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Proprotein convertase subtilisin/Kexin type-9 (PCSK-9) inhibitors induced liver injury - a retrospective analysis

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ABSTRACT

Background: Proprotein convertase subtilisin/Kexin type 9 (PCSK-9) inhibitors induced liver dysfunction in patients with or without previous liver injury, and this is not well discussed in the previous literature.

Methods: A total sample of 202 patients were retrospectively reviewed at the University of Missouri, Kansas City, from the year 2015 to 2018 based on predefined selection criteria. Inclusion criteria involved patients with dyslipidemia, with or without PCSK-9 inhibitors, liver function tests and lipid profile at baseline and at a mean of 6-month follow-up. The variables, including age, gender, and confounding factors like other medications (statin, oral antidiabetic, and antihypertensive) induced, or chronic secondary liver diseases causing liver injury were taken into consideration. Exclusion criteria included patients without dyslipidemia.

Results: The mean age of the study population was 64 ± 11 years (63% males and 37% females). The lipid profile including triglyceride and cholesterol levels during 6-month follow-up visit showed a mean of 184 ± 260 and 163 ± 50 mg/dL as compared to that at baseline of 227 ± 603 and 181 ± 70 mg/dL, respectively. In terms of clinical efficacy, a 6-month follows-up showed a drop in triglyceride and cholesterol levels by 38 and 15 mg/dL, respectively. A liver function test at 6 months in patients taking PCSK-9 inhibitors showed an increase in alanine transaminase (ALT) and aspartate transaminase (AST) by 5.8 mg/dL ($p = 0.037$) and 6.2 mg/dL ($p = 0.008$), respectively, from baseline values.

Conclusion: PCSK-9 inhibitors should be used cautiously with a follow-up liver function test.

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1. Introduction

Heart disease is one of the major causes of mortality in both males and females. The statistical data provided by the Center for Disease Control state that 610,000 people in the USA die of heart disease every year. This constitutes one out of every four deaths per year among Americans. Coronary artery disease (CAD) is a major contributor to this mortality rate of 370,000 per year [1]. CAD is caused by a variety of modifiable and non-modifiable risk factors. Dyslipidemia is the most significant modifiable risk factor involved in the pathogenesis of heart disease, including CAD. Dyslipidemia is defined as having abnormal lipid levels in the blood, which can include elevated total cholesterol, elevated low-density lipoprotein-cholesterol (LDL-C) and/or decreased levels of high-density lipoprotein (HDL) cholesterol. An estimated 53% (105,3000) of US adults had lipid abnormalities [2]. LDL is the single most major modifiable risk factor for atherogenesis. Therefore, reducing LDL-C is very important for cardiovascular disease prevention [3].

For treatment of hypercholesterolemia, there are several approaches, including non-pharmacological and pharmacological, to lower LDL. Some of the non-pharmacological approaches include a diet consisting of vegetables, fruits and low saturated fats; weight loss; and exercise. The pharmacological approach includes statins, niacin, ezetimibe, bile acid sequestrants, fibrates, fish oil, garlic and plant sterols. Proprotein convertase subtilisin/Kexin type-9 inhibitors (PCSK-9), a new medication for hyperlipidemia, slow the progression of atherosclerosis and prevent death in CAD with an effect as 70% that of a statin. Statin is a prototype of cholesterol-lowering medications and famous in CAD prevention and progression. Statins lower LDL by inhibiting the synthesis of LDL, but a new PCSK-9 inhibitor flipped the coin by causing more removal of LDL from blood rather than decreasing synthesis with a similar anti-oxidative effect on the vessels [4–7]. The Food and Drug Administration (FDA) has approved two PCSK-9 inhibitors including alirocumab and evolocumab for treatment of hyperlipidemia [8]. PCSK-9 inhibitors are considered as an addition in treatment regimen in

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dyslipidemia unresponsive to maximum dose of statins. In addition to therapeutic role, PCSK-9 inhibitors also cause hepatocyte damage, presenting as elevation in serum transaminases. PCSK-9 can enhance the liver injury in patients with risk factor of liver injury like hepatic steatosis [9]. Limited studies have been done discussing clinical efficacy and side effect profile of PCSK-9 inhibitors in hepatic steatosis/underlying liver injury. Our study investigated PCSK-9 inhibitors' effect on liver in patients with underlying liver dysfunction.

