Adherence with cardiovascular medications and the outcomes in patients with coronary arterial disease: “Real-world” evidence

Chen Chen MD¹ | Xiaoqing Li MD¹ | Yuhao Su MD¹ | Zhigang You MD, PhD¹ | Rong Wan PhD² | Kui Hong MD, PhD¹,²,³

¹Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China
²Jiangxi Key Laboratory of Molecular Medicine, Nanchang, Jiangxi, China
³Department of Genetic Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

Correspondence
Kui Hong, MD, PhD, Department of Cardiovascular Medicine and Jiangxi Key Laboratory of Molecular Medicine, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Rd, Nanchang, Jiangxi 330006, China.
Email: hongkui88@163.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: 31971041

Abstract

Background: Cardiovascular medications are vital for the secondary prevention of coronary arterial disease (CAD). However, the effect of cardiovascular medication may depend on the optimal adherence of the patients. This meta-analysis aims to determine the magnitude of adherence to vascular medications that influences the absolute and relative risks (RRs) of mortality in patients with CAD in real-world settings.

Methods: The Cochrane Library, PubMed, and EMBASE databases were searched through March 1, 2022. Prospective studies reporting association as RR and 95% confidence interval between cardiovascular medication adherence and any cardiovascular events and/or all-cause mortality in patients with CAD were included. A one-stage robust error meta-regression method was used to summarize the dose-specific relationships.

Results: A total of 18 studies were included. There is a significant inverse linear association between cardiovascular medication adherence and cardiovascular events ($p_{\text{nonlinearity}} = .68$) or mortality ($p_{\text{nonlinearity}} = .82$). The exposure-effect analysis showed that an improvement of 20% cardiovascular medication adherence was associated with 8% or 12% lower risk of any cardiovascular events or mortality, respectively. In subgroup analysis, the benefit was observed in adherence of stain (RR: 0.90, for cardiovascular events, RR: 0.85, for mortality), angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB)(RR: 0.90, for mortality), and antiplatelet agent (RR: 0.89 for mortality) but not in beta-blocker (RR: 0.90, $p = .14$, for cardiovascular events, RR: 0.97, $p = .32$ for mortality). Estimated absolute differences per 1 million individuals per year for mortality associated with 20% improvement were 175 cases for statin, 129 cases for antiplatelet, and 117 cases for ACEI/ARB.
1 | INTRODUCTION

Coronary arterial disease (CAD) is a highly prevalent disease, associated with increased costs, morbidity, and mortality. Cardiovascular medications, such as angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB), beta-blockers, antiplatelet agents, and statins, remain the most common medical interventions worldwide for the prevention of CAD. Although their beneficial effects have been established in the primary and secondary prevention of cardiovascular diseases (CVDs), their effort in real-world settings is inferior to that seen in random control trials (RCT), and this has been partly attributed to poor medication adherence. According to a recent study, almost 31% of myocardial infarction (MI) patients are no longer persistent with their prescribed medications by 6 months. A meta-analysis that included 1,978,919 patients showed that only 60% of patients were adherence to their cardiovascular medications. Additionally, compared with good adherence, the risk of cardiovascular events or mortality in those with poor adherence increased by 20% or 35%, respectively.

A systematic evaluation of the association between cardiovascular medication adherence and the outcomes in patients with CAD is of significance for understanding the role of medication adherence in secondary prevention. Furthermore, a quantitative analysis of adherence and their outcomes could provide more detailed guidelines and education information for patients with cardiovascular medication to have better outcomes (e.g., cardiovascular events and mortality). However, the quantitative association between cardiovascular medication adherence and long-term outcomes in patients with CAD remains to be determined. Moreover, considering well-designed RCTs might not reflect the actual adherence level or effectiveness of medication therapy in the "real" community. We conducted an exposure-effect meta-analysis based on prospective observational studies to (i) quantitatively investigate the relationship between adherence to cardiovascular medication and outcomes in patients with CAD in real-world settings and (ii) estimate the future absolute risk for cardiovascular events or mortality for suboptimum adherence to cardiovascular medication.

