



## Research article

## Closing gaps in medication taking for secondary prevention of coronary heart disease patients among US adults

Xiaowei Liu<sup>a</sup>, Lijiang Tang<sup>b</sup>, Ying Tang<sup>c</sup>, Changqing Du<sup>b</sup>, Xiaofeng Chen<sup>d</sup>, Cheng Xu<sup>e</sup>, Jing Yan<sup>a,\*</sup><sup>a</sup> The Second Clinical Medical College, Zhejiang Chinese Medical University, Hangzhou 310053, PR China<sup>b</sup> Department of Cardiology, Zhejiang Hospital, Hangzhou, Zhejiang 310013, PR China<sup>c</sup> Geriatrics Research Institute of Zhejiang Province, Zhejiang Provincial Key Lab of Geriatrics, Zhejiang Hospital, Hangzhou, Zhejiang 310013, PR China<sup>d</sup> Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis, IN 46202, USA<sup>e</sup> Department of Cardiology, Taizhou Hospital, Wenzhou Medical University, Taizhou, Zhejiang 317000, PR China

## ARTICLE INFO

## Keywords:

Coronary heart disease  
Secondary prevention  
Medications  
Co-morbidities

## ABSTRACT

**Background:** The secondary preventive medical remedies used in the U.S. general population, particularly those with numerous co-morbidities, are poorly understood. We aimed to assess health outcomes and the extent of their adherence to guideline-based secondary prevention medications among U.S. coronary heart disease (CHD) patients.**Methods:** We analysed information from the U.S. National Health and Nutrition Examination Survey (NHANES) from 1999 to 2018 on people in the United States aged 18 to 85 who had a personal history of coronary heart disease (CHD). Logistic regression analyses were used to identify characteristics related to healthcare access that were linked with not taking any indicated drugs among CHD and other co-morbidity patients in the U.S.**Results:** We gathered 4256 CHD patients aged 18 and above. Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), statins, and antiplatelet medications were taken by 50.94%, 48.26%, 53.41 %, and 19.78% of the population, respectively. Surprisingly, not received recommended drugs was reached up to 21.12%, and taking all four drugs was only 7.64%. In conclusion, the logistic regression analysis revealed that the chance of not taking prescribed drugs increased with age (18–39), race (Hispanic and Non-Hispanic Black), low income, lack of insurance, and the absence of co-morbidities (hypertension, heart failure, and diabetes mellitus).**Conclusions:** The gap between the proposed secondary preventative measures and their actual execution remains sizable. In order to achieve 'Healthy Aging', a systematic approach for prevention of CHD is urgently needed.

## 1. Introduction

Cardiovascular disease (CVD) is one of the most common diseases for mortality, morbidity, and disability not only in United States (U.S.) but also worldwide [1]. An estimated 25% of the over 800,000 myocardial infarctions (MI) that occur annually are reoccurring incidents, and 15% of Medicare recipients who undergo a percutaneous coronary intervention (PCI) have a cardiac re-hospitalization within 1 year [2]. The number of people living with CHD in the United States has risen to over 18 million. In 2008, those over the age of 75 accounted for 67% of all cardiovascular disease fatalities in the United States [3]. Coronary heart disease was the leading cause of death among people over the age of 75.

The economic impact of cardiovascular disease is staggering; between 2011 and 2025, the cost of CHD and stroke in low- and middle-income countries is expected to add up to \$US3.76 trillion [4]. Evidence-based pharmacotherapies and lifestyle treatments are given the most weight in clinical practise recommendations for secondary prevention [5].

Patients with CHD may benefit from treatment with statins, beta-blockers, Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), and anti-platelet medicines to decrease the risk of reinfarction and mortality [6,7,8,9,10,11,12,13]. It has been suggested that people take such drugs, but compliance with national standards for the therapy has been less than ideal [14,15,16,17]. Patients with several co-morbidities, in particular, were less likely to get the best

\* Corresponding author.

E-mail address: [zjyyan2021@163.com](mailto:zjyyan2021@163.com) (J. Yan).<https://doi.org/10.1016/j.heliyon.2022.e11530>

Received 8 March 2022; Received in revised form 29 July 2022; Accepted 3 November 2022

2405-8440/© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

possible care [18, 19]. Adequate adherence to suggested lifestyle and pharmacologic therapy was found insufficient in recent research by Wong et al. Focusing on data from the National Health and Nutrition Examination Survey (NHANES) on CHD in the US [20]. Concerningly, this research only included participants from two NHANES cycles (2007–2010). Therefore, the current research hypothesizes that there is a significant gap between recommendations and actual practice in the management on CHD in the US. Using NHANES data, we aimed to characterise characteristics of American CHD patients and assess their drug adherence in the real world in comparison to secondary preventive guidelines. Medical treatment plan adherence factors were also investigated.

## 2. Materials and methods

### 2.1. Methods and subjects in a study

This study employed 1999–2018 NHANES data (<https://www.cdc.gov/nchs/nhanes/about.htm>). The National Center for Health Statistics conducts the NHANES study of civilian, noninstitutionalized Americans. Data are made available to the public in cycles of two years after the national sample was recruited using a multistage, stratified sampling strategy. Ten survey cycles (1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2018) were analysed for this research. Between 57% and 84% of people responded to interviews over those years, while between 53% and 80% took the exams. Participants needed to meet two criteria: 1) be self-reporting a history of CHD, and 2) be at least 18 years old. Participants who failed to disclose a previous history of CHD or who were not currently pregnant were not included in the analysis. The question “Have you ever been advised by a doctor or health professional that you have angina pectoris, myocardial infarction (“heart attack”), or CHD?” was not answered by 462,38 of the 101,316 people who participated in the NHANES. Then, we took out 50822 people since they didn't have a self-reported history of coronary heart disease. All remaining individuals were non-pregnant, 4256 eligible subjects were enrolled, and missingness remained at less than 15% in each observation. As a result, we treated the dataset with no missing values and did not impute them.

