially in frail populations such as the elderly and comorbid patients.

5.5 Cost reduction and financial aid

Current evidence suggests that reducing medication costs improves patient adherence and clinical outcomes. A trial randomized 10,102 hospitalized patients with acute MI to a group of copayment vouchers for P2Y12 inhibitors or no vouchers. At 1 year, patient adherence was reported to be higher in the intervention group than in the control group (aOR 1.19, 95% CI 1.02–1.40), but no significant difference was observed in MACEs (aHR 1.07, 95% CI 0.93–1.25) [94]. Another positive result was found in the MI FREEE trial randomized 5855 hospitalized patients with AMI to full prescription coverage vs. usual coverage for BBs, statins, and ACEIs/ARBs over about 1 year. Adherence rates were increased in the full-coverage group compared with the usual coverage group by 5.6% for ACEI/ARBs (95% CI 3.4–7.7), by 4.4% for BBs (95% CI 2.3–6.5), by 6.2% for statins (95% CI 3.9–8.5), and by 5.4% for all three medication groups (95% CI 3.6–7.2). A significant reduction was observed in total MACEs in the full-coverage group (HR 0.89, 95% CI 0.90–0.99; $P = 0.03$) was observed, despite no significant differences in the first MACEs (HR 0.93; 95% CI 0.82–1.04; $P = 0.21$) [95].

Cost reduction strategies using either copayment reduction or financial incentives have shown modest changes in medication adherence, although further research is needed to determine the sustainability of these interventions. Another possible cost reduction solution is replacing brand-name medications with well-proven, equally effective, and less costly generic ones. In a study of over 300,000 privately insured adults aged ≥18, generic drug therapy improved adherence [96].

5.6 Healthcare team

Community health workers (e.g. community pharmacists) often regularly interact with patients and provide access, education, and support regarding medication use. Enhanced community health workers' involvement has been explored to improve medication adherence. Recent systematic reviews evaluating community health worker-led

intervention demonstrate improvement in adherence and reduction in secondary ASCVD (97% intervention vs. 92% control; OR 2.62, 95% CI 1.32–5.19) [79].

Pharmacist-led consultations improved medication adherence in CVD patients compared with usual care (4.5% difference, 95% CI 0.8–8.2, $P = 0.017$) [77]. Another standardized counseling intervention by pharmacists at hospital discharge of ACS patients showed (1) an increased medication adherence at 1 year (11.9% non-counseling receivers vs. 18.4% counseling receivers, $P = 0.19$) and (2) decreased cardiovascular readmission and all-cause mortality (17.6% intervention vs. 22.3% usual care, $P = 0.42$; and 3.4% intervention vs. 4.2% usual care, $P > 0.99$, respectively) [97].

The healthcare team plays an important role in patients' adherence by identifying medication nonadherence and adherence barriers and providing interventions that address these barriers. One of the consistent features of successful interventions has been regular follow-up with the healthcare team [98].

5.7 Fixed-dose therapy (polypill)

The relationship between polypill therapy and CVD outcomes was studied enormously, and most studies found positive findings. A systematic review and meta-analysis of eight studies involving 25,584 patients demonstrated that the use of polypills (1) significantly enhanced drug adherence (RR 1.31, 95% CI 1.11–1.55, (2) significantly reduced CVD risk factors (hypertension) and the risk of all-cause mortality (RR 0.90, 95% CI 0.81–1.00, $P < 0.05$) and MACEs (RR 0.85, 95% CI 0.70–1.02, $P > 0.05$) [99]. Another systematic review indicated that polypills improved adherence and reduced secondary ASCVD (86% intervention vs. 65% control, OR 1.33, 95% CI 1.26–1.41) [79]. A meta-analysis demonstrated significant improvement in adherence with the use of polypill of two or more antihypertensive drugs (OR 1.21, 95% CI 1.03–1.43, $P = 0.02$), but beneficial trends in BP and adverse effects [100]. Challenges can explain this in matching patients to a specific polypill and adjusting the dose of a component in a polypill.

In summary, since nonadherence factors are patient-specific, personalized interventions are required to enhance the impact of an intervention to improve medication adherence in CVD [98]. Evidence demonstrated that simple strategies requiring low healthcare resources such as simplifying the regimen, organizing medications in pillboxes, obtaining family and social support, using motivational interviewing, and educating patients on the importance of medication adherence appear cost-effective.