2 | METHODS

We conducted this meta-analysis according to preferred reporting items for systematic reviews and meta-analyses guidelines (Supporting Information: Table 1). All prospective studies (cohort, nested case-control), reporting data about medication adherence (statin, antiplatelet agents, ACEI/ARB, and beta-blockers) and any cardiovascular (defined as any fatal or nonfatal coronary heart disease) events, or all-cause death were considered eligible for the systematic review. A comprehensive literature search was performed using Cochrane Library, PubMed, and Embase databases, up to March 1, 2022. Two researchers (Chen Chen and Xiaoping Li) independently worked in the whole process of this meta-analysis from the literature search and selection to data analysis. Supporting Information: Table S2 provides a detailed description of the search strategy. All discrepancies were resolved through discussion with each other or through consultation with a third reviewer (Yuhao Su). We used a robust error meta-regression method for the exposure-effect analysis of cardiovascular medication adherence and any cardiovascular events and all-cause death. All statistical analyses were undertaken using Stata software (version 14.0; Stata Corp LP). Assessment of the quality of the included studies was performed using the Newcastle–Ottawa quality assessment scale (NOS), with a score over 6 defined as high quality. Full details of the literature search strategy, study selection criteria, quality assessment, and statistical analysis have been reported in Supporting Information: Methods. This study has been registered with PROSPERO (international prospective register of systematic reviews)–registration number–CRD42019116748.

3 | RESULTS

3.1 | Study selection

As shown in Figure 1, we initially identified studies in the Cochrane Library (n = 80), PubMed (n = 454), and Embase databases (n = 718). No additional studies were identified through manual searches. We excluded 955 studies based on screening the title or abstract, and the full text of the remaining 44 studies was reviewed. After a screening of the full-text articles, 26 studies did not meet the selection criteria and were excluded (the detailed reason was listed in Figure 1). Finally, 18 prospective studies comprising 402,201 participants were considered potentially eligible and were included in the exposure-effect analysis.

3.2 | Study characteristics and quality

Detailed characteristics of the included studies are presented in Table 1. Overall, these studies were published between 2002 and
| Author, publication year, country | Baseline population | Population source | Design | Mean age (years), male (%) | Adherence measure | Medicine | Outcome |
|----------------------------------|---------------------|-------------------|--------|---------------------------|------------------|----------|---------|
| Allonen 2012, Finland            | ACS                 | GPCAD study       | Cohort | 65.6, 69.6                | MPR             | Statin   | All-cause death |
| Hamood 2015, Israel              | Post-AMI            | LHS database      | Cohort | 66.36, 73.8               | PDC             | Statin, Aspirin, Beta-blocker, ACEI/ARB | All-cause death |
| Ho 2006, USA                     | Diabetes and IHD    | KPCO database     | Cohort | 69, 61                    | PDC             | Statin, Beta-blocker, ACEI/ARB | All-cause mortality |
| Kleiner 2009, USA                | Post-AMI            | Northeastern health database | Cohort | 65.93, 62                | PDC             | Beta-blocker | All-cause mortality |
| Lenzi 2014, Italy                | Post-AMI            | HDRs of LHA Database | Nested case-control | 77, 58.2          | PDC             | Statin, Antiplatelet, Beta-blocker, ACEI/ARB | All-cause mortality |
| Martino 2015, Italy              | Post-MI             | Regional hospital information system of Lazio | Nested case-control | 63.7 (men) 72.5 (women), 67.5 | PDC             | Statin, Beta-blocker, ACEI/ARB | All-cause mortality |
| Rasmussen 2007, Canada           | Post-AMI            | Ontario Myocardial Infarction Database | Cohort | ≥66 | PDC             | Statin, Beta-blocker | All-cause mortality |
| Rublee 2012, USA                 | CHD                 | I3 In Vision Data Mart insurance database | Cohort | 60.6, 64.6               | PDC             | Statin | Cardiovascular events |
| Ruokoniemi 2011, Finland         | Diabetes with CHD   | Administrative health databases in Finland | Nested case-control | 65.2, 68.9          | PDC             | Statin | Major coronary events |
| Tuppin 2010, France              | Post-MI             | SNIIRAM-PMSI      | Cohort | NA                        | PDC             | Statin, Beta-blocker, ACEI/ARB | Mortality or readmission for ACS |
| Shalev 2009, Israel              | CHD                 | MHS               | Cohort | 61.5, 55.7                | PDC             | Statin   | All-cause mortality |
| Wei 2002, UK                     | Post-MI             | MEMO record-linkage database 1985–1995 | Cohort | 67.26, 59.6         | PDC             | Statin   | All-cause mortality |
| WEI 2008, UK                     | Cardiovascular disease | MEMO record-linkage database 1993–2001 | Cohort | >65, 54.2          | MPR             | Statin, Aspirin | All-cause mortality recurrence of cardiovascular disease |
| Wei 2004, UK                     | Post-MI             | MEMO record-linkage database 1994–1995 | Cohort | 66.3, 59.4           | MPR             | Beta-blocker | All-cause mortality re-MI |
| Xie 2017, China                  | ACS                 | CPACS-1 and CPACS-2 | Cohort | 63.3, 70               | PDC             | Statin   | All-cause mortality, incident MI, stroke |
| McGinnis 2009, USA               | Undergoing Coronary event | CPCRS 2000–2005   | Cohort | 62, 70                 | PDC             | Statin   | All-cause mortality recurrent nonfatal cardiac events |
### Table 1 (Continued)

