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Efficacy of Evolocumab in Patients with Hypercholesterolemia

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Objectives: The FOURIER trial reported that inhibition of PCSK9 with evolocumab on a background of statin therapy lowered low-density lipoprotein (LDL) cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. Here, we report data from a single center focusing on the effect of a PCSK9 inhibitor antibody on hyperlipidemia.

Methods: We enrolled 29 hypercholesterolemia patients who had LDL cholesterol levels ≥ 70 mg per deciliter or non-HDL cholesterol ≥ 100 mg per deciliter and were divided into two groups (placebo n = 14, evolocumab n = 15), and participated in a 72 - 96 week, randomized, double-blind, placebo-controlled trial with statin therapy. Patients were randomly assigned to receive evolocumab (140 mg every 2 weeks or 420 mg monthly) or matched placebo via subcutaneous injection. Lipid changes during follow-up were analyzed.

Results: The median LDL cholesterol level at baseline was 88 mg per deciliter, and the average LDL cholesterol level was 101.8 ± 20.0 mg per deciliter. At 4 weeks, the median LDL cholesterol level was 39 mg per deciliter, and the average LDL cholesterol level was 34.8 ± 51.8 mg per deciliter. Compared to placebo group, the LDL cholesterol levels were significantly reduced after treatment ($P < 0.001$), as well as total cholesterol, ApoB, and ApoB / ApoA1 levels. During follow-up, no discomfort was reported at local injection sites, and no cases of abnormal liver function were observed.

Conclusions: Evolocumab significantly reduced LDL cholesterol levels and was well tolerated.

Key Words: Cholesterol LDL, Hypercholesterolemia, Proprotein convertase, Subtilisin-kexin type 9

Atherosclerosis is a major pathophysiological mechanism that can promote the development of cardiovascular and cerebrovascular diseases. Although statin therapy has been a mainstay of treatment for many years, some patients have experienced issues such as statin intolerance. As an important member of the proprotein convertase subtilisin/kexin type 9 (PCSK9) family, PCSK9 can target and bind the low-density lipoprotein receptor (LDLR) to influence lipid metabolism and has become an attractive target for lipid-regulating therapies and atherosclerosis intervention in recent years.

PCSK9 is a member of the family of preprotein-invertase and was first identified in rabbit aortic tissue by Seidah et al[1] in 2003. PCSK9 is the third gene that has been found to be associated with autosomal dominant familial hypercholesterolemia.[2] Studies have shown that PCSK9 can bind to LDLR in liver cells and

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guide its internalization to lysosomal degradation, thereby weakening the ability of the liver to metabolize LDL cholesterol and up-regulating LDL cholesterol levels.[3] However, PCSK9 inhibitor antibodies can specifically target PCSK9 and block its binding with LDLR, thereby increasing the clearance rate of LDL cholesterol and reducing LDL cholesterol levels.[4] PCSK9 not can only degrade LDLR and increase LDL cholesterol levels, it also has other biological functions such as contributing to the development of the nervous system and inducing apoptosis in nerve cells.[5]

Abifadel et al.[6] identified certain mutations in the PCSK9 gene that were associated with elevated serum LDL cholesterol levels and premature coronary heart disease (CHD), as well as certain mutations that were associated with low serum LDL cholesterol levels.[7] Over time, further research has shown that mutations associated with elevated serum LDL cholesterol levels are gain-of-function (GOF) mutations while those associated with low serum LDL cholesterol levels are loss of function (LOF) mutations. Strikingly, subjects with heterozygous LOF mutations exhibit lower serum PCSK9 levels and as much as an 88% reduction in the incidence of CHD over a 15-year period compared with noncarriers.[8] Moreover, despite a complete loss of PCSK9 and associated very low serum LDL cholesterol levels, two subjects who had been identified with compound heterozygote LOF mutations appeared healthy.[9]

LDL cholesterol is a well-established and modifiable risk factor for cardiovascular disease and monoclonal antibodies that inhibit PCSK9 have emerged as a new class of drugs that effectively lower LDL cholesterol levels.[4] Evolocumab is a human monoclonal antibody that has been reported to reduce LDL cholesterol levels by approximately 60%.[10-14]

The purpose of this study was to investigate the efficacy and safety of evolocumab in Korean patients with hypercholesterolemia.