6. Conclusions

Adherence to cardiovascular medication reduces substantial morbidity and mortality and reduces healthcare costs. Despite these advantages, medication nonadherence remains common due to multiple barriers from patients, providers, and system levels. Various interventions have been tested to overcome these barriers, and most of them have illustrated positive findings. A combination of interventions is more likely to be effective as several factors simultaneously influence adherence. The heterogeneity of effect within each intervention may result from the inappropriate matching of intervention and factors influencing adherence. Thus, after identifying medication nonadherence, clinicians should consider potential factor(s) influencing adherence to select intervention(s) targeting the identified factor(s).

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Author details

Suol Thanh Pham[1], Thi Anh Nguyen[1,2], Nghia Minh Tran[3], Hoang Thi Kim Cao[1], Khanh Kim Le[1], Chu Xuan Duong[1], Thao Huong Nguyen[4], Katja Taxis[5], Khanh Duy Dang[1*] and Thang Nguyen[1*]

1 Department of Pharmacology and Clinical Pharmacy, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam

2 School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

3 Faculty of Medicine, Can Tho University of Medicine and Pharmacy, Can Tho, Vietnam

4 Department of Clinical Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam

5 Groningen Research Institute of Pharmacy, University of Groningen, Groningen, The Netherlands

*Address all correspondence to: ddkhanh@ctump.edu.vn and nthang@ctump.edu.vn

References

[1] Stewart J, Manmathan G, Wilkinson P. Primary prevention of cardiovascular disease: A review of contemporary guidance and literature. JRSM Cardiovascular Disease. 2017;**6**:204800401668721

[2] Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: A systematic analysis for the global burden of disease study 2017. The Lancet. 2018;**392**(10159):1736-1788

[3] Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: A systematic analysis for the global burden of disease study 2019. The Lancet. 2020;**396**(10258):1204-1222

[4] Simon ST, Kini V, Levy AE, Ho PM. Medication adherence in cardiovascular medicine. British Medical Journal. 2021;**374**:n1493

[5] Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008;**117**(8):1028-1036

[6] Rudd P, Byyny RL, Zachary V, LoVerde ME, Mitchell WD, Titus C, et al. Pill count measures of compliance in a drug trial: Variability and suitability. American Journal of Hypertension. 1988;**1**(3 Pt 1):309-312

[7] Jackevicius CA. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. Journal of the American Medical Association. 2002;**288**(4):462

[8] Osterberg L, Blaschke T. Adherence to medication. The New England Journal of Medicine. 2005;**353**(5):487-497

[9] Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: Terminology and definitions. Value in Health. 2008;**11**(1):44-47

[10] Choudhry NK, Kronish IM, Vongpatanasin W, Ferdinand KC, Pavlik VN, Egan BM, et al. Medication adherence and blood pressure control: A scientific statement from the American Heart Association. Hypertension. 2022;**79**(1):1-14

[11] Kronish IM, Thorpe CT, Voils CI. Measuring the multiple domains of medication nonadherence: Findings from a Delphi survey of adherence experts. Translational Behavioral Medicine. 2021;**11**(1):104-113

[12] Faridi KF, Peterson ED, McCoy LA, Thomas L, Enriquez J, Wang TY. Timing of first Postdischarge follow-up and medication adherence after acute myocardial infarction. JAMA Cardiology. 2016;**1**(2):147

[13] Chew DP, Carter R, Rankin B, Boyden A, Egan H. Cost-effectiveness of a general practice chronic disease management plan for coronary heart disease in Australia. Australian Health Review. 2010;**34**(2):162

[14] Sabaté E, Bender B, Boulet LP, Chaustre I, Rand C, Weinstein A, et al. Adherence to Long-Term Therapies: Evidence for Action [Internet]. World Health Organization - Institutional Repository for Information Sharing; 2003. Available from: https://apps.who.int/iris/handle/10665/42682

[15] Leslie KH, McCowan C, Pell JP. Adherence to cardiovascular medication: A review of systematic reviews. Journal of Public Health. 2019;**41**(1):e84-e94

[16] Lee GKY, Wang HHX, Liu KQL, Cheung Y, Morisky DE, Wong MCS. Determinants of medication adherence to antihypertensive medications among a Chinese population using morisky medication adherence scale. Cameron DW, editor. PLoS ONE. 2013;**8**(4):e62775