| Author, publication year, country | Baseline population source | Population sample | Design | Outcome | Adherence measure | Medicine | Adherence year, country Baseline population | Population source | Medicine | Design | Outcome | Adherence measure |
|----------------------------------|-----------------------------|-------------------|--------|---------|-------------------|----------|-----------------------------------|-------------------|----------|--------|---------|-------------------|
| Hickson 2019, USA                | Post-AMI                    | CMS chronic conditions database 2007–2011 | Cohort | All-cause mortality | PDC | Statin | >51.45,7 | Post-AMI | CMS chronic conditions database 2007–2011 | All-cause mortality | PDC | Statin | All-cause mortality | PDC |
| Korhonen 2017, USA              | Post-AMI                    | CMS chronic conditions database 2007–2011 | Cohort | All-cause mortality | PDC | Statin | >51.45,2 | Post-AMI | CMS chronic conditions database 2007–2011 | All-cause mortality | PDC | Statin | All-cause mortality | PDC |

**Abbreviations:** ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ACS, acute coronary syndrome; AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CCB, calcium channel blockers; CD, chronic disease; CDK, coronary heart disease; CKD, chronic kidney disease; CDS, chronic disease score; CHD, coronary heart disease; CHF, congestive heart failure; COPC, clinical pathways for acute coronary syndromes in China; COPC, Kaiser Permanent Colorado and Clinical Pharmacy; ECG, electrocardiograph; GPCR, gene predisposition of coronary artery disease; HD, health; HHH, hospital discharge records; IHD, ischemic heart disease; IJDD, idiopathic systolic heart disease; KPCO, Kaiser Permanente of Colorado Hospital; LHA, local Health Authority; LMH, Leumit Health Services; MEMO, Medicine Monitoring Unit's; MHS, Maccabi Healthcare Services; MPR, medication possession ratio; NA, not applicable; NSTEMI, non-ST-elevation myocardial infarction; PMSI, système national d'informations interrégimes de l'assurance maladie (French hospital discharge database); TIA, transient ischemic attack.

* Categorized as no user (0), no regular user (poor adherence), and regular user (good adherence).

---

### 3.3 Medication adherence and all-cause death

Fifteen11-20,23,25-28 studies with available data on all-cause mortality outcomes. Statin adherence was the most commonly studied (n = 13). There were five studies that assessed the ACEI/ARB drugs, eight assessed beta-blockers, and 3 assessed antiplatelets, respectively.

No evidence of nonlinear association was observed between cardiovascular medication adherence and all-cause death (\( \rho_{\text{nonlinearity}} = .82 \)). An improvement of 20% cardiovascular medication adherence was associated with a 12% lower risk (relative risk [RR]: 0.88; 95% CI: 0.82–0.97, \( I^2 = 19\% \), \( p < .001 \)) for all-cause death, with low evidence of heterogeneity (Figure 2). In the nonlinear model, an inverse association was found between cardiovascular medication adherence and all-cause death (Figure 2). In subgroup analysis, a 20% adherence increment was associated with 15% (95% CI: 0.82–0.89, \( I^2 = 82\% \)) lower mortality risk for statin, 11% (95% CI: 0.85–0.92, \( I^2 = 97\% \)) for antiplatelet agents, and 10% (95% CI: 0.80–1.00, \( I^2 = 47\% \)) for ACEI/ARB. However, the benefit was not observed in beta-blocker (RR: 0.97, 95% CI: 0.93–1.03, \( I^2 = 97\% \)).

The association between good adherence and mortality persisted in almost all subgroup analyses defined by age, region, follow-up times, and other covariates (Supporting Information: Table S4).