2. Methods

2.1. Study population

Our study population consisted of hyperlipidemia patients followed at the University of Missouri, Kansas City, from 2015 to 2018. The study protocol strictly follows the Helsinki Ethical guidelines for animals and humans as reflected by the Institutional Review Board of the University of Missouri, Kansas City. The study strictly maintains the confidentiality of the reviewed data of the participants.

This retrospective study included a sample of 202 patients based on our selection criteria. Inclusion criteria involved patients with hyperlipidemia/dyslipidemia, with/without PCSK-9 inhibitors, liver injury markers for toxic insult (ALT and AST) and lipid profile (serum cholesterol and triglyceride [TG]) at baseline and at a mean of 6-month follow-up. All the study participants had a stable liver synthetic function (albumin and PT/PTT). When study participants were initiated on PCSK-9 inhibitor, either they were not on statins or sulfonylureas, or they have chronic stable normal baseline LFT with no prior insult, or if the patients were taking statin or sulfonylureas, then their doses have not been changed recently to decrease the confounding and to link the effect of liver dysfunction likely secondary to PCSK-9 inhibitors. Exclusion criteria included patients with no history of hyperlipidemia. The demographic variables including age and gender were taken into consideration. Among the study population, the following comorbidities were studied: diabetes mellitus, hypertension, congestive heart failure, kidney disease, liver disease and smoking status. Patients who were taking statins or sulfonylureas and had any previous abnormal LFTs were excluded from our study. The medications used for these comorbidities causing abnormal liver function test were studied to remove confounding factors; these medications include antiplatelet agents, antihypertensive agents, insulin, oral hypoglycemic agents and PCSK-9 inhibitors.

Table 1. Frequency of having chronic diseases in patients.

Comorbidities	Total percent	No PCSK-9 inhibitors (%)	On PCSK-9 inhibitors (%)
DM	51	85	15
HTN	86	83	17
CHF	30	100	0
Kidney diseases (KD)	20	100	0
Liver diseases (LD)	8	100	0
Never smoker (NS)	63	72	28
Former smoker (FS)	31	98	2
Current smoker (CS)	5	100	0

Table 2. Frequency of medication use in all patients.

Medications	Percent
Antiplatelets	63
Antihypertensive	75
Insulin	41
Oral antidiabetics	41
PCSK-9 inhibitors	19

2.2. Data collection and analysis

The demographic and clinical characteristics of the included patients were taken into account. The clinical data included liver function tests (ALT and AST) and lipid profile (serum cholesterol and TG) at the baseline and a mean 6-month duration. Continuous variables were compared using the independent *t*-test and nominal variables by using the χ^2 and Fisher's exact test using SPSS version 2.0. Values of $p \leq 0.05$ were considered significant. Continuous variables were compared using the independent *t*-test and nominal variables by using the χ^2 and Fisher's exact test using SPSS version 2.0. Values of $p \leq 0.05$ were considered significant.

3. Results

The mean age of the included population was 64 ± 11 years (63% males and 37% females). The mean baseline TG was 227 ± 603 mg/dL and mean cholesterol was 181 ± 70 mg/dL. The lipid profile at mean 6-month duration showed TG and cholesterol levels of 184 ± 260 and 163 ± 50 mg/dL, respectively. For the total study population, the TG and cholesterol levels drop from baseline levels to 38 and 15 mg/dL, respectively. The baseline characteristics of the patients in the two groups (no PCSK inhibitor and on PCSK-9 inhibitor) were comparable; 51% of the total patients have diabetes and 86% have hypertension (HTN); and only 15% of the diabetic and 17% of the HTN groups were on PCSK-9 inhibitors. All patients with CHF (30%), kidney disease (20%) and liver disease (8%) belonged to the non-PCSK-9 group. Most patients with smoking history were not in the PCSK-9 group (Table 1).

Due to the abovementioned comorbidities, patients were on medications described below, and none of the medications had an effect on liver enzymes or lipid panel, and hence, the confounding factors were excluded (Table 2).

There was no significant association of PCSK-9 use with the history of diabetes ($p = 0.16$) and HTN ($p = 0.33$). A moderately significant association of smoking with PCSK-9 use was determined ($p = 0.00$). There were not enough CHF and kidney and liver disease

Table 3. Association of chronic diseases with the PCSK-9 use.