[17] Hashmi SK, Afridi MB, Abbas K, Sajwani RA, Saleheen D, Frossard PM, et al. Factors associated with adherence to anti-hypertensive treatment in Pakistan. Baune B, editor. PLoS ONE. 2007;**2**(3):e280

[18] Wong MCS, Jiang JY, Griffiths SM. Factors associated with antihypertensive drug compliance in 83 884 Chinese patients: A cohort study. Journal of Epidemiology & Community Health. 2010;**64**(10):895-901

[19] Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. Clinical Medicine & Research. 2013;**11**(2):54-65

[20] Assawasuwannakit P, Braund R, Duffull SB. A model-based meta-analysis of the influence of factors that impact adherence to medications. Journal of Clinical Pharmacy and Therapeutics. 2015;**40**(1):24-31

[21] Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: A systematic review and meta-analysis. The Annals of Pharmacotherapy. 2010;**44**(9):1410-1421

[22] Nordstrom BL, Simeone JC, Zhao Z, Molife C, McCollam PL, Ye X, et al. Adherence and persistence with prasugrel following acute coronary syndrome with percutaneous coronary intervention. American Journal of Cardiovascular Drugs. 2013;**13**(4):263-271

[23] Bots SH, Inia JA, Peters SAE. Medication adherence after acute coronary syndrome in women compared with men: A systematic review and Meta-analysis. Front Glob Womens Health. 2021;**2**:637398

[24] Lima PRG, Gonçalves GMS, Rodrigues RCM, Oliveira-Kumakura AR d S. Factors related to patient adherence to the use of new oral anticoagulants. Revista da Escola de Enfermagem da U.S.P. 2022;**56**:e20210191

[25] Bowry ADK, Shrank WH, Lee JL, Stedman M, Choudhry NK. A systematic review of adherence to cardiovascular medications in resource-limited settings. Journal of General Internal Medicine. 2011;**26**(12):1479-1491

[26] Liyanage-Don NA, Cornelius T, Romero EK, Alcántara C, Kronish IM. Association of Hispanic ethnicity and linguistic acculturation with cardiovascular medication adherence in patients with suspected acute coronary syndrome. Preventive Medicine Reports. 2021;**23**:101455

[27] Ferdinand KC, Yadav K, Nasser SA, Clayton-Jeter HD, Lewin J, Cryer DR, et al. Disparities in hypertension and cardiovascular disease in blacks: The critical role of medication adherence. Journal of Clinical Hypertension. 2017;**19**(10):1015-1024

[28] Nielsen JØ, Shrestha AD, Neupane D, Kallestrup P. Nonadherence to anti-hypertensive medication in low- and middle-income countries: A systematic review and meta-analysis

of 92443 subjects. Journal of Human Hypertension. 2017;**31**(1):14-21

[29] Mishra P, Vamadevan AS, Roy A, Bhatia R, Naik N, Singh S, et al. Exploring barriers to medication adherence using COM-B model of behaviour among patients with cardiovascular diseases in low- and middle-income countries: A qualitative study. Power Purchase Agreement. 2021;**15**:1359-1371

[30] Schneider APH, Gaedke MÂ, Garcez A, Barcellos NT, Paniz VMV. Effect of characteristics of pharmacotherapy on nonadherence in chronic cardiovascular disease: A systematic review and meta-analysis of observational studies. International Journal of Clinical Practice. 2018;**72**(1):e13044

[31] Barankay I, Reese PP, Putt ME, Russell LB, Loewenstein G, Pagnotti D, et al. Effect of patient financial incentives on statin adherence and lipid control: A randomized clinical trial. JAMA Network Open. 2020;**3**(10):e2019429

[32] Burnier M, Egan BM. Adherence in hypertension: A review of prevalence, risk factors, impact, and management. Circulation Research. 2019;**124**(7):1124-1140

[33] Smits E, Andreotti F, Houben E, Crijns HJGM, Haas S, Spentzouris G, et al. Adherence and persistence with once-daily vs twice-daily direct Oral anticoagulants among patients with atrial fibrillation: Real-world analyses from the Netherlands, Italy and Germany. Drugs—Real World Outcomes. 2022;**9**:199-209 [Internet]. Available from: https://link.springer.com/10.1007/s40801-021-00289-w.s. [Accessed: February 24, 2022]