MATERIALS AND METHODS

A 72-96 weeks, randomized, double-blind, placebo-controlled (n = 14) study of evolocumab (n = 15) was conducted between July 2014 and May 2016 with 29 hypercholesterolemia patients who had LDL cholesterol ≥ 70 mg per deciliter or non-HDL cholesterol levels ≥ 100 mg per deciliter with statin therapy (moderate intensity was defined with atorvastatin 10-20 mg or rosuvastatin 5-10 mg; high intensity was defined with atorvastatin 40-80 mg or rosuvastatin 10-20 mg) in our single center, and no patients interrupted statin therapy. Patients were randomized equally and evolocumab or placebo was administered subcutaneously every 4 weeks and lipid changes were assessed. Eligible patients were randomly assigned in a 1:1 ratio to receive subcutaneous injections of evolocumab (either 140 mg every 2 weeks or 420 mg every month, according to patient preference) or matching placebo.

Study visits were scheduled at screening and day 1, and then at weeks 2, 4, 8, and 12. Patients

received subcutaneous evolocumab or placebo on day 1 and at weeks 4 and 8 (3 doses). Blood samples for all assessments were collected after an overnight fast (water only) and analyzed by a central laboratory. After screening, investigators, site staff, and study team members were blinded to all assessment results.

The institutional review board or independent ethics committee at each site approved the protocol and informed consent form. All patients provided written informed consent before study procedures were performed.

Statistical methods: Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are presented as N (%). To determine whether differences between CAD cases and controls were significant for continuous and categorical variables, Student t-test and chi-squared test were used, respectively. All statistical analyses were two-sided and performed with SPSS (Version 22.0, SPSS Inc., Chicago IL, USA), with the threshold for significance set at $P < 0.05$ for all analyses performed.

RESULTS

Of the 36 patients screened, 29 were randomized (evolocumab n = 15; placebo n = 14) (Table 1). Seven patients did not meet the criteria and were excluded from the analyses. Table 1 shows that the patients' characteristics at baseline were similar among the two groups, and most of the enrolled patients were men, but evolocumab group was older than placebo group, the reason may be caused by single center phenomenon. There was no significant difference in lipid levels between the placebo group and the evolocumab group before administration (Table 2). The median LDL cholesterol level at baseline was 88 mg per deciliter, and the average of LDL cholesterol level was 101.8 ± 20.0 mg per deciliter. At 4 weeks, the median LDL cholesterol level was 39 mg per deciliter, and the average of LDL cholesterol level was 34.8 ± 51.8 mg per deciliter, compared to placebo group the LDL cholesterol levels significantly decreased after treatment ($P < 0.001$) (Table 2) (Fig. 1). The median total cholesterol level at baseline was 187 mg per deciliter, and the average total cholesterol level was 179.5 ± 27.8 mg per deciliter. At 4 weeks, the median total cholesterol level was 80 mg per deciliter, and the average total cholesterol level was 105.9 ± 57.7 mg per deciliter, compared to placebo group total cholesterol levels significantly decreased after treatment ($P < 0.001$) (Table 2) (Fig. 2). The median ApoB level at baseline was 107 mg per deciliter, and the average ApoB level was 87.5 ± 27.7 mg per deciliter. At 4 weeks, the median ApoB level was 26 mg per deciliter, and the average ApoB level was 41.5 ± 34.3 mg per deciliter, compared to placebo group ApoB significantly decreased after treatment ($P < 0.001$) (Table 2) (Fig. 2). The median ApoB / ApoA1 level at baseline was 0.59 mg per deciliter, and the average for ApoB / ApoA1 was 0.6 ± 0.2 mg per deciliter. At 4 weeks, the median ApoB / ApoA1 level was 0.16 mg per deciliter, and the average for ApoB / ApoA1 was 0.3 ± 0.2 mg per deciliter, compared to placebo group the ApoB /