### 2.2. Data collection

Participating respondents were given in-depth interviews at their homes and had the opportunity to undergo a standardized physical examination at a mobile examination facility. high-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C), glycated haemoglobin (HbA1c), total cholesterol (TC), serum creatinine (SCr), and blood glucose (BG) were all measured from the subjects' blood samples following protocols outlined in the NHANES Laboratory/Medical Technologists Procedures Manual. Self-reported demographics, socioeconomic position, lifestyle factors, health-related questions, and medical problems such as a prior diagnosis of stroke or congestive heart failure (HF) were all collected through in-person and telephone interviews by trained interviewers. All survey takers also provided their informed consent.

Participants were questioned at home about whether they had ever been informed by a doctor that they had CHD, myocardial infarction, or angina pectoris. Those who replied “yes” were classified as CHD patients. According to the AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic Vascular Disease Guidelines [21], this research focused on pharmacologic therapy such as blockers, ACEIs/ARBs, statins, and antiplatelet medicines. At the time of the in-home interview, participants were queried about any prescription medication usage in the prior 30 days. This pharmaceutical information was gathered from that data. The interviewer will get the

medicine name from the pill container if the respondent selected “yes.” In the absence of the medicine container, the interviewer requested the subjects to orally state the name of the drug.

Expert doctors at the mobile examination facilities used a conventional method to take the participants' blood pressure (BP) in the sitting area after they had rested for 5 min. Following an accurate measurement of each participant's upper arm circumference, the appropriately sized cuff was applied. The doctors took readings three times for each patient, averaging the results to get a final BP reading of stolic blood pressure (SBP) and diastolic blood pressure (DBP). Waist circumference and body mass index (BMI) were also assessed in the MECs using the same methods as the NHANES study.

### 2.3. Definition of co-morbidities and some social factors

A affirmative response to the question “Are you now taking prescribed medication because of your diabetes/high blood sugar?” or a medical diagnosis of diabetes mellitus (DM) were used to diagnose DM [22]. Hypertension was defined as either having a systolic blood pressure (SBP) more than 140 mm Hg, a diastolic blood pressure (DBP) less than 90 mm Hg (130/80 mm Hg if DM), or needing to take medication to control any of these conditions [23]. Glomerular filtration rate (GFR, 60 ml/min/1.73 m<sup>2</sup>) was used to identify chronic kidney disease (CKD), and it was calculated using the Modification of Diet in Renal Disease equation [GFR = 186 × serum creatinine<sup>-1.154</sup> × age<sup>-0.203</sup> × (1.212 if black)] × (0.742 if female) [24]. Three of the following were used to characterize metabolic syndrome [25]: (1) waist size greater than 89 cm for women and greater than 102 cm for men; (2) HDL-C less than 40 mg/dl for men or less than 50 mg/dl for women; (3) fasting TG greater than 150 mg/dl; (4) high blood pressure (systolic or diastolic) or being treated; and (5) impaired fasting glucose, which is defined as 100–125 mg/dl.

Annual household income was used to categorize people into low, medium, and high socioeconomic groups: those with an annual income of less than \$35,000, between \$35,000 and \$75,000, and above \$75,000. Associate degree or above (AA or high), high school diploma or equivalent (high), and less than high school (low) were the categories used to describe educational attainment. In this study, “no medication” meant that the subject was not using any beta-blocker, ACEI/ARB, statin, or anti-platelet drug. While taking medicine meant using one of the aforementioned secondary preventive medications.

### 2.4. Statistical analysis

Cross-tabulations using Chi-square testing determined the % of patients taking at least one drug by sex, age (65 and >65), socioeconomic status, race/ethnicity, degree of education, current health insurance coverage (insured and uninsured), and co-morbidities. Student's t-tests were used to compare systolic and diastolic blood pressure, serum lipids (LDL-C, HDL-C, and TC), and medication compliance. The estimates included beta blockers, ACEIs/ARBs, and diuretics. Chi-square tests compared medication use in persons with and without co-morbidities such hypertension, MS, stroke, HF, DM, and CKD.

To begin, we used the likelihood ratio test in univariate logistic regression to determine which factors were associated with patients failing to take their medication as directed. Gender, age (18–39), age (40–49), age (50–59), age (60–69), year (1999–2002, 2003–2006, 2007–2010, 2011–2014, and 2018–2019), race, socioeconomic status, education level, insurance status, and the existence of co-morbidities were all included as independent factors. We used multivariate logistic regression to examine the factors associated with not taking medications as recommended, omitting just stroke and MS.

The SAS 9.4 software (SAS Institute, Cary, North Carolina) was used for all statistical analyses, and a p value of <0.05 was considered statistically significant.

### 3. Results

Among the 101316 people in the United States who were recruited over 20 years for NHANES, 4256 (18–85-year-olds) reported having been notified by a doctor or other health care practitioner that they had CHD (Table 1). Of that, 899 (21.12%) subjects were not taking any recommend drugs (not taking group), and 3357 (78.88%) subjects were taking one or more of the secondary prevention medications (taking group). The whole average age was 67.83 years, and the patients in taking group were older than not taking group (69.42 ± 10.72 years vs. 61.90 ± 16.58 years,  $P < 0.0001$ ). The not taking drugs were more likely than taking drugs to be female, Hispanic, non-Hispanic black, low household income, and uninsured persons. The not taking group had greater levels of diastolic blood pressure (70.22 ± 14.89 mm Hg vs. 65.99 ± 15.62 mm Hg), LDL-C (118.98 ± 37.40 mg/dl vs. 94.75 ± 35.92 mg/dl), LDL-C (52.36 ± 17.37 mg/dl vs. 48.77 ± 14.84 mg/dl), TC (200.36 ± 42.21 mg/dl vs. 172.50 ± 43.34 mg/dl), all  $p < 0.0001$ ). Although the not taking person were more often to be current smokers, but less likely to have BMI ≥25 kg/m<sup>2</sup>, central obesity, and co-morbidities except stroke.