[34] Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. Medicine. Jan 2017;**96**(4):e5641

[35] Goldstein CM, Gathright EC, Garcia S. Relationship between depression and medication adherence in cardiovascular disease: The perfect challenge for the integrated care team. Power Purchase Agreement. 2017;**11**:547-559

[36] Hennein R, Hwang SJ, Au R, Levy D, Muntner P, Fox CS, et al. Barriers to medication adherence and links to cardiovascular disease risk factor control: The Framingham heart study: Medication adherence and CVD risk. Internal Medicine Journal. 2018;**48**(4):414-421

[37] Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. Journal of the American Medical Association. 2007;**297**(2):177

[38] Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. Circulation. 2009;**119**(23):3028-3035

[39] Liu M, Zheng G, Cao X, Chang X, Zhang N, Liang G, et al. Better medications adherence lowers cardiovascular events, stroke, and all-cause mortality risk: A dose-response meta-analysis. Journal of Cardiovascular Development and Disease. 2021;**8**(11):146

[40] Yang Q, Chang A, Ritchey MD, Loustalot F. Antihypertensive medication adherence and risk of cardiovascular disease among older adults: A population-based cohort study. Journal of the American Heart Association. 2017;**6**(6):e006056 [Internet]. Available

from: https://www.ahajournals.org/doi/10.1161/JAHA.117.006056. [Accessed: February 23, 2022]

[41] Raebel MA, Dyer W, Nichols GA, Goodrich GK, Schmittdiel JA. Relationships between medication adherence and cardiovascular disease risk factor control in elderly patients with diabetes. Pharmacotherapy. 2017;**37**(10):1204-1214

[42] Bansilal S, Castellano JM, Garrido E, Wei HG, Freeman A, Spettell C, et al. Assessing the impact of medication adherence on long-term cardiovascular outcomes. Journal of the American College of Cardiology. 2016;**68**(8):789-801

[43] Shang P, Liu GG, Zheng X, Ho PM, Hu S, Li J, et al. Association between medication adherence and 1-year major cardiovascular adverse events after acute myocardial infarction in China. Journal of the American Heart Association. 2019;**8**(9):e011793 [Internet]. Available from: https://www.ahajournals.org/doi/10.1161/JAHA.118.011793. [Accessed: February 23, 2022]

[44] Shau WY, Lai CL, Huang ST, Chen ST, Li JZ, Fung S, et al. Statin adherence and persistence on secondary prevention of cardiovascular disease in Taiwan. Heart Asia. 2019;**11**(2):e011176

[45] Hood SR, Giazzon AJ, Seamon G, Lane KA, Wang J, Eckert GJ, et al. Association between medication adherence and the outcomes of heart failure. Pharmacotherapy. 2018;**38**(5):539-545

[46] Ryou IS, Chang J, Son JS, Ko A, Choi S, Kim K, et al. Association between CVDs and initiation and adherence to statin treatment in patients with newly diagnosed hypercholesterolaemia: A retrospective cohort study. BMJ Open. 2021;**11**(4):e045375

[47] Zhao B, He X, Wu J, Yan S. Adherence to statins and its impact on clinical outcomes: A retrospective population-based study in China. BMC Cardiovascular Disorders. 2020;**20**(1):282

[48] Chen PS, Cheng CL, Kao Yang YH, Li YH. Statin adherence after ischemic stroke or transient ischemic attack is associated with clinical outcome. Circulation Journal. 2016;**80**(3):731-737

[49] Wei L. Adherence to statin treatment and readmission of patients after myocardial infarction: A six year follow up study. Heart. 2002;**88**(3):229-233

[50] Xie G, Sun Y, Myint PK, Patel A, Yang X, Li M, et al. Six-month adherence to statin use and subsequent risk of major adverse cardiovascular events (MACE) in patients discharged with acute coronary syndromes. Lipids in Health and Disease. 2017;**16**(1):155

[51] Korhonen MJ, Ruokoniemi P, Ilomäki J, Meretoja A, Helin-Salmivaara A, Huupponen R. Adherence to statin therapy and the incidence of ischemic stroke in patients with diabetes. Pharmacoepidemiology and Drug Safety. 2016;**25**(2):161-169

[52] Rea F, Biffi A, Ronco R, Franchi M, Cammarota S, Citarella A, et al. Cardiovascular outcomes and mortality associated with discontinuing statins in older patients receiving polypharmacy. JAMA Network Open. 2021;**4**(6):e2113186