### 3.4 Medication adherence and any CVD events

Among six studies19,21,22,24-26 reporting on cardiovascular events, statin adherence was the most commonly studied (n = 5). Two studies assessed the antiplatelet agents and two assessed beta-blockers. Only one study was identified in the literature search that assessed the association of ACEI/ARB compliance with cardiovascular events. There was no evidence of a nonlinear relationship between cardiovascular medication adherence level and the risk of cardiovascular events (\( \rho_{\text{nonlinearity}} = .68 \)). The exposure-effect analysis showed an improvement in cardiovascular medication adherence of 20% was associated with an 8% lower risk of any cardiovascular events (RR: 0.92; 95% CI: 0.87–0.98, \( I^2 = 0\% \), \( p = .02 \)), with no evidence of heterogeneity (Figure 3). In the nonlinear model, an inverse association was found between cardiovascular medication adherence and CVD events (Figure 3).

In subgroup analysis, there was also evidence of a linear association between statin (\( \rho_{\text{nonlinearity}} = .64 \)) and beta-blockers (\( \rho_{\text{nonlinearity}} = .48 \)) and any cardiovascular events. The corresponding RRs were 0.90 (95% CI: 0.86–0.95, \( I^2 = 78\% \)) for statin, 0.90 (95% CI: 0.67–1.21, \( I^2 = 0\% \)) for beta-blockers per 20% adherence increase, respectively. The subgroup analysis
for antiplatelet and ACEI/ARB and antiplatelet agents was not available because of a limited number of studies.

### 3.5 Absolute risk difference associated with poor adherence

Using the cardiovascular events rate from the studies based on the US population, we estimated a 20% adherence improvement in cardiovascular medication was associated with 93 cardiovascular cases and 140 all-cause death per 1 million individuals per year in absolute risk differences. Especially, the absolute risk differences per 1 million individuals per year were 118 cardiovascular cases and 175 all-cause death for statins, 129 all-cause death for antiplatelet, and 117 all-cause death for ACEI/ARB for a 20% cardiovascular medication adherence improvement.

### 3.6 Sensitivity analyses and publication bias

The omission of any single study did not significantly alter the pooled RRs. There was no statistical evidence of publication bias (Supporting Information: Figure S1).

### 4 DISCUSSION

To the best of our knowledge, this is the first meta-analysis that quantitatively analyzes the effect of cardiovascular medication adherence on outcomes among patients with CAD in a real-world setting. By incorporating 18 prospective studies with 402,201 patients, we novelty found a 20% cardiovascular medication adherence unit increased could reduce the risk for cardiovascular events by 8% and
all-cause mortalities by 12%, respectively. Furthermore, by using incidence rates from the general US population, we found the absolute risk difference associated with per 20% medication adherence to cardiovascular medication was 93 per 1 million cardiovascular cases per year and 140 per 1 million all-cause death. This meta-analysis strengthens and extends the understanding of the positive impact of cardiovascular medication adherence on secondary prevention among people with CAD, further supporting the notion that improved cardiovascular medication adherence was associated with better outcomes in patients with CAD.

Medication adherence has been defined as the extent to which a patient takes medications as prescribed by their healthcare providers. In clinical practice, medication nonadherence is one of the main factors that reduce the effectiveness of drug therapies. However, a previous study reported that almost 40% of the patients who initiated the use of ACEIs/ARBs, beta-blockers, or statins following hospitalization for MI became nonadherent during the first treatment year. Moreover, many patients seemed to do so already during the first 6 months. Therefore, better adherence to cardiovascular treatment should be highlighted in the clinical secondary prevention in patients with CAD.

We subsequently found the inverse association between cardiovascular medication adherence and outcomes in patients with CAD risk was found. A 20% improvement in cardiovascular medication adherence was associated with an 8% reduction in cardiovascular case risk. In addition, this cardiovascular event risk reduction would be translated into a reduction of all-cause mortality (decreased by 12%). However, this benefit was not observed in good beta-blocker adherence. This reason might be the majority of the included sample were patients with post-MI. Recently, several studies reported that beta-blocker might have no benefit on post-AMI patients without heart failure or ventricular dysfunction (so-called reperfusion era). Actually, the evidence of benefits associated with beta-blocker use is mostly from trials predating the advent of
the era of early revascularization. A meta-analysis of randomized clinical trials also showed that beta-blocker use has no mortality benefit for patients without heart failure. Another study also showed patients adherent to ACE inhibitors/ARBs and statins only had similar mortality rates as those adherents to ACE inhibitors/ARBs and statins and beta-blocker, suggesting a limited additional benefit for beta-blockers in patients with post-MI. By combining evidence from observational studies, a systematic review suggested that the majority of the included studies failed to demonstrate a benefit in survival or cardiovascular events with long-term beta-blockers in post-MI patients with normal left ventricular function. However, because of a lack of or limited data, subgroup analysis by subtypes of heart failure was not available. Further studies are needed to explore the impact of beta-blockers adherence on the outcomes in post-MI patients (especially in patients with normal left ventricular function).