The achieving recommended medical therapy goals for secondary prevention of CHD were given in Table 2 and Figure 1 About half of the people in the study were given some kind of statin, ACEI/ARB, or blocker. The male, older (≥65 years), and insured persons were more likely to take β blockers, ACEIs/ARBs and statins in each compare group. Meanwhile, non-Hispanic White and ≥associate degree subjects were more often to take β blockers and ACEIs/ARBs and statins. Although there were some differences in antiplatelet drugs application, but its rates were all low, it was only 19.78% overall. The combination therapy information was shown in Table 3 and Figure 2. With the increased in the number of drugs, the usage rate gradually decreased, taking three drugs as well as four drugs were very low. For example, only 325 (7.64%) patients taking all four drugs, and not received recommended drugs was reached up to 21.12% (Table 1). Exciting that, the rate of taking one or two drugs was well, and these situations were more likely appeared in male, older, Non-Hispanic White, middle/high income, ≥high school degree, insured patients.

The percentage of CHD patients with co-morbidities who were prescribed medical treatment is seen in Table 4. It was very interesting that those with co-morbidities excepted stroke were more often to take β blockers, ACEIs/ARBs, and statins. Unfortunately, antiplatelet medications and four-drug taken were both low among those with or without comorbidities.

Predictors of medication adherence in CHD patients were analysed using a multivariate logistic regression model (Table 5). The variables for the ensuing multivariate logistic regression analysis were first determined using univariate logistic regression. After that, we used a multivariate logistic regression to determine risk factors for failing to take prescribed drugs, and we found that age, gender, race, education, income, and whether or not we had health insurance all played a role. Multivariate logistic regression analysis identified the following factors as significant predictors of not taking any of the proven CHD secondary prevention drugs: age (18–39), race (Hispanic and Non-Hispanic Black), low income, uninsured, and absence of co-morbidities (hypertension, heart failure, and diabetes mellitus).

### 4. Discussion

According to the AHA/ACCF Secondary Prevention and Risk Reduction recommendations and other relevant guidelines [26, 27], the current research, which examined real-world individuals in the United States, shed light on one component of CHD secondary prevention. Although this benefit has been the subject of extensive research and that such drugs are commonly recommended for the preventative treatment of patients with known CHD, the results of the present study showed that there was a significant discrepancy between pharmaceutical secondary prevention guidelines and actual practice among CHD adults in the United States.

**Table 1.** Characteristics of the final analytic sample of participants (n = 4256).

Characteristics	Overall (n = 4256)	Not Taking (n = 899)	Taking (n = 3357)	P Value
<b>Age (yrs), mean ± SD</b>	67.83 ± 12.57	61.90 ± 16.58	69.42 ± 10.72	<0.0001
<b>Gender, n (%)</b>				0.0003
Male	2565 (60.27)	495 (55.06)	2070 (61.66)	
Female	1691 (39.73)	404 (44.94)	1287 (38.34)	
<b>Race, n (%)</b>				<0.0001
Non-Hispanic White	2496 (62.40)	465 (54.32)	2031 (64.60)	
Hispanic	777 (19.43)	216 (25.23)	561 (17.84)	
Non-Hispanic Black	727 (18.18)	175 (20.44)	552 (17.56)	
<b>Socioeconomic Status, n (%)</b>				0.0009
Low	1322 (55.29)	245 (63.97)	1077 (53.64)	
Middle	723 (30.24)	95 (24.80)	628 (31.27)	
High	346 (14.47)	43 (11.23)	303 (15.09)	
<b>Education Status, n (%)</b>				<0.0001
<high school	1540 (36.33)	385 (43.26)	1155 (34.49)	
High school diploma	1028 (24.25)	187 (21.01)	841 (25.11)	
AA or high	1671 (39.42)	318 (35.73)	1353 (40.40)	
<b>Current Health Insurance Status, n (%)</b>				<0.0001
Uninsured	233 (7.95)	111 (22.38)	122 (5.01)	
Insured	2696 (92.05)	385 (77.62)	2311 (94.99)	
<b>CHD Risk Factor</b>				
SBP (mmHg), mean ± SD	132.91 ± 22.34	132.12 ± 22.13	133.12 ± 22.39	0.27
DBP (mmHg), mean ± SD	66.86 ± 15.56	70.22 ± 14.89	65.99 ± 15.62	<0.0001
LDL-C (mg/dL), mean ± SD	98.48 ± 37.17	118.98 ± 37.40	94.75 ± 35.92	<0.0001
HDL-C (mg/dL), mean ± SD	49.37 ± 15.35	52.36 ± 17.37	48.77 ± 14.84	<0.0001
TC (mg/dL), mean ± SD	177.18 ± 44.38	200.36 ± 42.21	172.50 ± 43.34	<0.0001
Current smoking, n (%)	934 (21.95)	279 (31.03)	655 (19.51)	<0.0001
BMI ≥30 kg/m <sup>2</sup> , n (%)	1623 (43.15)	292 (38.47)	1331 (44.34)	<0.0001
Central obesity, n (%)	2432 (67.52)	430 (57.80)	2002 (70.05)	<0.0001
<b>Co-morbidities, n (%)</b>				
Metabolic syndrome	694 (57.26)	75 (32.05)	619 (63.29)	<0.0001
Hypertension	3225 (75.78)	480 (53.39)	2745 (81.77)	<0.0001
Stroke	729 (17.13)	136 (15.13)	593 (17.66)	0.07
Heart failure	1183 (27.80)	182 (20.24)	1001 (29.82)	<0.0001
Diabetes mellitus	1430 (33.60)	148 (16.46)	1282 (38.19)	<0.0001
Chronic kidney disease	691 (28.39)	62 (15.05)	629 (31.11)	<0.0001

Data are presented as n (%) or mean ± standard deviation (SD).

Not taking: not taking any β blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), statin, or anti-platelet agent.

Taking: taking one or more of the above secondary prevention medications.

Socioeconomic status: low, <\$35,000; middle, \$35,000-\$75,000; high, >\$75,000.

Central obesity: waist circumference >102 cm for men or >89 cm for women.

CHD: coronary heart disease; AA: associate degree; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; BMI: body mass index. P value indicates comparison of means or proportions between not taking and taking groups.