[53] Leibowitz M, Karpati T, Cohen-Stavi CJ, Feldman BS, Hoshen M, Bitterman H, et al. Association between achieved low-density lipoprotein levels and major adverse cardiac events in

patients with stable ischemic heart disease taking statin treatment. JAMA Internal Medicine. 2016;**176**(8):1105

[54] Sotorra-Figuerola G, Ouchi D, Giner-Soriano M, Morros R. Impact of adherence to drugs for secondary prevention on mortality and cardiovascular morbidity: A population-based cohort study. IMPACT study. Pharmacoepidemiology & Drug Safety. 2021;**30**(9):1250-1257

[55] Ishii M, Kuramitsu S, Yamanaga K, Matsuo H, Horie K, Takashima H, et al. Association of guideline-directed medical therapy adherence with outcomes after fractional flow reserve-based deferral of revascularization. The European Heart Journal—Cardiovascular Pharmacotherapy. 2022;**8**(6):600-608

[56] Dopheide JF, Veit J, Ramadani H, Adam L, Papac L, Vonbank A, et al. Adherence to statin therapy favours survival of patients with symptomatic peripheral artery disease. European Heart Journal—Cardiovascular Pharmacotherapy. 2021;**7**(4):263-270

[57] Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. The American Journal of Managed Care. 2010;**16**(8):568-576

[58] Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost–effectiveness of interventions: Alternative approaches. Bulletin of the World Health Organization. 2015;**93**(2):118-124

[59] De Smedt D, Annemans L, De Backer G, Kotseva K, Rydèn L, Wood D, et al. Cost-effectiveness of optimized adherence to prevention guidelines in European patients with coronary heart disease: Results from the EUROASPIRE IV survey. International Journal of Cardiology. 2018;**272**:20-25

[60] Megiddo I, Chatterjee S, Nandi A, Laxminarayan R. Cost-effectiveness of treatment and secondary prevention of acute myocardial infarction in India: A modeling study. Global Heart. 2014;**9**(4):391

[61] Rea F, Ronco R, Martini N, Maggioni AP, Corrao G. Cost-effectiveness of posthospital management of acute coronary syndrome: A real-world investigation from Italy. Value in Health. 2022;**25**(2):185-193

[62] Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health Affairs. 2011;**30**(1):91-99

[63] Fitzpatrick C, Gillies C, Seidu S, Kar D, Ioannidou E, Davies MJ, et al. Effect of pragmatic versus explanatory interventions on medication adherence in people with cardiometabolic conditions: A systematic review and meta-analysis. BMJ Open. 2020;**10**(7):e036575

[64] Ogungbe O, Byiringiro S, Adedokun-Afolayan A, Seal SM, Dennison Himmelfarb CR, Davidson PM, et al. Medication adherence interventions for cardiovascular disease in low- and middle-income countries: A systematic review. Power Purchase Agreement. 2021;**15**:885-897

[65] Schwalm JD, Ivers NM, Natarajan MK, Taljaard M, Rao-Melacini P, Witteman HO, et al. Cluster randomized controlled trial of delayed educational reminders for long-term medication adherence in ST-elevation myocardial infarction (DERLA-STEMI). American Heart Journal. 2015;**170**(5):903-913

[66] Jia JJ, Dong PS, Du LJ, Li ZG, Lai LH, Yang XM, et al. Impact of physician-coordinated intensive follow-up on long-term medical costs in patients with unstable angina undergoing percutaneous coronary intervention. Acta Cardiologica Sinica. 2017;**33**(2):173-181

[67] Du L, Dong P, Jia J, Li Z, Lai L, Yang X, et al. Impacts of intensive follow-up on the long-term prognosis of percutaneous coronary intervention in acute coronary syndrome patients—A single center prospective randomized controlled study in a Chinese population. European Journal of Preventive Cardiology. 2016;**23**(10):1077-1085

[68] Nieuwkerk PT, Nierman MC, Vissers MN, Locadia M, Greggers-Peusch P, Knape LPM, et al. Intervention to improve adherence to lipid-lowering medication and lipid-levels in patients with an increased cardiovascular risk. The American Journal of Cardiology. 2012;**110**(5):666-672