Table 1. Study participants' baseline data

Variables	Placebo (n = 14)	Evolocumab (n = 15)	*P*-value
Age, yrs	64.8 ± 7.3	72.9 ± 6.5	0.004
Male	11 (78.6)	14 (93.3)	0.272
BMI, kg/m^2	25.1 ± 4.5	25.6 ± 3.1	0.752
LVEF, %	56.8 ± 13.4	54.4 ± 9.5	0.607
Risk factors, n (%)			
Current smoking	1 (7.1)	1 (6.7)	0.741
HTN	8 (57.1)	6 (40.0)	0.356
Diabetes	6 (42.9)	4 (26.7)	0.300
Medication at enrollment, n (%)			
Aspirin	13 (92.9)	15 (100)	0.292
Clopidogrel	11 (78.60)	11 (73.3)	0.742
ACEI/ARB	3 (21.4)	3 (20)	0.657
CCB	9 (64.3)	13 (86.7)	0.159
Antidiabetic	5 (35.7)	4 (26.7)	0.674
Statin dose	Statin dose		0.996
Moderate intensity	12 (85.7)	14 (93.3)	
High intensity	2 (14.3)	1 (6.7)	
Lipid measurement			
Total cholesterol, mg/dl	164.9 ± 38.4	179.5 ± 27.8	0.246
Triglycerides, mg/dl	121.4 ± 58.0	145.7 ± 58.1	0.270
HDL-C, mg/dl	44.1 ± 11.0	48.7 ± 12.2	0.297
LDL-C, mg/dl	93.4 ± 37.9	101.8 ± 20.0	0.455
Lipoprotein(a), mmol/l	64.6 ± 90.1	62.5 ± 64.4	0.941
ApoA1, g/l	130.9 ± 19.8	139.2 ± 34.7	0.442
ApoB, mg/dl	81.8 ± 17.9	87.5 ± 27.7	0.521
ApoB / ApoA1, mg/dl	0.6 ± 0.1	0.6 ± 0.2	0.810

Data are presented as mean ± SD or number (%).
BMI = body mass index; LVEF = left ventricular ejection fraction; HTN = hypertension; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blockers; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B.

ApoA1 level significantly decreased after treatment ($P < 0.001$) (Table 2) (Fig. 2). During follow-up, AST and ALT levels remained within the normal range, and no cases of abnormal liver function were found (Fig. 3).

DISCUSSION

The FOURIER study[15] revealed that evolocumab lowered LDL cholesterol levels by 59% from baseline levels as compared with placebo, from a median of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter). Our results showed that the median LDL cholesterol level in the placebo group was 88 mg per deciliter, and the average LDL cholesterol level

Table 2. Laboratory data at baseline and after 4 weeks

Variables	Baseline			4 weeks		
	Placebo (n = 14) (n = 14)	Evolocumab (n = 15)	*P*-value	Placebo (n = 14)	Evolocumab (n = 15)	*P*-value
AST,	23.5 ± 6.5	22.9 ± 5.4	0.777	21.4 ± 5.0	21.2 ± 5.9	0.939
ALT,	24.3 ± 8.9	25.0 ± 14.9	0.878	21.1 ± 11.9	24.0 ± 11.0	0.508
HbA1c	6.3 ± 1.1	6.6 ± 1.0	0.394	6.3 ± 1.1	7.0 ± 1.4	0.162
Total-C	164.9 ± 38.4	179.5 ± 27.8	0.246	165.1 ± 35.9	105.9 ± 57.7	<0.001
Triglyceride	121.4 ± 58.0	145.7 ± 58.1	0.270	123.1 ± 41.3	112.7 ± 48.6	0.541
HDL-C	44.1 ± 11.0	48.7 ± 12.2	0.297	48.1 ± 10.7	48.1 ± 8.6	0.999
LDL-C	93.4 ± 37.9	101.8 ± 20.0	0.455	96.0 ± 30.5	34.8 ± 51.8	<0.001
ApoA1	130.9 ± 19.8	139.2±34.7	0.442	135.9 ± 20.5	137.3 ± 16.5	0.840
ApoB	81.8 ± 17.9	87.5 ± 27.7	0.521	80.1 ± 19.5	41.5 ± 34.3	<0.001
ApoB/ApoA1	0.6 ± 0.1	0.6 ± 0.2	0.810	0.6 ± 0.2	0.3 ± 0.2	<0.001
Lipoprotein(a)	64.6 ± 90.1	62.5 ± 64.4	0.941	60.3 ± 68.0	42.8 ± 46.6	0.470