Associations	Test	Value	*df*	*p*-Value
Diabetes Mellitus (DM) and PCSK-9 inhibitors	Pearson chi-square	1.8	1	0.16
HTN and PCSK-9 inhibitors	Pearson chi-square	0.94	1	0.33
congestive heart failure (CHF) and PCSK-9 inhibitors	None as PCSK-9 is constant			
KD and PCSK-9 inhibitors	None as PCSK-9 is constant			
LD and PCSK-9 inhibitors	None as PCSK-9 is constant			
[a]Smoking and PCSK-9 inhibitors	Pearson chi-square	22.29	2	0.00

[a]Cramer's *v* value was 0.33 (moderate association).

patients in the PCSK-9 group to determine the statistical difference from the non-PCSK-9 group (Table 3).

The mean decrease in the TG levels with the PCSK-9 use was found to be 17 mg/dL which was ironically lower than the levels in the patients not on PCSK-9 (42 mg/dL). This value was, however, not statistically significant (p = 0.75). There was no significant variance in the TG levels between the two groups (Levene's test p = 0.57). Patients with PCSK-9 use had a significant mean cholesterol fall of 61 mg/dL compared to only 5 mg/dL fall with no use of the drug (p = 0.00). There was a significant variability on Levene's test (p = 0.001); hence, a modified t-test value was interpreted (Tables 4 and5).

To determine the safety of PCSK-9 inhibitor use, we determined the baseline liver function tests in both groups and compared them to the 6-month levels. There was a mean increase of about 5.8 mg/dL in the ALT and 6.2 mg/dL in the AST with the use of PCSK-9 inhibitors (Table 6). None of the patients in our sample had acute liver failure with AST/ALT more than 10 times elevation from baseline and liver synthetic function abnormality. Both ALT and AST elevation was statistically significant, with a p-value of 0.037 and 0.008, respectively. The independent t-test and Levene's test values are shown in Table 7.

4. Discussion

The FDA approved two new cholesterol-lowering medications named alirocumab and evolocumab for patients with familial hypercholesterolemia or heavy burden of atherosclerotic disease on cholesterol-lowering diet and maximally tolerated statin dose [7]. There are numerous factors that affect the concentration of lipids in the blood. Some of these include dietary intake, certain medications and medical conditions such as hypothyroidism and genetic diseases including familial hypercholesterolemia. All of these conditions can expose the arteries to high levels of atherogenic lipoproteins like LDL and can cause an increased risk of a premature cardiovascular event [4].

A PCSK-9 is a proprotein convertase enzyme primarily expressed in the liver, central nervous system and kidneys. A PCSK-9 gene is located on the short arm p32.3 of chromosome 1. A PCSK-9 enzyme is secreted as a soluble enzyme [1,2,8]. Its major action is to enhance LDL-receptor (LDL-R) recycling. PCSK-9 inhibitors are antibodies involved in the regulation of LDL-C levels by blocking the recycling of LDL-R [10]. A PCSK-9 antibody attaches with LDL-R and inhibits clathrin-mediated receptor endocytosis and breakdown. A simplified version of the mechanism of action of PCSK-9 inhibitors is shown in Figure 1.

PCSK-9: proprotein convertase subtilisin/Kexin type-9; LDL-R: low-density lipoprotein receptor; LDL-C: low-density lipoprotein cholesterol.

Other potential mechanisms of PCSK-9 inhibition to control LDL-C include gene silencing including antisense oligonucleotide, small interfering RNA (siRNA), peptides that mimic PCSK-9 and small molecule inhibitors of PCSK-9 [11]. A gain or loss of function is also found in PCSK-9 gene mutations [11]. A gain of function of PCSK-9 is due to missense mutations and increases levels/affinity of PCSK-9. A loss of function of PCSK-9 is due to non-sense /missense mutations and decreases levels/affinity of PCSK-9 [11].

In terms of efficacy of PCSK-9 inhibitor alirocumab, a LONGTERM trial by Seidah et al., 2341 patients showed up to 61% of the improvement in LDL-C levels with alirocumab [12]. There are a variety of trials that showed persistent improvement

Table 4. Mean fall in lipid panel with the PCSK-9 inhibitor use.