In general, the impact of age on "statin adherence" in the secondary prevention of CAD remains controversial. Actually, statins are generally not sufficient to recommend among older patients (aged ≥ 75) with known CVD by current guidelines. The 2013 ACC/AHA guideline recommend and the US Preventive Services Task Force did not recommend it. A recent meta-analysis of RCTs showed significant reductions in major coronary events in all age groups (including those older than 75 years) among participants with known vascular disease. However, in a propensity-adjusted analysis of real-world data, Rothschild et al. found statin therapy had no significant effect on long-term survival in older adults hospitalized patients with CAD, but without adjustment for medication adherence. In contrast, another observational study based on patients with atherosclerotic CVD found high-intensity statins were associated with a small but significant survival advantage compared with moderate-intensity statins (hazard ratio [HR], 0.90; 95% CI, 0.87–0.94) compared with those receiving submaximal doses. In the current study, we found that good adherence was associated with reduced mortality in patients with CAD regardless of age (<65 or >65 years), which suggested the benefit of statins persisted in older patients with CAD. However, due to the scarcity of data, we can't perform a subgroup analysis based on sex over 75 years. Therefore, the benefit of the effect of good adherence to statin in CAD patients with older age needs to be further investigated.

The exposure-effect relationship emphasizes the importance of medication adherence. For example, numerous studies have reported that patients taking a statin before undergoing an MI event is more prone not adherence to a statin, since they may believe that statin therapy is ineffective in preventing future events, despite experiencing an MI event should not necessarily be viewed as a failure of statin therapy. To date, the effect of good adherence to cardiovascular medications has been validated. For example, over a period of 4 years of statin use results in a reduction of 1 mmol/L (39 mg/dl) in the level of low-density lipoprotein cholesterol, which translates into a 13% reduction in death from all-cause death. Some authors have raised the idea of "it is not too late to improve statin adherence" among patients whether they were adherent to statin therapy pre-AMI. We also suggest clinicians should emphasize this idea in health propaganda education when patients discharging from the hospital. Besides, poor adherence was affected by lots of factors (i.e., sex, age, race). Another simple method to solve this problem is to develop predictive screen models to better identify at-risk for nonadherence patients prospectively. On the other hand, we suggest physicians pay more attention to these patients with a high-risk factor of nonadherence (e.g., older, depression, cognitive dysfunction). Also, the doctors should improve the communication between doctors and patients or their family and the health-related beliefs of patients, which has been shown to contribute to patient adherence. Furthermore, some innovations aid can be used to improve adherence management, such as pill-boxes, calendars, and mobile applications.

5 | LIMITATION

We acknowledged that some limitations exist in this study. First, most research included in this meta-analysis was focused on statins, the number of studies about beta-blockers, antiplatelet, and ACEI/ARB is limited, resulting in some subgroup analyses for each drug were not available. Second, because of data restriction on medication doses, we could not estimate what proportion of the risk of cardiovascular events and/or all-cause death that has been attributed in this review to poor adherence is in fact explained by the prescription of suboptimal medication doses. Third, some studies only defined "regular use" and "no use" adherence without an accurate exposure of adherence and were, therefore, unable to describe the exposure-effect relationship. So a part of published studies was excluded from current studies, which might cause a selection bias. Lastly, a number of studies showed cardiovascular medication discontinuation is associated with an increased risk of all-cause death in CAD patients. For example, Ho et al. showed statin discontinuation is associated with a 2.86-fold increased risk of mortality (HR, 2.86; 95% CI, 1.47–5.55) over the 1-year study; however, because of data-type restriction, the exposure-effect analysis was not available.

6 | CONCLUSION

In summary, poor adherence is dose-dependently associated with significantly increased risk of cardiovascular events and all-cause mortality in patients with CAD. Cardiovascular medication adherence should be a target for quality improvement interventions to maximize the outcomes of secondary prevention of CAD.