Overall, less than half of the subjects were given beta-blockers, ACEIs/ARBs, or statins, and even fewer were given antiplatelet medications. To our surprise, more than 20% of subjects were not taking any recommended medications. In addition, combination therapy also presents

**Table 2.** Achievement of recommended medical therapy in coronary heart disease (CHD) patients.

Group	β blockers	ACEIs/ARBs	Statins	Antiplatelets
<b>Overall</b>	2168 (50.94)	2054 (48.26)	2273 (53.41)	842 (19.78)
<b>Gender</b>				
Male	1363 (53.14)**	1279 (49.86)*	1510 (58.87)**	570 (22.22)**
Female	805 (47.60)	775 (45.83)	763 (45.12)	272 (16.09)
<b>Age (yrs)</b>				
<65	678 (44.49)**	675 (44.29)**	693 (45.47)**	275 (18.04)*
≥65	1490 (54.54)	1379 (50.48)	1580 (57.83)	567 (20.75)
<b>Race</b>				
Non-Hispanic White	1346 (53.93)**	1189 (47.64)	1414 (56.65)**	487 (19.51)
Hispanic	324 (41.70)	374 (48.13)	362 (46.59)	153 (19.69)
Non-Hispanic Black	356 (48.97)	356 (48.97)	338 (46.49)	137 (18.84)
<b>Socioeconomic Status</b>				
Low	737 (55.75)	689 (52.12)	769 (58.17)**	310 (23.45)
Middle	437 (60.44)	406 (56.15)	488 (67.50)	184 (25.45)
High	186 (53.76)	190 (54.91)	244 (70.52)	93 (26.88)
<b>Education Status</b>				
< high school	728 (47.27)**	710 (46.10)	741 (48.12)**	305 (19.81)
High school diploma	542 (52.72)	516 (50.19)	579 (56.32)	208 (20.23)
AA or high	893 (53.44)	825 (49.37)	949 (56.79)	327 (19.57)
<b>Current Health Insurance Status</b>				
Uninsured	75 (32.19)**	85 (36.48)**	75 (32.19)**	36 (15.45)**
Insured	1586 (58.83)	1454 (53.93)	1704 (63.20)	666 (24.70)

Data are presented as n (%).

ACEIs/ARBs: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; AA: associate degree.

\*p < 0.05, \*\*p < 0.01 between gender, age, socioeconomic, educational, or current health insurance statuses.

similar results. Multivariate logistic regression analysis confirmed that age (18–39), race (Hispanic and Non-Hispanic Black), low income, lack of insurance, and the absence of co-morbidities (hypertension, heart failure, and diabetes mellitus) were all significant predictors of not receiving CHD secondary prevention drugs.

Reductions in mortality and re-infarction have been seen in individuals with preexisting CHD who take a beta-blocker, according to clinical studies with compelling data. β-blockers reduce heart rate by delaying conduction in the sinoatrial node and atrioventricular node

through negative conduction, negative inotropy, and negative chronotropy, reducing myocardial contractility and thus reducing myocardial oxygen consumption [28]. Since the seminal BHAT trial in 1982 demonstrated that beta-blockers may lower all-cause mortality and CHD-related mortality in patients with myocardial infarction (MI), they have steadily gained more and more attention [29]. Taken in the real world, beta-blockers still don't have a lot of hope. The current investigation showed that only half of patients with CHD were prescribed beta blockers, and that even in patients with other medical conditions, beta blocker usage was inadequate. Comparatively higher than the Prospective Urban Rural Epidemiology (PURE) study (20.4% for blockers) [30], but lower than a study in British [31], which indicated that the treatment use rate was 63% for blockers. Our results are consistent with the study of De Wilde S et al (50% for blockers), previous NHANES (55% for blockers) [32] and one electronic health record study (48.63% for blockers). The differences in demographic characteristics, sample size, and geographical location across these studies may help explain the discrepancies in their use.

Patients with CHD who take ACEIs/ARBs had their risk of death and future major cardiovascular events reduced, according to meta-analyses and large-scale randomized controlled clinical studies [33,34,35]. Therefore, the guidelines clearly recommend that patients with CHD complicated by DM or hypertension should use ACEIs/ARBs indefinitely, and it is recommended that all CHD patients without contraindications should use ACEIs [36]. Unfortunately, taking ACEIs/ARBs rate even

**Table 3.** Number of recommended drugs taken in coronary heart disease (CHD) patients.

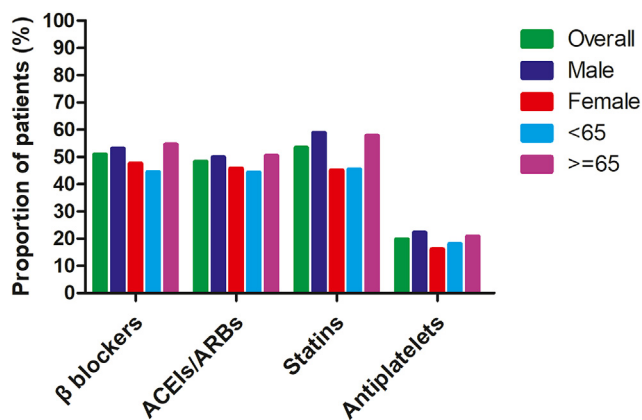
Group	One	Two	Three	Four
<b>Overall</b>	3357 (78.88)	2398 (56.34)	1257 (29.53)	325 (7.64)
<b>Gender</b>				
Male	2070 (80.70)**	1554 (60.58)**	867 (33.80)**	231 (9.01)**
Female	1287 (76.11)	844 (49.91)	390 (23.06)	94 (5.56)
<b>Age (yrs)</b>				
<65	1049 (68.83)**	747 (49.02)**	406 (26.64)**	119 (7.81)
≥65	2308 (84.48)	1651 (60.43)	851 (31.15)	206 (7.54)
<b>Race</b>				
Non-Hispanic White	2031 (81.37)**	1455 (58.29)**	749 (30.01)*	201 (8.05)*
Hispanic	561 (72.20)	395 (50.84)	197 (25.35)	60 (7.72)
Non-Hispanic Black	552 (75.93)	383 (52.68)	214 (29.44)	38 (5.23)
<b>Socioeconomic Status</b>				
Low	1077 (81.47)**	826 (62.48)**	467 (35.33)*	135 (10.21)
Middle	628 (86.86)	512 (70.82)	298 (41.22)	77 (10.65)
High	303 (87.57)	232 (67.05)	137 (39.60)	41 (11.85)
<b>Education Status</b>				
< high school	1155 (75.00)**	797 (51.75)**	419 (27.21)*	113 (7.34)
High school diploma	841 (81.81)	611 (59.44)	311 (30.25)	82 (7.98)
AA or high	1353 (80.97)	986 (59.01)	525 (31.42)	130 (7.78)
<b>Current Health Insurance Status</b>				
Uninsured	122 (52.36)**	86 (36.91)**	50 (21.46)**	13 (5.58)*
Insured	2311 (85.72)	1796 (66.62)	1023 (37.95)	280 (10.39)