Group statistics					
Difference	PCSK-9	*N*	Mean	Std. deviation	Std. error of mean
TG	No	164	−42.99	479.0	37.41
	Yes	36	−17.61	87.4	14.57
Cholesterol	No	163	−5.77	45.91	3.59
	Yes	36	−61.97	57.21	9.53

Table 5. *t*-Test analysis for mean differences in the lipid profile with the use of PCSK-9 inhibitors.

Analyte	Levene's test		*t*-Test for equality of means					
	F	Sig.	*t*	*df*	*p*-Value	Mean difference	95% confidence interval of the difference	
TG	0.317	0.57	−0.31	198	0.75	−25.37	−183.71	132.95
Cholesterol	10.594	0.001	5.51	45.46	0.00	56.19	35.67	76.72

Table 6. Mean differences in the liver enzymes with the use of PCSK-9 inhibitors.

Difference	PCSK-9 inhibitors	*N*	Mean	Std. deviation	Std. error of mean
ALT	No	164	−6.26	33.16	2.58
	Yes	37	5.72	30.29	4.98
AST	No	164	−7.95	28.15	2.19
	Yes	37	6.13	32.56	5.35

almost all of these trials showed positive results in lowering cholesterol and decreasing cardiovascular mortality [14]. These 14 trials include LAPLACE-2, YUKAWA-2, GAUSS-2, GAUSS-3, MENDEL-2, RUTHERFORD-2, TAUSSIG, TESLA, TAUSSIG, THOMAS-1/2, DESCARTES, FOURIER, OSLER-2 and GLAGOV trials [14]. PCSK-9 inhibitors not

Table 7. *t*-Test for the mean differences in the liver enzymes with the use of PCSK-9 inhibitors.

Variables	Levene's test for equality of variances		*t*-Test for equality of means					
	F	Sig.	*t*	*df*	*p*-Value	Mean difference	Confidence interval	
ALT	0.04	0.83	−2.13	57.18	0.037	−11.99	−23.23	−0.75
AST	1.17	0.28	−2.66	199	0.008	−14.09	−24.50	−3.68

of LDL-C and prevention of cardiovascular disease with PCSK-9 inhibitors; these trials include double-blinded ODYSSEY trials (CHOICE I/II, COMBO I/II, OPTIONS I/II, FHI/II, HIGH FH, ALTERNATIVE and MONO) [13,14]. Based on phase II/MENDEL trial for evolocumab, an LDL reduction up to 60% is seen with twice-monthly scheduled evolocumab and statins. The major phase III trials of evolocumab are in program PROFICIO (Program to reduce LDL-C and cardiovascular outcomes following inhibition of PCSK-9 in different populations) [15]. There are 14 trials included in this program to assess the efficacy of evolocumab in combination with statins, and only have shown to decrease LDL-C but also cause a significant reduction in atheroma size, progression, rupture and instability as shown by Global Assessment of Plaque Regression with a PCSK-9 Antibody as Measured by Intravascular Ultrasound (GLAGOV) trial [16]. Furthermore, PCSK-9 inhibitors can reduce lipoprotein by 36% and TG by 12–31% and can cause a modest increase in HDL-cholesterol by 5–9% [17,18]. PCSK-9 inhibitors reduce LDL-C and TG in a dose-dependent fashion and can reduce up to 70% and 31% of LDL-C and TG levels, respectively [19–21]. Our study showed the mean decrease in cholesterol level of 61 mg/dL