Data are presented as mean ± SD.
AST = aspartate aminotransferase; ALT = alanine aminotransferase; HbA1c = hemoglobin A1c, Total-C = total cholesterol, other abbreviations as for Table 1.

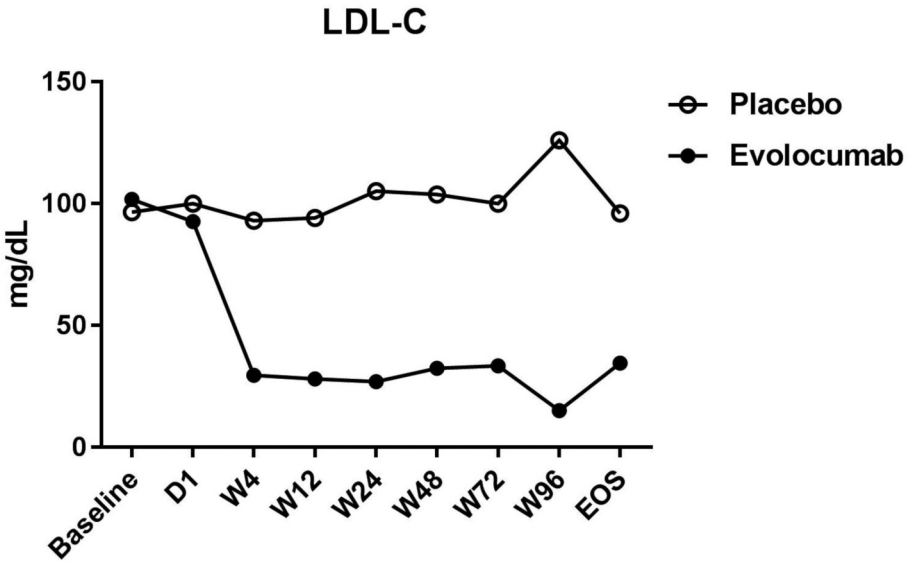

Fig. 1. Effect of Evolocumab on Levels of Low-Density Lipoprotein Cholesterol
EOS = end of study, other abbreviations as for Table 1.

of the placebo group was 101.8 ± 20.0 mg per deciliter. After treatment, the median LDL cholesterol level in the evolocumab group was 39 mg per deciliter, and the average LDL cholesterol level in the evolocumab group was 34.8 ± 51.8 mg per deciliter, with the evolocumab group