Data are presented as n (%).

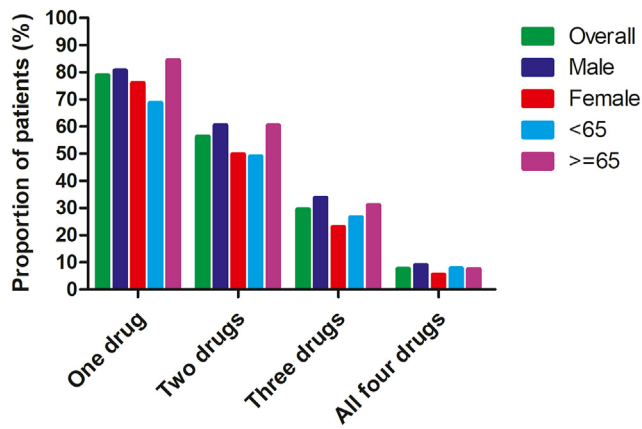
One: taking one of beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), statins, or antiplatelets.

Two: taking two kinds of different drugs; Three: taking three kinds of different drugs; Four: taking all above drugs.

\*p < 0.05, \*\*p < 0.01 between gender, age, socioeconomic, educational, or current health insurance statuses.



**Figure 1.** Shows the percentage (%) of US people with CHD who are taking recommended drugs, broken down by gender and age (years). ARB, or angiotensin receptor blocker, stands for angiotensin converting enzyme inhibitor.



**Figure 2.** Shows the percentage of US people with CHD who are taking the recommended drugs, broken down by gender and age group. ARB, or angiotensin receptor blocker, stands for angiotensin converting enzyme inhibitor.

lower than  $\beta$ -blockers, less than half usage. Our findings were similar to NHANES 2007 to 2010 [37] and the European Action on Secondary and Primary Prevention by Intervention to Reduce Events III (EUROASPIRE III) survey and another electronic health record study [38], all indicated roughly 70% of ACEI/ARBs. this is higher than the well-known PURE study and the electronic follow-up study by Hu (32.92% for ACEIs) [39, 40].

Although the degree of lipid lowering varies among different types of statins, the benefit of statins for secondary prevention of CHD is beyond

**Table 4.** Proportion of coronary heart disease (CHD) patients with co-morbidities receiving recommended medical therapy.

Group	$\beta$ blockers	ACEIs/ARBs	Statins	Antiplatelets	All 4 drugs
<b>Hypertension</b>					
Yes	1793 (55.60)	1809 (56.09)	1829 (56.71)	682 (21.15)	273 (8.47)
No	375 (36.37)**	245 (23.76)**	444 (43.06)**	160 (15.52)**	52 (5.04)**
Yes	439 (63.26)	439 (63.26)	441 (63.54)	177 (25.50)	81 (11.67)
No	237 (45.75)**	188 (36.29)**	266 (51.35)**	107 (20.66)*	40 (7.72)*
<b>Stroke</b>					
Yes	379 (51.99)	372 (51.03)	384 (52.67)	211 (28.94)	72 (9.88)*
No	1789 (50.72)	1682 (47.69)	1889 (53.56)	631 (17.89)**	253 (7.17)
<b>HF</b>					
Yes	704 (59.51)**	653 (55.20)**	665 (56.21)*	252 (21.30)	101 (8.54)
No	1464 (47.64)	1401 (45.59)	1608 (52.33)	590 (19.20)	224 (7.29)
<b>DM</b>					
Yes	839 (58.67)**	890 (62.24)**	917 (64.13)**	367 (25.66)**	165 (11.54)**
No	1329 (47.03)	1164 (41.19)	1356 (47.98)	475 (16.81)	160 (5.66)
<b>CKD</b>					
Yes	462 (66.86)**	396 (57.31)**	458 (66.28)**	189 (27.35)**	76 (11.00)
No	915 (52.50)	886 (50.83)	1022 (58.63)	387 (22.20)	169 (9.70)

Data are presented as % (n).

MS: metabolic syndrome; HF: Heart failure; DM: diabetes mellitus; CKD: chronic kidney disease.

ACEIs/ARBs: angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

\* $p < 0.05$ , \*\* $p < 0.01$  between groups with or without co-morbidities.

doubt [41]. A lot of large-scale randomized controlled trials have confirmed that statins could reduce major cardiovascular events including CHD death, coronary revascularization, non-fatal myocardial infarction (MI), PAD, acute coronary syndrome, stroke, angina, cardiac arrest and heart failure by lowering LDL-C [41, 42]. Statins have not only been shown to improve quality of life by reducing event rates, but have also been shown to prolong life by reducing overall mortality in 4S [43], LIPID [44], and HPS [45] clinical trials. The present study revealed that the rate of statins usage was the highest among the four types of drugs, but it was still less than 60%, accounting for only 53.41%. Our results were similar to the above electronic health record (52.62% for statins)