[69] Keyserling TC, Sheridan SL, Draeger LB, Finkelstein EA, Gizlice Z, Kruger E, et al. A comparison of live Counseling with a web-based lifestyle and medication intervention to reduce coronary heart disease risk: A randomized clinical trial. JAMA Internal Medicine. 2014;**174**(7):1144

[70] Palacio AM, Uribe C, Hazel-Fernandez L, Li H, Tamariz LJ, Garay SD, et al. Can phone-based motivational interviewing improve medication adherence to antiplatelet medications after a coronary stent among racial minorities? A randomized trial. Journal of General Internal Medicine. 2015;**30**(4):469-475

[71] Chen C, Li X, Sun L, Cao S, Kang Y, Hong L, et al. Post-discharge short message service improves short-term clinical outcome and self-care behaviour in chronic heart failure: Post-discharge SMS in short-term clinical outcome and self-care behaviour. ESC Heart Failure. 2019;**6**(1):164-173

[72] Rinfret S, Rodés-Cabau J, Bagur R, Déry JP, Dorais M, Larose É, et al. Telephone contact to improve adherence to dual antiplatelet therapy after drug-eluting stent implantation. Heart. 2013;**99**(8):562-569

[73] Derose SF, Green K, Marrett E, Tunceli K, Cheetham TC, Chiu VY, et al. Automated outreach to increase primary adherence to cholesterol-lowering medications. JAMA Internal Medicine. 2013;**173**(1):38

[74] Vollmer WM, Owen-Smith AA, Tom JO, Laws R, Ditmer DG, Smith DH, et al. Improving adherence to cardiovascular disease medications with information technology. The American Journal of Managed Care. 2014;**20**(11 Spec No 17):SP502-SP510

[75] Senoo K, Miki T, Ohkura T, Iwakoshi H, Nishimura T, Shiraishi H, et al. A smartphone app to improve oral anticoagulation adherence in patients with atrial fibrillation: Prospective observational study. JMIR mHealth and uHealth. 2022;**10**(1):e30807

[76] Kawada K, Kubo T, Ishida T, Jobu K, Morisawa S, Hamada T, et al. Assisted living and medication adherence in super-aged patients with heart failure in the Japanese population. Journal of Cardiovascular Pharmacology. 2021; Publish Ahead of Print [Internet]. Available from: https://journals.lww.com/10.1097/FJC.0000000000001212. [Accessed: March 2, 2022]

[77] Hovland R, Bremer S, Frigaard C, Henjum S, Faksvåg PK, Sæther EM, et al.

Effect of a pharmacist-led intervention on adherence among patients with a first-time prescription for a cardiovascular medicine: A randomized controlled trial in Norwegian pharmacies†. International Journal of Pharmacy Practice. 2020;**28**(4):337-345

[78] Pladevall M, Brotons C, Gabriel R, Arnau A, Suarez C, de la Figuera M, et al. Multicenter cluster-randomized trial of a multifactorial intervention to improve antihypertensive medication adherence and blood pressure control among patients at high cardiovascular risk (the COM99 study). Circulation. 2010;**122**(12):1183-1191

[79] Fuller RH, Perel P, Navarro-Ruan T, Nieuwlaat R, Haynes RB, Huffman MD. Improving medication adherence in patients with cardiovascular disease: A systematic review. Heart. 2018;**104**(15):1238-1243

[80] Ivers NM, Schwalm JD, Bouck Z, McCready T, Taljaard M, Grace SL, et al. Interventions supporting long term adherence and decreasing cardiovascular events after myocardial infarction (ISLAND): Pragmatic randomised controlled trial. British Medical Journal. 2020;**369**:m1731

[81] Faridi KF. Medication adherence and cardiovascular outcomes. Journal of the American College of Cardiology. 2017;**69**(5):598-599

[82] Reddy A, Huseman TL, Canamucio A, Marcus SC, Asch DA, Volpp K, et al. Patient and partner feedback reports to improve statin medication adherence: A randomized control trial. Journal of General Internal Medicine. 2017;**32**(3):256-261

[83] Wu JR, Mark B, Knafl GJ, Dunbar SB, Chang PP, DeWalt DA. A multi-component, family-focused and literacy-sensitive intervention to improve medication adherence in patients with heart failure—a randomized controlled trial. Heart & Lung. 2019;**48**(6):507-514