AUTHOR CONTRIBUTIONS

Kui Hong was responsible for the entire project and revised the draft. Chen Chen and Xiaoqing Li performed the systematic literature review and drafted the first version of the manuscript. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.
ACKNOWLEDGMENT
This study was supported by grants from the National Natural Science Foundation of China (31971041).

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Kui Hong http://orcid.org/0000-0001-9416-0862

REFERENCES
1. Yusuf S, Hawken S, Öunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364:937-952.

2. Thompson AM, Hu T, Eshelbrenner CL, Reynolds K, He J, Bazzano LA. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis. JAMA. 2011;305:913-922.

3. Thavendiranathan P, Bagai A, Brookhart MA, Choudhry NK. Primary prevention of cardiovascular diseases with statin therapy: a meta-analysis of randomized controlled trials. Arch Intern Med. 2006;166:2307-2313.

4. Ridker PM, Cook NR, Lee I-M, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352:1293-1304.

5. Mathews R, Wang TY, Honeycutt E, et al. Persistence with secondary prevention medications after acute myocardial infarction: insights from the TRANSLATE-ACS study. Am Heart J. 2015;170:62-69.

6. Choudhry NK, Khan A, Heydon E, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34:2940-2948.

7. Silverman SL. From randomized controlled trials to observational studies. Am J Med. 2009;122:114-120.

8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Open Med. 2009;3:e123-e130.

9. Xu C, Liu Y, Jia PL, et al. The methodological quality of dose-response meta-analyses needed substantial improvement: a cross-sectional survey and proposed recommendations. J Clin Epidemiol. 2019;107:1-11.

10. Liu X, Ma J, Huang L, et al. Fluoroquinolones increase the risk of serious arrhythmias: a systematic review and meta-analysis. Medicine. 2017;96:e8273.

11. Alkonen J, Nieminen MS, Lokki M, et al. Mortality rate increases steeply with nonadherence to statin therapy in patients with acute coronary syndrome. Clin Cardiol. 2012;35:E22-E27.

12. Di Martino M, Kirchmayer U, Agabiti N, et al. The impact of time-window bias on the assessment of the long-term effect of medication adherence: the case of secondary prevention after myocardial infarction. BMJ. 2015;5:e007866.

13. Hamood H, Hamood R, Green MS, Almog R. Effect of adherence to evidence–based therapy after acute myocardial infarction on all-cause mortality. Pharmacoepidemiol Drug Saf. 2015;24:1093-1104.

14. Hickson RP, Robinson JG, Annis IE, Killelay-Jones LA, Fang G. It’s not too late to improve statin adherence: association between changes in statin adherence from before to after acute myocardial infarction and all-cause mortality. J Am Heart Assoc. 2019;8:e011378.

15. Ho PM, Prochazka AV, Magid DJ, et al. Adherence to cardioprotective medications and mortality among patients with diabetes and ischemic heart disease. BMC Cardiovasc Disord. 2006;6:48.

16. Kleiner SA, Vogt WB, Gladowski P, et al. Beta-blocker compliance, mortality, and reinfarction: validation of clinical trial association using insurer claims data. Am J Med Qual. 2009;24:512-519.

17. Korhonen MJ, Robinson JG, Annis IE, et al. Adherence tradeoff to multiple preventive therapies and all-cause mortality after acute myocardial infarction. J Am Coll Cardiol. 2017;70:1543-1554.

18. Lenzi J, Rucci P, Castaldini I, et al. Does age modify the relationship between adherence to secondary prevention medications and mortality after acute myocardial infarction? A nested case-control study. Eur J Clin Pharmacol. 2015;71:243-250.

19. McGinnis BD, Olson KL, Delate T, Stolcpart RS. Statin adherence and mortality in patients enrolled in a secondary prevention program. Am J Manag Care. 2009;15:689-695.

20. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007;297:177-186.

21. Rublee DA, Chen SY, Maredkian J, Wu N, Rao P, Boulanger L. Evaluation of cardiovascular morbidity associated with adherence to atorvastatin therapy. Am J Ther. 2012;19:24-32.

22. Ruokoniemi P, Korhonen MJ, Helin-Salmivaara A, et al. Statin adherence and the risk of major coronary events in patients with diabetes: a nested case-control study. Br J Clin Pharmacol. 2011;71:766-776.