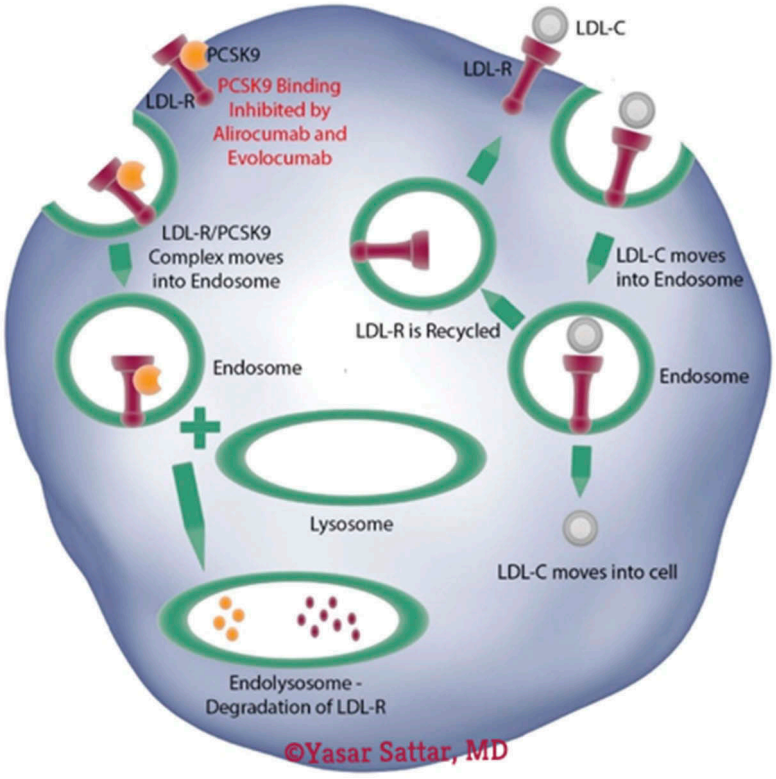

Figure 1. LDL-receptor endocytosis by combination with PCSK-9 and lysosome-induced damage to LDL-R. PCSK-9 inhibitors inhibit the formation of PCSK-9 and LDL-R complex, preventing degradation of LDL leading to increased levels of LDL-R on cells and enhanced LDL-C update.

compared to only 5 mg/dL fall with no use of the drug ($p = 0.00$), and mean drop of TG is 17 mg/dL as compared to a level of 42 mg/dL for patients not on PCSK with a non-statistically significant p-value of 0.57.

Clinical benefits of PCSK-9 outweigh the side-effect profile. PCSK-9 inhibitors can cause a variety of side effects including neurocognitive side effects, rhabdomyolysis, liver damage, new-onset diabetes mellitus and risk of local allergy at the injection site [22]. The literature review showed both neutral and positive side effects on liver. A meta-analysis by Guedeney et al. found no liver dysfunction in patients taking PCSK-9 inhibitors [23]. Another study by Theocharidou et al. reported that high intrahepatic and serum concentration of PCSK-9 can enhance the underlying liver damage, and use of PCSK-9 inhibitors slows this damage through inhibition of PCSK-9 expression and insulin resistance [24]. Our study found a negative side effect of PCSK-9 inhibitors on liver; our results showed a mean increase in ALT and AST of 5.8 mg/dL ($p = 0.037$) and 6.2 mg/dL ($p = 0.008$) on a 6-month follow-up as compared to baseline, respectively.

5. Limitations

The side-effect profile varies from neutral, negative or positive in the published literature. Our study failed to show any clear temporal relationship of PCSK-9-induced liver dysfunction (negative side-effect profile) in patients with underlying liver disease. Our study is limited due to small sample size and limited use of PCSK-9 inhibitors due to cost; more large-scale cohort and randomized clinical trials are necessary to develop the follow-up of patients taking PCSK-9 inhibitors and to study the liver function tests in these patients. Further limitations of our study are that none of our patients had a long-term follow-up to further characterize liver dysfunction to significant liver dysfunction (ALT/AST >10 times elevated), synthetic liver dysfunction or any acute liver failure. Another caveat of our study is the failure to show that transaminitis was transient or persistent due to short follow-up and loss of follow-up.

6. Conclusion

Our study showed that PCSK-9 inhibitors can cause abnormal LFTs. A follow-up with liver function test should be done in patients taking PCSK-9 inhibitors.

Disclosure statement

No potential conflict of interest was reported by the authors.

Author contribution

Yousuf Zafar: Coordinated the data collection.
Waqas Ullah and Sohaib Roomi: Performed statistical analysis and helped in manuscript preparation.
Yasar Sattar: Wrote the manuscript and created figure.
Mammon-Ur- Rashid: Did literature review and data collection.
Laura Schmidt: Did the critical review and proofread.

