International Journal of Cardiology 249 (2017) 18–24

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Real-world study of low-density lipoprotein cholesterol levels and cardiovascular outcomes in Chinese: A retrospective cohort study in post-percutaneous coronary intervention acute coronary syndrome patients

Yun Wang [a,1], Bryan P. Yan [b,1], Michael B. Nichol [c,1], Brian Tomlinson [d,1], Vivian W.Y. Lee [e,*,1,2]

[a] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China
[b] Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China
[c] Department of Health Policy and Management, University of Southern California, United States
[d] Department of Medicine & Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China
[e] School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong, China

ARTICLE INFO

Article history:
Received 28 March 2017
Received in revised form 12 June 2017
Accepted 7 July 2017

Keywords:
Low-density lipoprotein cholesterol (LDL-C)
Lipid goal
Acute coronary syndrome (ACS)
Major adverse cardiovascular events (MACE)
Chinese

ABSTRACT

Background: This study aimed to assess the effect of low-density lipoprotein cholesterol (LDL-C) goal attainments (of <2.6 mmol/L and <1.8 mmol/L) on first major adverse cardiovascular events (MACEs) for acute coronary syndrome (ACS) patients who underwent percutaneous coronary intervention (PCI).
Methods: A retrospective cohort study was conducted using case reviews of post-PCI ACS patients at an acute public hospital in Hong Kong between January 2009 and August 2015. Patients were followed from the date of PCI procedure until the first documented MACE (including all-cause death, myocardial infarction, heart failure, documented unstable angina, revascularization, and stroke) or to the end of the first year. Kaplan-Meier estimates were used to evaluate the impact of LDL-C goal attainments prior to the event on event-free time.
Results: A total of 1684 patients were identified (79.0% males). At one-year endpoint, 658 (39.1%) attained the LDL-C goal of <1.8 mmol/L, 727 (43.2%) had the LDL-C level between 1.8 mmol/L and 2.6 mmol/L, and 299 (17.8%) had the LDL-C level ≥ 2.6 mmol/L. About 10% experienced a MACE within one year. After adjustment for other available risk factors, attainment of LDL-C goal <2.6 mmol/L was significantly associated with lower rates of MACEs during the one-year follow-up; and those who achieved the LDL-C level of 1.8 mmol/L did not seem to carry any incremental clinical benefits.
Conclusions: Among post-PCI ACS patients, we merely observed a high correlation between the lipid goal attainment of <2.6 mmol/L and MACEs through one-year follow-up, but not for the goal of <1.8 mmol/L.

1. Introduction

Acute coronary syndrome (ACS) is a severe type of coronary heart disease (CHD) related to the rupture of atherosclerotic plaque and thrombosis in the coronary artery [1] and a major cause of death in the Asian populations [2]. Elevated low-density lipoprotein cholesterol (LDL-C) levels have been shown to be continuously correlated with CHD risk [3]. The previous National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines recommended a goal of LDL-C level to be <2.6 mmol/L (<100 mg/dL) [4] in patients with established atherosclerotic cardiovascular disease (ASCVD) and a lower LDL-C target of <1.8 mmol/L (<70 mg/dL) [5] as optimal in highest-risk patients. In 2013, the American College of Cardiology (ACC)/American Heart Association (AHA) [6] published a new guideline on the treatment of blood cholesterol. This guideline [6] was significantly different from the prior ATP III guidelines [4] and emphasized

Abbreviations: MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; CHD, coronary heart disease; CDARS, Clinical Data Analysis and Reporting System; ACA, American College of Cardiology; AHA, American Heart Association; MI, myocardial infarction; UA, unstable angina; ASCVD, atherosclerotic cardiovascular disease; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NTE, New Territories East; ICD-9 CM, International Classification of Diseases, Ninth Revision, Clinical Modification; CVD, cardiovascular diseases; HDL-C, high-density lipoprotein cholesterol; AOR, adjusted odds ratios; PS, propensity-score; ATE, the average effect; ATT, average treatment effect; CI, Confidence Interval; HR, hazard ratio.

* Corresponding author at: School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China.
E-mail address: vivianlee@cuhk.edu.hk (V.W.Y. Lee).

[1] VWY Lee and BP Yan designed the study; Y Wang and VWY Lee analyzed data and wrote the paper; BP Yan, MB Nichol, and B Tomlinson offered expert opinions and revised the paper.