**Table 5.** Odds ratios by multivariate logistic regression for not receiving recommended medications.

	OR	95% CI	P value
<b>Age (yrs)</b>			
18–39	1	reference	-
40–49	0.45	0.22–0.90	0.03
50–59	0.24	0.13–0.46	<0.0001
60–69	0.11	0.06–0.21	<0.0001
>70	0.06	0.03–0.12	<0.0001
<b>Years</b>			
1999–2002	1	reference	-
2003–2006	0.31	0.09–1.09	0.09
2007–2010	0.61	0.1–3.6	0.58
2011–2014	0.82	0.57–1.16	0.23
2015–2018	1.07	0.77–1.50	0.68
<b>Gender</b>			
Male	1	reference	-
Female	1.32	0.99–1.77	0.06
<b>Race</b>			
Non-Hispanic White	1	reference	-
Hispanic	1.49	1.03–2.15	0.04
Non-Hispanic Black	1.67	1.14–2.43	0.008
<b>Socioeconomic Status</b>			
Low	1	reference	-
Middle	0.71	0.51–1.00	0.05
High	0.62	0.39–0.97	0.04
<b>Education Status</b>			
<high school	1	reference	-
High school diploma	0.61	0.41–0.91	0.02
AA or high	0.76	0.54–1.08	0.13
<b>Current Health Insurance Status</b>			
Uninsured	1	reference	-
Insured	0.45	0.29–0.70	0.0003
<b>Hypertension</b>			
Yes	1	reference	-
No	3.68	2.71–4.99	<0.0001
<b>Heart failure</b>			
Yes	1	reference	-
No	1.62	1.13–2.31	0.008
<b>Diabetes mellitus</b>			
Yes	1	reference	-
No	2.59	1.85–3.64	<0.0001
<b>Chronic kidney disease</b>			
Yes	1	reference	-
No	1.00	0.67–1.50	0.98

Not receiving recommended medications: not taking any of beta blockers, ACEIs/ARBs, statins, or antiplatelets.

Socioeconomic status: low, <\$35,000; middle, \$35,000–\$75,000; high, >\$75,000.

AA: associate degree; CI: confidence interval; OR: odds ratio.

were all significantly below the guideline-recommended target [38], it also less than PURE study or SWEDEHEART registry (the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapy) and an electronic followup study by King in United Kingdom [40, 46, 47]. The low rate of statin used in this study may be related to some doctors' over-concern about statins-induced elevation of liver enzymes or myolysis or other adverse reactions, and may lack of efficient electronic follow-up system. For example, the usage rate of statins,  $\beta$ -blockers, ACEIs could be increased from 52.62%, 48.63%, 32.92%–93.10%, 61.33%, 61.82%, respectively, following careful electronic monitoring and following by designated nursing personnel [38].

Antiplatelet therapy is the cornerstone for preventing cardiac and systemic ischemic events in patients with CHD. Patients with ACS should take dual antiplatelet treatment (DAPT) for at least 1 year with or without PCI, and patients with CCS having PCI should get DAPT for  $\geq 1$  month, as recommended by many recommendations [48,49,50]. In addition, at least one antiplatelet drug is advised for long-term secondary prevention of CHD according to the recommendations of the American Heart Association (AHA)/American College of Cardiology Foundation (ACCF) [21]. Unfortunately, only 842 (19.78%) subjects received antiplatelet therapy, significantly lower than SWEDEHEART study (66.4% for DAPT). One of the very common reasons for this low taking rate is that both patients and doctors are concerned about the risk of bleeding.

The combination therapy was also not ideal in the present study. A study have shown that compared with without drug treatment, taking antiplatelet drugs,  $\beta$  blockers, ACEIs/ARBs and statins could reduce the five-year cardiovascular event rate by 25%, 25%, 25% and 30% in CHD patients, and the combined use could reduce the relative risk of cardiovascular events by 70%–75% [51]. However, taking all four drugs was only 7.64%, and not received any recommended drugs was reached up to 21.12%. Logistic regression analysis identified risk variables related with drug non-adherence. It showed that people were less likely to take their prescribed prescriptions if they were between the ages of 18 and 39; Hispanic or non-Hispanic; poor; uninsured; or suffering from hypertension, heart failure, or diabetes mellitus. Other possible causes include patients' and physicians' lack of knowledge of the necessity for lifelong treatment with such effective medicine after an acute vascular event, as well as the absence of a structured project for healthy ageing preventative care [52,53]. Further, the unaffordability of even universal pharmaceuticals, the hassle and expense involved with seeing a primary care doctor, and the presence of co-morbidities are all factors that detract from the benefits of even excellent medications. Because of these reasons, individuals may continue to report feeling well years after an acute occurrence, leading to a decrease in the use of the indicated medications [54,55,56].

The NHANES data provide a large, nationally representative, multi-stage probability sample of the civilian and noninstitutionalized population in the United States, which is a primary strength of our research. Because of this, assessments of older persons and non-Hispanic blacks in secondary prevention of CHD may be conducted, two groups under-represented in previous research. Examination, measurement, home interview, data records, and the inclusion of respondents with varying levels of education, socioeconomic status, and other personal information were all standardised for the NHANES. For instance, in the secondary preventive drugs application process, data was gathered by qualified interviewers using a standard in-person, home interview technique, with claimed prescriptions checked against actual pill containers. It may be useful for reducing the potential for bias in participants' self-reported medication usage. In addition, we evaluated the proportion of CHD cases with additional co-morbidities who met secondary prevention of CHD targets; this was not often reported in prior research.

However, the current research has a number of caveats. To begin, the NHANES data were cross-sectional, so they couldn't accurately portray individual-level changes over time. Second, to reduce the impact of memory bias, participants were asked to recollect any pharmacologic

therapy they had had in the previous month. Accordingly, those CHD patients who took a secondary preventive medicine during the recall period of one month are considered to be nonusers. Therefore, we estimate the prevalence may in some way be affected by certain select this study recall period. Finally, although we did look at how demographics (such as gender and ethnicity) and co-morbidities (such as lack of health insurance) would influence whether or not a person with CHD received prescribed medical therapy, many additional characteristics were either unavailable or beyond the scope of our research.

