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Clinical Outcomes according to the Achievement of Target Low Density Lipoprotein-Cholesterol in Patients with Acute Myocardial Infarction

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Background and Objectives: The clinical outcome of patient with an acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI), with or without achievement of target low density lipoprotein-cholesterol (LDL-C), has little known information. This study investigated if target LDL-C level (below 70 mg/dL) achievements in patients with AMI showed better clinical outcomes or not.
Subjects and Methods: Between May 2008 and September 2012, this study enrolled 13473 AMI patients in a large-scale, prospective, multicenter Korean Myocardial Infarction (KorMI) registry. 12720 patients survived and 6746 patients completed a 1-year clinical follow up. Among them 3315 patients received serial lipid profile follow-ups. Propensity score matching was applied to adjust for differences in clinical baseline and angiographic characteristics, producing a total of 1292 patients (646 target LDL-C achievers vs. 646 non-achievers). The primary end point was the composite of a 1-year major adverse cardiac event (MACE) including cardiac death, recurrent myocardial infarction (MI), target lesion revascularization (TLR) and coronary artery bypass grafting.
Results: After propensity score matching, baseline clinical and angiographic characteristics were similar between the two groups. Clinical outcomes of the propensity score matched patients who showed no significant differences in cardiac death (0.5% vs. 0.5%, p=1.000), recurrent MI (1.1% vs. 0.8%, p=0.562), TLR (5.0% vs. 4.5%, p=0.649), MACEs (6.5% vs. 5.9%, p=0.644) and stent thrombosis (2.5% vs. 1.9%, p=0.560).
Conclusion: In this propensity-matched comparison, AMI patients undergoing PCI with a target LDL-C (below 70 mg/dL) achievement did not show better clinical outcomes. **(Korean Circ J 2017;47(1):31–35)**

KEY WORDS: Myocardial infarction; Low density lipoprotein-cholesterol; Treatment outcome.

Introduction

Lots of studies have reported that the risk of cardiovascular (CV) events decreases with low density lipoprotein-cholesterol (LDL-C)

reduction, and the risk of recurrent cardiovascular events and survival improvement in patients with acute myocardial infarction (AMI) is reduced by using statin.[1][2] Therefore, statin is a class IA American College of Cardiology (ACC)/American Heart Association (AHA) recommendation for secondary prevention of atherosclerotic coronary heart disease.[3]

In 2011, the European Atherosclerosis Society (EAS)/European Society of Cardiology (ESC) joint guidelines emphasized that LDL-C is still the most important marker to treat targets, regardless of LDL-C levels, with target LDL-C <70 mg/dL, statin therapy should be initiated after AMI,[4][5] However, there are still arguments for the use of statin in low LDL-C patients; on the other hands, lots of hyperlipidemia patients with AMI in current practice do not attain the guideline-recommended target LDL-C level.[6][7] In addition, the influence of the intensity of statin therapy as represented by the achieved level of LDL-C on cardiovascular outcomes in patients

with AMI has not been fully evaluated.[8]

Now, the clinical outcome of patients suffering from AMI undergoing percutaneous coronary intervention (PCI) with or without achievement of target LDL-C has little known information. This study investigated is target LDL-C level (below 70 mg/dL) achievements in patients with AMI showed better clinical outcomes or not.