[2] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcard.2017.07.016
0167-5273/

administration of high-potency statin (or moderate-potency statins for patients above 75 years) therapy instead of 'treat to target' goals for LDL-C levels.

The existing guideline-recommended LDL-C goals [4–9] were made based on the results of randomized control trials, meta-analyses, and observational studies reviewed by the guideline writers in cohorts of mostly white men and women. However, it was not clear whether these LDL-C goals could be applied to Chinese patients. Both cholesterol levels and CHD mortality were perceived to be lower in Chinese populations when compared to Western populations [10–13]. In our previous research [14] in 402 Chinese myocardial infarction (MI) patients, the attainment of the LDL-C goal of <2.6 mmol/L resulted in a significant reduction in mortality, but not for the attainment of the goal of <1.8 mmol/L.

Accordingly, we sought to determine the proportion of ACS patients who achieved the target LDL-C levels of <2.6 mmol/L (100 mg/dL) and <1.8 mmol/L (70 mg/dL) following the ATP III guidelines, and who reached the ACC/AHA guideline-recommended goal of ≥50% LDL-C reduction. Furthermore, we aimed to estimate the rates of major adverse cardiovascular events (MACEs) in post-PCI ACS patients who reached the corresponding LDL-C goals.

2. Methods

Hong Kong local government has the total population covered through a universal healthcare system [15], an ideal situation to generate complete health care databases of all local citizens [16]. The present study was based on the retrospective cross-sectional case reviews using Hong Kong Hospital Authority Clinical Data Analysis and Reporting System (CDARS) database. The application of this database approach was described in other studies [17,18]. The study was approved by the Joint Clinical Research Ethics Committee of The Chinese University of Hong Kong and New Territories East Cluster (CUHK-NTEC), Hong Kong, and the protocol was compliant to the Declaration of Helsinki.

Our study population consisted of all ACS patients [19] who received a first documented percutaneous coronary intervention (PCI) in the inclusion period between January 1, 2009, and August 15, 2015, and were continuously enrolled in CDARS for 1 year (defined as 'monitoring period') after their PCI procedure, from an acute public hospital, the PCI-capable hospital in the NTEC of Hong Kong. Patients were eligible for this study if they met all of the following criteria:1) documented ACS patients-either acute MI with or without electrocardiographic evidence of ST-segment elevation or unstable angina (UA), identified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 411.x and 410.x; 2) underwent an index PCI procedure (ICD-9 procedure codes 36.0x) during the inclusion period; 3) ≥21 years of age; 4) had at least one LDL-C laboratory value available during the monitoring period; 5) ethnic Chinese. In order to examine the new cases of safety events which were potentially correlated with statin use, we excluded patients with any adverse safety events in the past 6 months prior to the index PCI procedure, including rhabdomyolysis (ICD-9 code 728.88), myopathy (ICD-9 code 359.x, 728.x, 729.1, 791.3), renal (ICD-9 code 580.x, 581.x, 583.x, 584.x, 585.x, 586.x), hepatic dysfunction (ICD-9 code 570.x, 572.x, 573.x, 782.4, 790.4) [20]; or those who were being treated by hemodialysis (ICD-9 procedure code 39.95) or peritoneal dialysis (ICD-9 procedure code 54.98).

A comprehensive search of patient records, including the patients' socio-demographics, operations, prescriptions, laboratory results, medical charts at emergency departments, outpatient and inpatient clinics, during the study period between 6 months prior to the index PCI procedure and 12 months after the index procedure was accomplished. All use of any lipid-lowering drugs was extracted for the study period, corresponding to the 6 months of statin availability prior to the index procedure, to define the below statin scenarios (in Table 1) according to the classification of statin groups in the ACC/AHA guidelines [6]: 1) stable users of high-potency statin (comprising atorvastatin 40–80 mg and rosuvastatin 20–40 mg); 2) stable users of moderate-potency statin (including atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, pravastatin 40–80 mg, lovastatin 40 mg, fluvastatin xl 80 mg, and fluvastatin 40 mg twice daily); 3) stable users of low-potency statin (that was simvastatin 10 mg, pravastatin 10–20 mg, lovastatin 20 mg, and fluvastatin 20–40 mg); 4) others, including statin switchers, patients on lipid-lowering combination therapy (statin/fibrate, statin/niacin, statin/bile acid resin, and statin/ezetimibe [21]) and non-users of any lipid-lowering drugs. In local clinical practice, not all patients had their cholesterol goal measured at each 3-month point [22,23]; therefore, we followed other researchers [23] and adopted the endpoint LDL-C goal attainments from the final follow-up laboratory results prior to the patients' first documented MACE or the end of the one-year monitoring period (for event-free patients). Since the measurement of LDL-C level at the index ACS event was not a routine clinical practice in Hong Kong, the baseline LDL-C measurements were extracted from the laboratory results nearest to the index PCI procedure (within the period between 180 days prior to the index day and 180 days post the index day). The study flow chart is summarized in Supplemental Fig. 1.