## 5. Conclusions

According to our findings, there is a significant need for more education and awareness campaigns on the use of secondary preventive medicines for CHD among adults in the US. The low proportion of secondary drugs application may contribute to increased morbidity in CHD and failure to achieve 'Healthy Aging'. The main goals for secondary CHD prevention are to prevent or delay progression of disease that results in clinical events such as myocardial infarction, stroke, or CKD. Therefore, in order to close the gap in secondary prevention medication taking among US CHD patients, a systematic approach for prevention of CHD is urgently needed.

## Declarations

### Author contribution statement

Conceived and designed the experiments: Jing Yan and Lijiang Tang.  
 Performed the experiments: Xiaowei Liu and Ying Tang.  
 Analyzed and interpreted the data: Xiaowei Liu, Ying Tang and Cheng Xu.  
 Contributed reagents, materials, analysis tools or data: Changqing Du and Xiaofeng Chen.  
 Wrote the paper: Xiaowei Liu.

### Funding statement

This work was supported by Scientific and Technological Projects for Medicine and Health of Zhejiang Province [2015128660].

### Data availability statement

Data included in article/supp. material/referenced in article.

### Declaration of interest's statement

The authors declare no conflict of interest.

### Additional information

No additional information is available for this paper.

## Acknowledgements

We thank all the staffs of the NHANES and the reviewers who participated in the review during the preparation of this manuscript.

## References

- [1] A.S. Go, D. Mozaffarian, V.L. Roger, et al., Heart disease and stroke statistics–2013 update: a report from the American Heart Association, *Circulation* 127 (1) (2013) e6–e245.
- [2] S.S. Virani, A. Alonso, E.J. Benjamin, et al., Heart disease and stroke statistics–2020 update: a report from the American heart association, *Circulation* 141 (9) (2020) e139–e596.
- [3] J.L. Fleg, D.E. Forman, K. Berra, et al., Secondary prevention of atherosclerotic cardiovascular disease in older adults: a scientific statement from the American Heart Association, *Circulation* 128 (22) (2013) 2422–2446.