Subjects and Methods

The Korean Acute Myocardial Infarction Registry (KAMIR), is a prospective, open, observational, multicenter, online, nationwide registry of AMI, conducted from November 2005 to January 2008, and its successor, the Korean Myocardial Infarction (KorMI) registry, conducted from January 2008; these registries were supported by the Korean Working Group of Acute Myocardial Infarction. The aims and protocols of the registries have been published. The protocols of the two prospective cohorts were similar. Participating centers included 53 university or community hospitals that have high volumes of patients with facilities for primary PCI and onsite cardiac surgery. The study protocol was reviewed and approved by the institutional review board at each participating center. AMI was diagnosed by characteristic clinical presentations, serial changes on the electrocardiogram suggesting infarction or injury, and increase in cardiac enzymes. We analyzed baseline demographic characteristics, initial presentation, initial vital signs, electrocardiographic findings, results of laboratory tests, procedural data, and medications. Blood samplings for baseline laboratory tests, except for the lipid measurement, were collected at admission or before PCI. Patients were required to fasting overnight and the following day blood was sampled for lipid levels. The LDL-C levels were calculated by the Friedewald formula. Patients with a triglyceride (TG) level ≥400 mg/dL were excluded. A left ventricular ejection fraction was determined by 2-dimensional echocardiography. In-hospital complications and their management were also recorded. 12-month major adverse cardiac events (MACEs) were defined as the composite of a 1-year MACEs including cardiac death, recurrent myocardial infarction (MI), target lesion revascularization (TLR) and coronary artery bypass grafting (CABG). Follow up data were obtained by reviewing medical records and telephone interviews with patients. All data were recorded on an electronic Web page–based case-report form.

Statistical analysis

Data are expressed as a mean±SD and frequencies are expressed as percentages. Propensity score matching to adjust for potential biases
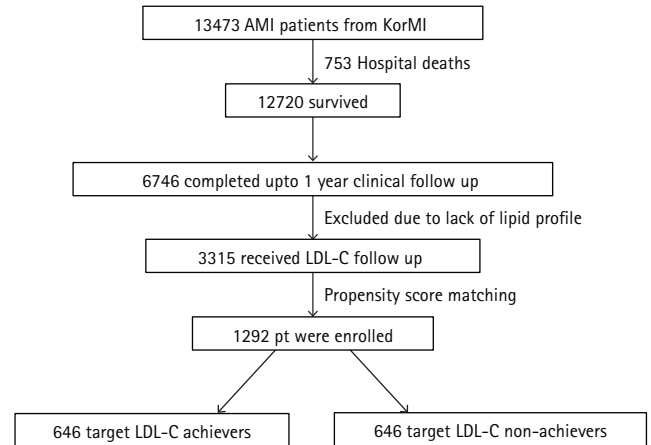
Fig. 1. Patients disposition. AMI: acute myocardial infarction, KorMI: Korean Myocardial Infarction, LDL-C: low density lipoprotein-cholesterol.

and confounding was applied to adjust for differences in clinical baseline and angiographic characteristics, producing a total of 1292 patients (646 target LDL-C achievers vs. 646 non-achievers). In the propensity-matched cohort, all comparisons between the two groups were tested using a paired t-test for continuous variables and Mc Nemar test for categorical variables. A probability value of $p<0.05$ was considered significant. All statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient disposition and baseline characteristics

The flow of subjects through the study is shown in Fig. 1. Between January 2008 and September 2012, 13473 patients were enrolled in the KorMI, with a final diagnosis of AMI. There were 753 (5.6%) hospital deaths; therefore, a total of 12720 patients survived and 6746 patients completed a 1-year clinical follow up. Among them 3315 patients received an LDL-C follow up. Propensity score matching was applied to adjust for differences in clinical baseline and angiographic characteristics, producing a total of 1292 patients (646 target LDL-C achievers vs. 646 non-achievers). After propensity score matching, baseline clinical and angiographic characteristics were similar between the two groups (Table 1). Baseline LDL-C was 120.9±28.6 mg/dL in target LDL-C achievers and 120.5±32.8 mg/dL in non-achievers, respectively.

Follow up LDL-C and clinical outcomes

The LDL-C target achiever's LDL-C level was 56.8±9.5 mg/dL and nonachiever's LDL-C was 96.3±24.3 mg/dL, respectively (Table 2). Total cholesterol (121.8±19.4 mg/dL vs. 163.1±29.8 mg/dL,