[84] Palmer MJ, Machiyama K, Woodd S, Gubijev A, Barnard S, Russell S, et al. Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Heart Group, editor. Cochrane Database of Systematic Reviews. 2018;**6**(6):CD012675 [Internet]. Available from: http://doi.wiley.com/10.1002/14651858.CD012675.pub3. [Accessed: March 2, 2022]

[85] Adler AJ, Martin N, Mariani J, Tajer CD, Serrano NC, Casas JP, et al. Mobile phone text messaging to improve adherence to cardiovascular disease secondary prevention interventions. In: The Cochrane Collaboration, editor. Cochrane Database of Systematic Reviews [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2015. p. CD011851. Available from: https://doi.wiley.com/10.1002/14651858.CD011851. [Accessed: March 13, 2022]

[86] Thakkar J, Kurup R, Laba TL, Santo K, Thiagalingam A, Rodgers A, et al. Mobile telephone text messaging for medication adherence in chronic disease: A meta-analysis. JAMA Internal Medicine. 2016;**176**(3):340

[87] Morawski K, Ghazinouri R, Krumme A, Lauffenburger JC, Lu Z, Durfee E, et al. Association of a smartphone application with medication adherence and blood pressure control: The MedISAFE-BP randomized clinical trial. JAMA Internal Medicine. 2018;**178**(6):802

[88] Al-Arkee S, Mason J, Lane DA, Fabritz L, Chua W, Haque MS, et al. Mobile apps to improve medication

adherence in cardiovascular disease: Systematic review and Meta-analysis. Journal of Medical Internet Research. 2021;**23**(5):e24190

[89] Mondesir FL, Carson AP, Durant RW, Lewis MW, Safford MM, Levitan EB. Association of functional and structural social support with medication adherence among individuals treated for coronary heart disease risk factors: Findings from the REasons for Geographic and Racial Differences in Stroke (REGARDS) study. Akinyemiju TF, editor. PLoS ONE. 2018;**13**(6):e0198578

[90] DiMatteo MR. Social support and patient adherence to medical treatment: A meta-analysis. Health Psychology. 2004;**23**(2):207-218

[91] Magrin ME, D'Addario M, Greco A, Miglioretti M, Sarini M, Scrignaro M, et al. Social support and adherence to treatment in hypertensive patients: A meta-analysis. Annals of Behavioral Medicine. 2015;**49**(3):307-318

[92] Burton A, Walters K, Marston L, Osborn D. Is there an association between perceived social support and cardiovascular health behaviours in people with severe mental illnesses? Social Psychiatry and Psychiatric Epidemiology. 2020;**55**(12):1659-1669

[93] Lin TK, Hsu BC, Li YD, Chen CH, Lin JW, Chien CY, et al. The impact of sources of perceived social support on readmissions in patients with heart failure. Journal of Psychosomatic Research. 2022;**154**:110723

[94] Wang TY, Kaltenbach LA, Cannon CP, Fonarow GC, Choudhry NK, Henry TD, et al. Effect of medication co-payment vouchers on P2Y 12 inhibitor use and major adverse cardiovascular events among patients with myocardial infarction: The ARTEMIS randomized clinical trial. Journal of the American Medical Association. 2019;**321**(1):44

[95] Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. The New England Journal of Medicine. 2011;**365**(22):2088-2097

[96] Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Medical Care. 2005;**43**(6):521-530

[97] Neville HL, Mann K, Killen J, Callaghan M. Pharmacist intervention to improve medication adherence in patients with acute coronary syndrome: The PRIMA-ACS study. Canadian Journal of Hospital Pharmacy. 2021;**74**(4):350-360 [Internet]. Available from: https://www.cjhp-online.ca/index.php/cjhp/article/view/3198. [Accessed: March 2, 2022]

[98] Xu HY, Yu YJ, Zhang QH, Hu HY, Li M. Tailored interventions to improve medication adherence for cardiovascular diseases. Frontiers in Pharmacology. 2020;**11**:510339

[99] Rao S, Jamal T, Khan MS, Michos E, Navar AM, Wang TJ, et al. Association of polypill therapy with cardiovascular outcomes, mortality, and adherence: A systematic review and meta-analysis of randomized controlled trials. Progress in Cardiovascular Diseases. 2022;**73**:48-55. S0033062022000056

[100] Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: A meta-analysis. Hypertension. 2010;**55**(2):399-407