23. Shalev V, Chodick G, Silber H, Kokka E, Jan J, Heymann AD. Continuation of statin treatment and all-cause mortality: a population-based cohort study. Arch Intern Med. 2009;169:260-268.

24. Tuppin P, Neumann A, Danchin N, et al. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. Arch Cardiovasc Dis. 2010;103:363-375.

25. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. Br J Clin Pharmacol. 2008;66:110-116.

26. Wei L, Flynn R, Murray GD, MacDonald TM. Use and adherence to beta-blockers for secondary prevention of myocardial infarction: who is not getting the treatment? Pharmacoepidemiol Drug Saf. 2004;13:761-766.

27. Wei L, Wang J, Thompson P, Wong S, Struthers AD, MacDonald TM. Adherence to statin treatment and readmission of patients after myocardial infarction: a six year follow up study. Heart. 2002;88:229-233.

28. Xie G, Sun Y, Myint PK, 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 Health Dis. 2017;16:155.

29. Members WG, Mozaffarian D, Benjamin EJ, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation. 2016;133:e38-e360.

30. Bosworth HB, Granger BB, Mendys P, et al. Medication adherence: a call for action. Am Heart J. 2011;162:421-424.

31. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487-497.

32. Lauffenburger JC, Robinson JG, Oramasionwu C, Fang G. Racial/ethnic and gender gaps in the use of and adherence to evidence-based preventive therapies among elderly Medicare Part D beneficiaries after acute myocardial infarction. Circulation. 2014;129:754-763.
patients: a systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother. 2018;5:12-20.

34. Dondo TB, Hall M, West RM, et al. β-Blockers and mortality after acute myocardial infarction in patients without heart failure or ventricular dysfunction. J Am Coll Cardiol. 2017;69:2710-2720.

35. Steg PG, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients without heart failure or ventricular dysfunction. J Am Coll Cardiol. 2017;69:2710-2720.

36. Bangalore S, Makani H, Radford M, et al. Clinical outcomes with β-blockers for myocardial infarction: a meta-analysis of randomized trials. Am J Med. 2014;127:939-953.

37. Hong J, Barry AR. Long-term beta-blocker therapy after myocardial infarction in the reperfusion era: a systematic review. Pharmacotherapy. 2018;38:546-554.

38. Stone NJ, Robinson JG, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 2013;62:2889-2934.

39. US Preventive Services Task F, Bibbins-Domingo K, Grossman DC, et al. Statin use for the primary prevention of cardiovascular disease in adults: US Preventive Services Task Force recommendation statement. JAMA. 2016;316:1997-2007.

40. Armitage J, Baigent C, Barnes E, et al. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. Lancet. 2019;393:407-415.

41. Rothschild DP, Novak E, Rich MW. Effect of statin therapy on mortality in older adults hospitalized with coronary artery disease: a propensity-adjusted analysis. J Am Geriatr Soc. 2016;64:1475-1479.

42. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:47-54.

43. Bijlsma MJ, Janssen F, Hak E. Estimating time-varying drug adherence using electronic records: extending the proportion of days covered (PDC) method. Pharmacoepidemiol Drug Saf. 2016;25:325-332.

44. Bao L, Chen W, Zhang H, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet. 2008;371:117-125.

45. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol. 2004;19:357-362.

46. Son Y-J, Kim H-G, Kim E-H, Choi S, Lee S-K. Application of support vector machine for prediction of medication adherence in heart failure patients. Healthc Inform Res. 2010;16:253-259.

47. Bourdès V, Ferrières J, Amar J, et al. Prediction of persistence of combined evidence-based cardiovascular medications in patients with acute coronary syndrome after hospital discharge using neural networks. Med Biol Eng Comput. 2011;49:947-955.

48. Kalichman SC, Cain D, Cherry C, Kalichman M, Pope H. Pillboxes and antiretroviral adherence: prevalence of use, perceived benefits, and implications for electronic medication monitoring devices. AIDS Patient Care STDs. 2005;19:833-839.

49. Hawes EM. Medication management and treatment adherence. Chronic Illness Care. Springer; 2018:175-185.

50. Ho PM, Spertus JA, Masoudi FA, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med. 2006;166:1842-1847.

SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chen C, Li X, Su Y, You Z, Wan R, Hong K. Adherence with cardiovascular medications and the outcomes in patients with coronary arterial disease: "real-world" evidence. Clin Cardiol. 2022;45:1220-1228. doi:10.1002/clc.23898