Table 1. Baseline characteristics

Characteristics	LDL–C target achievers (n=646)	LDL–C target non–achievers (n=646)	p
Age (years)	60.1±11.5	60.7±12.2	0.428
Male (%)	491 (76.0)	498 (77.1)	0.646
Diabetes (%)	135 (20.9)	131 (20.3)	0.783
Hypertension (%)	301 (46.6)	306 (47.4)	0.780
Dyslipidemia (%)	66 (10.6)	76 (12.2)	0.389
Prior history of IHD	36 (5.6)	43 (6.7)	0.416
Family history of CAD	70 (11.4)	58 (9.4)	0.254
Current smoking	313 (48.5)	306 (47.4)	0.697
SBP (mmHg)	130.5±26.4	129.3±28.0	0.464
DBP (mmHg)	80.0±16.0	79.4±17.4	0.473
HR (/min)	75.8±17.0	75.0±17.8	0.447
Baseline lipid profile (mg/dL)			
Total cholesterol	189.1±33.4	187.5±38.5	0.417
Triglyceride	134.5±109.2	135.7±98.6	0.826
HDL-C	44.2±11.7	43.5±19.3	0.461
LDL-C	120.9±28.6	120.5±32.8	0.810
Type of AMI			
STEMI	330 (51.1)	338 (52.3)	0.579
NSTEMI	316 (48.9)	308 (47.7)	0.579
Treatment			
PCI procedure	646 (100)	646 (100)	1.000
Successful PCI	636 (98.5)	636 (98.5)	1.000
Medical therapy			
Aspirin	643 (99.7)	639 (99.2)	0.255
Clopidogrel	642 (99.4)	643 (99.7)	0.414
ACEi or ARBs	565 (87.5)	559 (86.5)	0.825
Beta blockers	556 (86.1)	554 (85.8)	0.873
CCB	48 (7.6)	54 (8.7)	0.254
Statin	512 (79.3)	509 (78.8)	0.604

Values presented as mean±standard deviation or number (%). LDL-C: low density lipoprotein-cholesterol, IHD: ischemic heart disease, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, HDL-C: high density lipoprotein-cholesterol, STEMI: ST-elevation myocardial infarction, NSTEMI: non ST-elevation myocardial infarction, PCI: percutaneous coronary intervention, ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker

p=0.0001), TG (127.7±94.6 mg/dL vs. 143.7±79.0 mg/dL, p=0.001) were different significantly but not different in high density lipoprotein-cholesterol (HDL-C) (42.3±16.8 mg/dL vs. 43.3±12.5 mg/dL, p=0.276). There were 3 (0.5%) cardiac deaths, 7 (1.1%) recurrent myocardial infarctions, 32 (5.0%) TLRs, 14 (2.2%) target

Table 2. One year follow up lipid profile

Follow up lipid profile (mg/dL)	LDL–C target achievers (n=646)	LDL–C target non–achievers (n=646)	p
Total cholesterol	121.8±19.4	163.1± 9.8	0.0001
Triglyceride	127.7±94.6	143.7±79.0	0.001
HDL-C	42.3±16.8	43.3±12.5	0.276
LDL-C	56.8±9.5	96.3±24.3	0.0001

Values presented as mean±standard deviation. LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol

Table 3. Cumulative clinical outcomes and stent thrombosis up to 1-year

Variables, n (%)	LDL–C target achievers (n=646)	LDL–C target non–achievers (n=646)	p
Cardiac death	3 (0.5)	3 (0.5)	1.000
Non cardiac death	0 (0)	1 (0.2)	0.317
Recurrent myocardial infarction	7 (1.1)	5 (0.8)	0.562
TLR	32 (5.0)	29 (4.5)	0.649
TVR	14 (2.2)	8 (1.2)	0.197
CABG	1 (0.2)	1 (0.2)	1.000
Total MACE	42 (6.5)	38 (5.9)	0.644
ST	15 (2.5)	12 (1.9)	0.560

Values presented as number (%). LDL-C: low density lipoprotein cholesterol, TLR: target lesion revascularization, TVR: target vessel revascularization, CABG: coronary artery bypass graft, MACE: major adverse cardiac event, ST: stent thrombosis

vessel revascularizations (TVR), 1 (0.2%) CABG, and 15 (2.5%) stent thromboses in LDL-C target achievers Results for LDL-C non-achievers included 3 (0.5%) cardiac deaths, 1 (0.2%) non-cardiac deaths, 5 (0.8%) recurrent MIs, 29 (4.5%) TLRs, 8 (1.2%) TVRs, 1 (0.2%) CABGs, and 12 (1.9%) stent thromboses. Clinical outcomes of the propensity score matched two groups showed no significant differences in cardiac deaths (0.5% vs. 0.5%, p=1.000), recurrent MIs (1.1% vs. 0.8%, p=0.562), TLRs (5.0% vs. 4.5%, p=0.649), MACEs (6.5% vs. 5.9%, p=0.644) and stent thromboses (2.5% vs. 1.9%, p=0.560, Table 3).