- [4] S. Mendis, O. Chestnov, The global burden of cardiovascular diseases: a challenge to improve, *Curr. Cardiol. Rep.* 16 (5) (2014) 486.
- [5] M. Aggarwal, D. Ornish, R. Josephson, et al., Closing gaps in lifestyle adherence for secondary prevention of coronary heart disease, *Am. J. Cardiol.* 145 (2021) 1–11.
- [6] S. Yusuf, Two decades of progress in preventing vascular disease, *Lancet* 360 (9326) (2002) 2–3.
- [7] C. Baigent, L. Blackwell, J. Emberson, et al., Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials, *Lancet* 376 (9753) (2010) 1670–1681.
- [8] S. Yusuf, R. Peto, J. Lewis, et al., Beta blockade during and after myocardial infarction: an overview of the randomized trials, *Prog. Cardiovasc. Dis.* 27 (5) (1985) 335–371.
- [9] S. Yusuf, P. Sleight, J. Pogue, et al., Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators, *N. Engl. J. Med.* 342 (3) (2000) 145–153.
- [10] Collaborative overview of randomised trials of antiplatelet therapy—II: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients, *Antiplatelet Trialists' Collaboration* 308 (6921) (1994) 81–106. *BMJ*.
- [11] N.J. Wald, M.R. Law, A strategy to reduce cardiovascular disease by more than 80%, *BMJ* 326 (7404) (2003) 1419.
- [12] Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI), *Lancet* 1 (8478) (1986) 397–402.
- [13] L. Tang, C. Patao, J. Chuang, et al., Cardiovascular risk factor control and adherence to recommended lifestyle and medical therapies in persons with coronary heart disease (from the National Health and Nutrition Examination Survey 2007–2010), *Am. J. Cardiol.* 112 (8) (2013) 1126–1132.
- [14] D. Vulich, B.T. Lee, J. Dede, et al., Extent of control of cardiovascular risk factors and adherence to recommended therapies in US multiethnic adults with coronary heart disease: from a 2005–2006 national survey, *Am. J. Cardiovasc. Drugs* 10 (2) (2010) 109–114.
- [15] K. Kotseva, D. Wood, G. De Backer, et al., EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries, *Eur. J. Cardiovasc. Prev. Rehabil.* 16 (2) (2009) 121–137.
- [16] D.L. Bhatt, P.G. Steg, E.M. Ohman, et al., International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis, *JAMA* 295 (2) (2006) 180–189.
- [17] S. Yusuf, S. Islam, C.K. Chow, et al., Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey, *Lancet* 378 (9798) (2011) 1231–1243.
- [18] R.L. Castellino, B.V. Bajorek, T.F. Chen, Targeting suboptimal prescribing in the elderly: a review of the impact of pharmacy services, *Ann. Pharmacother.* 43 (6) (2009) 1096–1106.
- [19] R.M. Wright, R. Sloane, C.F. Pieper, et al., Underuse of indicated medications among physically frail older US veterans at the time of hospital discharge: results of a cross-sectional analysis of data from the Geriatric Evaluation and Management Drug Study, *Am. J. Geriatr. Pharmacother.* 7 (5) (2009) 271–280.
- [20] L. Tang, C. Patao, J. Chuang, et al., Cardiovascular risk factor control and adherence to recommended lifestyle and medical therapies in persons with coronary heart disease (from the National Health and Nutrition Examination Survey 2007–2010), *Am. J. Cardiol.* 112 (8) (2013) 1126–1132.
- [21] S.J. Smith, E.J. Benjamin, R.O. Bonow, et al., AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American heart association and American College of Cardiology foundation, *Circulation* 124 (22) (2011) 2458–2473.
- [22] B. Draznin, V.R. Aroda, G. Bakris, et al., 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2022, *Diabetes Care* 45 (Supplement\_1) (2022) S17–S38.
- [23] T. Unger, C. Borghi, F. Charchar, et al., International society of hypertension global hypertension practice guidelines, *Hypertension* 75 (6) (2020) 1334–1357.
- [24] A.S. Levey, J.P. Bosch, J.B. Lewis, et al., A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group, *Ann. Intern. Med.* 130 (6) (1999) 461–470.
- [25] S.M. Grundy, J.I. Cleeman, S.R. Daniels, et al., Diagnosis and management of the metabolic syndrome: an American heart association/national heart, lung, and blood Institute scientific statement, *Circulation* 112 (17) (2005) 2735–2752.
- [26] M.D. Jensen, D.H. Ryan, C.M. Apovian, et al., AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American heart association task force on practice guidelines and the obesity society, *Circulation* 129 (25 Suppl 2) (2014) S102–S138.
- [27] R.H. Eckel, J.M. Jakicic, J.D. Ard, et al., AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American heart association task force on practice guidelines, *Circulation* 129 (25 Suppl 2) (2014) S76–S99.
- [28] S.T. O'Rourke, Antianginal actions of beta-adrenoceptor antagonists, *Am. J. Pharmacol. Educ.* 71 (5) (2007) 95.
- [29] A randomized trial of propranolol in patients with acute myocardial infarction. II. Morbidity results, *JAMA* 250 (20) (1983) 2814–2819.
- [30] S. Yusuf, S. Islam, C.K. Chow, et al., Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey, *Lancet* 378 (9798) (2011) 1231–1243.
- [31] S.E. Ramsay, R.W. Morris, O. Papacosta, et al., Secondary prevention of coronary heart disease in older British men: extent of inequalities before and after implementation of the National Service Framework, *J. Public Health* 27 (4) (2005) 338–343.
- [32] N.F. Murphy, C.R. Simpson, K. Macintyre, et al., Prevalence, incidence, primary care burden and medical treatment of angina in Scotland: age, sex and socioeconomic disparities: a population-based study, *Heart* 92 (8) (2006) 1047–1054.
- [33] S. Yusuf, P. Sleight, J. Pogue, et al., Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients, *N. Engl. J. Med.* 342 (3) (2000) 145–153.
- [34] K.M. Fox, Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study), *Lancet* 362 (9386) (2003) 782–788.
- [35] G.R. Dagenais, J. Pogue, K. Fox, et al., Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials, *Lancet* 368 (9535) (2006) 581–588.
- [36] R.L. Sacco, R. Adams, G. Albers, et al., Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline, *Circulation* 113 (10) (2006) e409–e449.
- [37] L. Tang, C. Patao, J. Chuang, et al., Cardiovascular risk factor control and adherence to recommended lifestyle and medical therapies in persons with coronary heart disease (from the National Health and Nutrition Examination Survey 2007–2010), *Am. J. Cardiol.* 112 (8) (2013) 1126–1132.
- [38] X. Hu, X. Zhu, L. Gao, Intensive nursing care by an electronic followup system to promote secondary prevention after percutaneous coronary intervention: a randomized trial, *J. Cardiopulm Rehabil Prev* 34 (6) (2014) 396–405.
- [39] K. Kotseva, D. Wood, G. De Backer, et al., EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries, *Eur. J. Cardiovasc. Prev. Rehabil.* 16 (2) (2009) 121–137.
- [40] W. King, A. Lacey, J. White, et al., Socioeconomic inequality in medication persistence in primary and secondary prevention of coronary heart disease - a population-wide electronic cohort study, *PLoS One* 13 (3) (2018), e194081.
- [41] D.L. Bhatt, P.G. Steg, E.A. Brinton, et al., Rationale and design of REDUCE-IT: reduction of cardiovascular events with icosapent ethyl-intervention trial, *Clin. Cardiol.* 40 (3) (2017) 138–148.
- [42] C. Baigent, A. Keech, P.M. Kearney, et al., Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, *Lancet* 366 (9493) (2005) 1267–1278.
- [43] T.R. Pedersen, J. Kjekshus, K. Berg, et al., Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994, *Atherosclerosis Suppl.* 5 (3) (2004) 81–87.
- [44] I.R. Reid, W. Hague, J. Emberson, et al., Effect of pravastatin on frequency of fracture in the LIPID study: secondary analysis of a randomised controlled trial. Long-term Intervention with Pravastatin in Ischaemic Disease, *Lancet* 357 (9255) (2001) 509–512.
- [45] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial, *Lancet* 360 (9326) (2002) 7–22.
- [46] T. Jernberg, M.F. Attebring, K. Hambraeus, et al., The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDHEART), *Heart* 96 (20) (2010) 1617–1621.
- [47] B. Lindahl, T. Baron, D. Erlinge, et al., Medical therapy for secondary prevention and long-term outcome in patients with myocardial infarction with nonobstructive coronary artery disease, *Circulation* 135 (16) (2017) 1481–1489.
- [48] G.N. Levine, E.R. Bates, J.A. Bittl, et al., Guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery, *Circulation* 134 (10) (2016) e123–e155. ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS.
- [49] G.N. Levine, E.R. Bates, J.C. Blankenship, et al., ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, *J. Am. Coll. Cardiol.* 67 (10) (2016) 1235–1250.
- [50] J. Knuuti, W. Wijns, A. Saraste, et al., ESC Guidelines for the diagnosis and management of chronic coronary syndromes, *Eur. Heart J.* 41 (3) (2020) 407–477.
- [51] S.B. Soumerai, T.J. McLaughlin, D. Spiegelman, et al., Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction, *JAMA* 277 (2) (1997) 115–121.
- [52] R.B. Haynes, E. Ackloo, N. Sahota, et al., Interventions for enhancing medication adherence, *Cochrane Database Syst. Rev.* (2) (2008) D11.

- [53] L.M. Niens, A. Cameron, E. Van de Poel, et al., Quantifying the impoverishing effects of purchasing medicines: a cross-country comparison of the affordability of medicines in the developing world, *PLoS Med.* 7 (8) (2010).
- [54] D. Xavier, P. Pais, P.J. Devereaux, et al., Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data, *Lancet* 371 (9622) (2008) 1435–1442.
- [55] A. Cameron, I. Roubos, M. Ewen, et al., Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries, *Bull. World Health Organ.* 89 (6) (2011) 412–421.
- [56] M.S. van Mourik, A. Cameron, M. Ewen, et al., Availability, price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO/HAI data, *BMC Cardiovasc. Disord.* 10 (2010) 25.