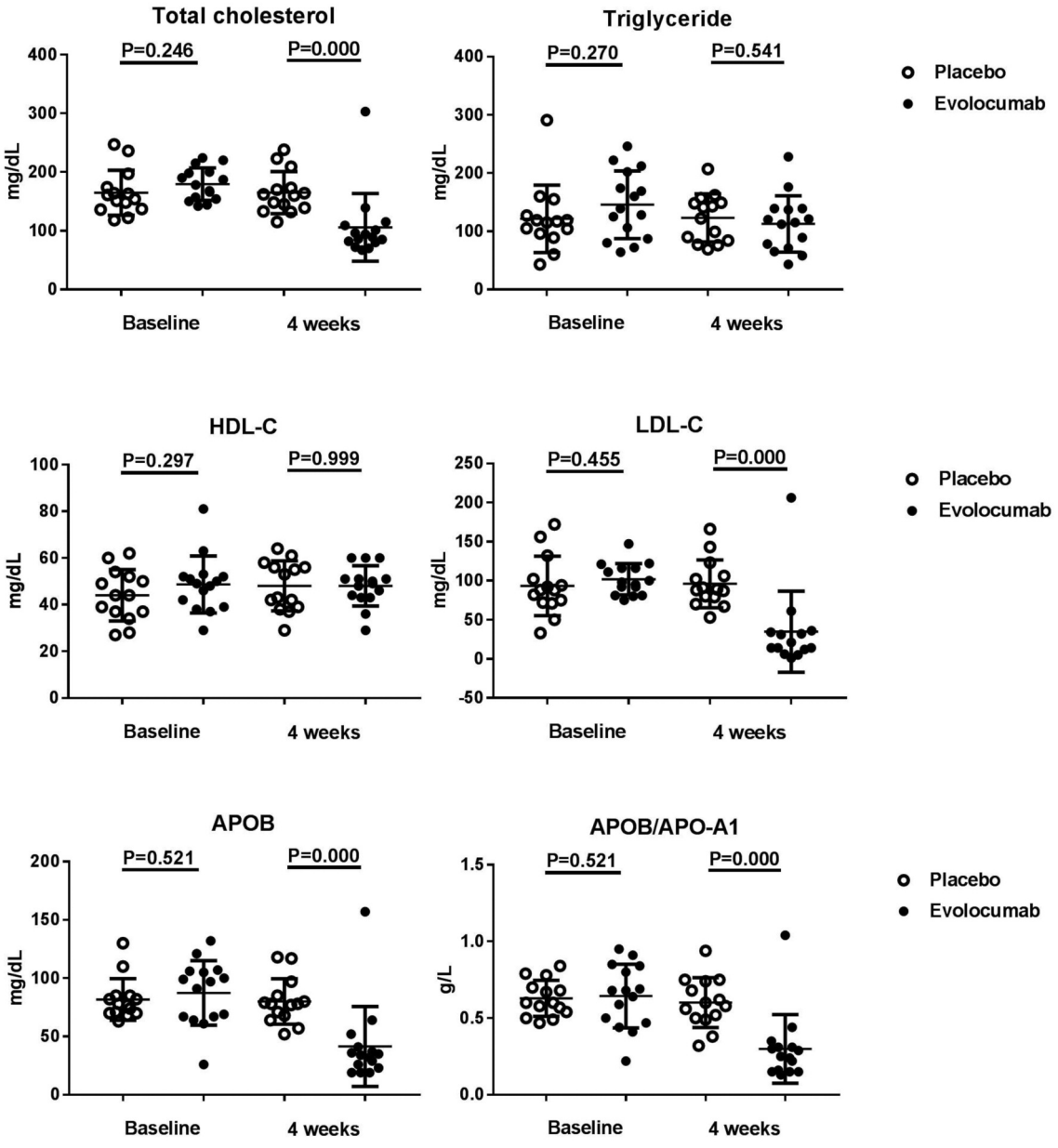

Fig. 2. Changes in Lipid Profile Following Evolocumab Administration
Abbreviations as for Table 1.

showing reduced LDL cholesterol levels by 56% compared to the placebo group. The FOURIER study[15] reported no significant differences in the overall rates of adverse events between the two groups, and injection site reactions were rare, although they were more frequent with evolocumab (2.1% vs. 1.6%). However, there were no adverse reactions during treatment and no injection site reactions observed in our study. The baseline statin dose for the patients in our study was lower than that used in the FOURIER study, as Asian patients are less likely to be prescribed with high-dose statins than their Caucasian counterparts.