The primary outcomes of interest were LDL-C goal attainments achieved before the first documented MACE or at the one-year endpoint (for event-free patients). The classification of LDL-C goal attainments based on the ATP III guidelines and the ACC/AHA guideline were <2.6 mmol/L (100 mg/dL) [4], <1.8 mmol/L (70 mg/dL) [5], and ≥50% reduction [6], respectively. The secondary outcome measure was the first occurrence of any MACE [24–26] between 30 days [27] and 365 days, including all-cause death, MI, heart failure (ICD-9-CM codes 428.x), documented UA, revascularization with either PCI or coronary-artery bypass grafting (ICD-9-CM codes 36.1 to 36.99, V45.81), and stroke (ICD-9-CM codes 430 to 432, 433 to 437). We examined the patients' potential adverse effects through the new incidence of rhabdomyolysis, myopathy, renal dysfunction or hepatic dysfunction, hemodialysis, and peritoneal dialysis.

3. Statistical methods

Descriptive statistics were used to analyze the demographic data, the pattern of lipid-lowering therapy, and lipid profile parameters (Table 1). We identified all candidate variables that could be of potential relevance to LDL-C goal attainments from a literature review [28,29]: age, sex, comorbidities of diabetes and hypertension, prior cardiovascular diseases (CVDs), baseline LDL-C levels, and statin scenarios. The relative strength of these candidate predictor variables toward LDL-C goal attainments was further analyzed by multivariate backward stepwise logistic regression models with a stay criterion of 0.1 [30], and the adjusted odds ratios (AORs) are only reported for the statistically significant predictor variables in Table 2.

Univariate and multivariable Cox regression analyses (after confirming the appropriateness of the proportional hazards assumption) were performed in order to assess the associations of MACEs (Table 3) with LDL-C goal attainments and statin scenarios. Covariates which were evaluated in the multivariable Cox regression analysis included age, sex, comorbidities of diabetes and hypertension, baseline LDL-C levels, endpoint high-density lipoprotein cholesterol (HDL-C) and triglycerides levels, and prior CVD history [31,32]. In Fig. 1, the cumulative event-free survival is estimated by Kaplan-Meier survival curves.

4. Sensitivity analysis

Initially, we stratified the study population into 5 mutually non-exclusive subgroups stratified by age (≥75 years vs <75 years); sex; diabetes; hypertension; prior CVDs. Accordingly, the associations between LDL-C goal attainments and incidence of MACEs were assessed separately within each of the subgroup strata (Supplemental Fig. 2). Secondly, we applied Cox regression analysis to test the absolute reduction in LDL-C levels from baseline as a continuous variable (Table 3). Thirdly, we first looked into the baseline characteristics of lipid goal achievers (Supplemental Table 1) and further assessed the associations of statin potency, absolute reduction in LDL-C levels from baseline, and LDL-C goal attainments of 2.6 mmol/L, 1.8 mmol/L, and 50% reduction with MACEs categorized on patients' baseline LDL-C levels as low (≤1.8 mmol/L), moderate (1.8–2.6 mmol/L), or high (≥2.6 mmol/L) risk groups. To verify the possible high correlation regarding the lipid goal attainments and baseline LDL-C levels, we also tested the interaction term of lipid goal attainments and baseline LDL-C levels in Cox regression analyses. Lastly, to further confirm the associations of MACEs and LDL-C goal achievements, we conducted propensity-score (PS) weighted [33] Cox proportional hazards models to obtain an unbiased estimate of the average treatment effect (ATE) or average treatment effect for the treated (ATT), because the LDL-C goal achievers probably differed significantly from the non-achievers across the baseline characteristics. Table 3 also presents the results from the weighted Cox proportional hazards models.

All analyses were two-tailed, with the statistical significance defined as $p < 0.05$. All statistical analyses were carried out using STATA software (Stata Corp LP, College Station, TX, US).