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References

[1] CDC. Heart disease facts CDC.gov. 2017. Available from: https://www.cdc.gov/heartdisease/facts.htm
[2] Toth PP, Potter D, Ming EE. Prevalence of lipid abnormalities in the United States: the national health and nutrition examination survey 2003–2006. J Clin Lipidol. 2012 Jul–Aug;6(4):325–330.
[3] Agabiti Rosei E, Salvetti M. Management of hypercholesterolemia, appropriateness of therapeutic approaches and new drugs in patients with high cardiovascular risk. High Blood Press Cardiovasc Prev. 2016 Sep;23(3):217–230.
[4] Gurgoze MT, Muller-Hansma AHG, Schreuder MM, et al. Adverse events associated with PCSK9 inhibitors: a real-world experience. Clin Pharmacol Ther. 2019 Feb;105(2):496–504.
[5] Gupta S. LDL cholesterol, statins and PCSK 9 inhibitors. Indian Heart J. 2015 Sep–Oct;67 (5):419–424.
[6] Seidah NG, Awan Z, Chretien M, et al. PCSK9: a key modulator of cardiovascular health. Circ Res. 2014 Mar 14;114(6):1022–1036.
[7] Robinson JG, Rosenson RS, Farnier M, et al. Safety of very low low-density lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. J Am Coll Cardiol. 2017 Feb 7;69(5):471–482.
[8] McDonagh M, Peterson K, Holzhammer B, et al. A systematic review of PCSK9 inhibitors alirocumab and evolocumab. J Manag Care Spec Pharm. 2016 Jun;22(6):641–653q.
[9] Roth EM, Davidson MH. PCSK9 inhibitors: mechanism of action, efficacy, and safety. Rev Cardiovasc Med. 2018;19(S1):S31–s46.
[10] Kosenko T, Golder M, Leblond G, et al. Low density lipoprotein binds to proprotein convertase subtilisin/Kexin type-9 (PCSK9) in human plasma and inhibits PCSK9-mediated low density lipoprotein receptor degradation. J Biol Chem. 2013 Mar 22;288 (12):8279–8288.
[11] Pitts RN, Eckel RH. The emerging role of PCSK9 inhibitors in preventive cardiology. Eur Cardiol. 2014;9(2):65–70.
[12] Seidah NG, Benjannet S, Wickham L, 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 Feb 4;100(3):928–933.

[13] Ray KK, Colhoun HM, Szarek M, et al. Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial. Lancet Diabetes Endocrinol. 2019 Aug;7(8):618–628.
[14] Chaudhary R, Garg J, Shah N, et al. PCSK9 inhibitors: a new era of lipid lowering therapy. World J Cardiol. 2017;9(2):76–91.
[15] Stroes E, Robinson JG, Raal FJ, et al. Consistent LDL-C response with evolocumab among patient subgroups in PROFICIO: a pooled analysis of 3146 patients from phase 3 studies. Clin Cardiol. 2018 Oct;41(10):1328–1335.
[16] Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. Jama. 2016 Dec 13;316(22):2373–2384.
[17] Robinson JG, Nedergaard BS, Rogers WJ, 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 May 14;311(18):1870–1882.
[18] Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. Atherosclerosis. 2016;244:138–146.
[19] Ference BA. Mendelian randomization studies: using naturally randomized genetic data to fill evidence gaps. Curr Opin Lipidol. 2015 Dec;26(6):566–571.
[20] McKenney JM, Koren MJ, Kereiakes DJ, et al. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/Kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol. 2012 Jun 19;59(25):2344–2353.
[21] Tziomalos K. The role of proprotein convertase subtilisin-Kexin type 9 inhibitors in the management of dyslipidemia. Curr Pharm Des. 2017;23(10):1495–1499.
[22] Mefford MT, Rosenson RS, Cushman M, et al. PCSK9 variants, low-density lipoprotein cholesterol, and neurocognitive impairment: reasons for geographic and racial differences in stroke study (REGARDS). Circulation. 2018 Mar 20;137(12):1260–1269.
[23] Guedeney P, Giustino G, Sorrentino S, et al. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. Eur Heart J. 2019 Jul 3.
[24] Theocharidou E, Papademetriou M, Reklou A, et al. The role of PCSK9 in the pathogenesis of non-alcoholic fatty liver disease and the effect of PCSK9 inhibitors. Curr Pharm Des. 2018;24(31):3654–3657.