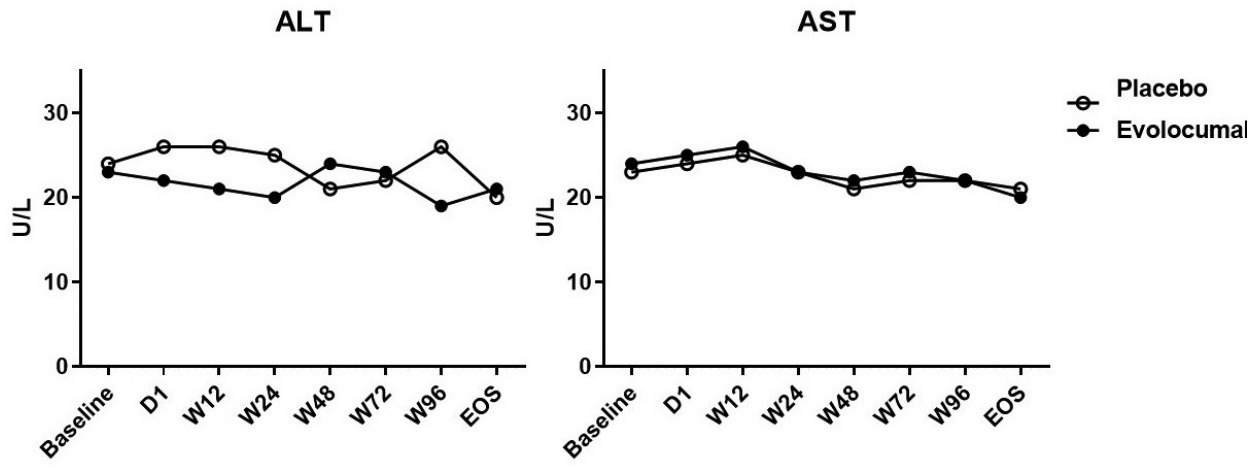

Fig. 3. Changes in Hepatic Enzyme During Follow-up
Abbreviations as for Figure 1 and Table 2.

Statins are the most efficacious agents for alleviating LDL cholesterol levels, although some patients cannot tolerate treatment primarily due to muscle-related side effects, and sometimes higher doses are required to achieve target LDL cholesterol levels.[16] Nevertheless, statin-intolerant patients require more effective LDL cholesterol-lowering therapies. Our findings suggest that evolocumab combined with statin therapy can effectively reduce lipid LDL-C levels.

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REFERENCES

1. Seidah NG, Benjannet S, Wickham L, Marcinkiewicz J, Jasmin SB, Stifani S, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. Proc Natl Acad Sci U S A 2003;100:928-33.
2. Abifadel M, Guerin M, Benjannet S, Rabès JP, Le Goff W, Julia Z, et al. Identification and characterization of new gain-of-function mutations in the PCSK9 gene responsible for autosomal dominant hypercholesterolemia. Atherosclerosis 2012:223:394-400.
3. Elagoz A, Benjannet S, Mammarbassi A, Wickham L, Seidah NG. Biosynthesis and Cellular Trafficking of the Convertase SKI-1/S1P Ectodomain Shedding Requires SKI-1 Activity. J Biol Chem 2002;277:11265-75.
4. Giugliano RP, Sabatine MS. Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? J Am Coll Cardiol 2015;65:2638-51.
5. Rousselet E, Marcinkiewicz J, Kriz J, Zhou A, Hatten ME, Prat A, et al. PCSK9 reduces the protein levels of the LDL receptor in

mouse brain during development and after ischemic stroke. J Lipid Res 2011;52:1383-91.
6. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34:154-6.
7. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet 2005;37:161-5.
8. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006;354:1264-72.
9. Hooper AJ, Marais AD, Tanyanyiwa DM, Burnett JR. The C679X mutation in PCSK9 is present and lowers blood cholesterol in a Southern African population. Atherosclerosis 2007;193:445-8.
10. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014;370:1809-19.
11. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate-or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. Jama 2014;311:1870-83.
12. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J, et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2531-40.
13. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 2014;63:2541-8.
14. Raal FJ, Stein EA, Dufour R, Turmer T, Civeira F, Burgess L, et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:331-40.
15. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
16. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. Jama 2012;308:2497-506.