Discussion

Elevation of total cholesterol and LDL-C has received the most attention, particularly because it can be modified by lifestyle changes and drug therapies. Significant associations between higher total cholesterol and LDL-C levels and a higher incidence of cardiovascular events have been repeatedly published.[9-11] Meta-

analyses of many trials show a clear dose-dependent relative reduction in cardiovascular disease with LDL-C lowering.[12-14] Every 1.0 mmoL/L reduction in LDL-C is associated with a corresponding 20-25% reduction in cardiovascular mortality and non-fatal myocardial infarction.[14-18] More recently, trials have confirmed that lowering LDL-C to <1.8 mmoL/L (70 mg/dL) is associated with the lowest risk of recurrent cardiovascular events in secondary prevention populations. Therefore, LDL-C is a cornerstone of secondary prevention and reporting evidence-based approached to risk reduction after an AMI. Based on the results from the TNT and other randomized controlled studies, "the lower, the better" hypothesis has been widely advocated with regard to optimal treatment LDL-C levels in patients with coronary artery disease.[1] However, it has not yet been proven whether a lower level of LDL-C itself was the predominant mechanism of better outcomes in the atorvastatin 80 mg group of the TNT study.[1]

Statin, by decreasing LDL-C, reduces cardiovascular morbidity and mortality as well as the need for coronary artery interventions. Statin effectively reduces LDL-C by 50% also seems to halt progression or even contribute to regression of coronary atherosclerosis. Experimental studies have demonstrated that statin therapy decreases the extent of myocardial necrosis, preserves myocardial viability, and results in increased ventricular function in models of myocardial ischemia reperfusion injury. Statins' cardioprotective effect after AMI during long-term treatment can be partly explained by their pleiotropic effects, such as anti-inflammatory, antiplatelet, and antithrombotic properties, and improvements in endothelial function. It is obvious that statin therapy with its LDL-C lowering effect provides clinical benefits in the secondary prevention for AMI patients. However, a considerable number of untreated patients with AMI are still eligible for statin therapy.[19-23] There are still arguments of the use of statin in having patients with a low LDL-C.[24,25]

The main finding of this study is that achieved target LDL-C levels <70 mg/dL were not associated with a lower risk for cardiovascular events as compared with target LDL-C non-achievers. Although the nonachiever's LDL-C levels are relatively low (96.3±24.3 mg/dL) and 78.8% of patients use statin, we can suggest that just a low LDL-C level itself, regardless use of statin, is not always related to better clinical outcomes, suggesting that the LDL-C level itself might not critically influence the risk for cardiovascular events. Thus, "the lower the better" may not be always applicable. It also might be possible that even with less LDL-C reduction, the pleiotropic effects of the statin influenced the risk reduction even in the LDL-C ≥70 mg/dL group. We do not currently know the specific threshold level of LDL-C above which the high level of LDL-C level itself can be an independent risk factor for future cardiovascular events.[26-28] This study may suggest that LDL-C levels ≥70 mg/dL might not be

a risk for future cardiovascular events. And "makes LDL-C lower with statin" should be always addressed in secondary prevention, however more intensive LDL-C lowering may not be recommended just only based on LDL-C level.

Limitations

There are several potential limitations of our study. First, our analyses depended on patients who participated in serial laboratory studies which could make them less representative of the general AMI patients. Second, we were unable to examine long term adherence to specific medications prescribed at the time of discharge and we couldn't analyze according to the specific statin type, dose, and lower-cost but, generic statins were also used.

In conclusion, in this propensity-matched comparison, target LDL-C (below 70 mg/dL) achievement in AMI patients undergoing PCI did not show the better clinical outcomes.

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