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REVIEW ARTICLE

Pragmatic Analysis of Dyslipidemia Involvement in Coronary Artery Disease: A Narrative Review

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Abstract: ***Background*:** Dyslipidemia is the main factor involved in the occurrence and progression of coronary artery disease.

***Objective*:** The research strategy is aimed at analyzing new data on the pathophysiology of dyslipidemia involvement in coronary artery disease, the modalities of atherogenic risk estimation and therapeutic advances.

***Methods*:** Scientific articles published in PubMed from January 2017 to February 2018 were searched using the terms "dyslipidemia" and "ischemic heart disease".

***Results*:** PCSK9 contributes to the increase in serum levels of low-density lipoprotein-cholesterol and lipoprotein (a). The inflammation is involved in the progression of hyperlipidemia and atherosclerosis. Hypercholesterolemia changes the global cardiac gene expression profile and is thus involved in the increase of oxidative stress, mitochondrial dysfunction, and apoptosis initiated by inflammation. Coronary artery calcifications may estimate the risk of coronary events. The cardio-ankle vascular index evaluates the arterial stiffness and correlates with subclinical coronary atherosclerosis. The carotid plaque score is superior to carotid intima-media thickness for risk stratification in patients with familial hypercholesterolemia and both can independently predict coronary artery disease. The lipoprotein (a) and familial hypercholesterolemia have a synergistic role in predicting the risk of early onset and severity of coronary atherosclerosis. A decrease in atherosclerotic coronary plaque progression can be achieved in patients with plasma LDL-cholesterol levels below 70 mg/dL. A highly durable RNA interference therapeutic inhibitor of PCSK9 synthesis could be a future solution.

***Conclusion*:** The prophylaxis and treatment of coronary artery disease in a dyslipidemic patient should be based on a careful assessment of cardio-vascular risk factors and individual metabolic particularities, so it may be personalized.

Keywords: Cholesterol, coronary artery disease, dyslipidemia, proprotein convertase subtilisin/kexin type 9, statins, triglycerides.

1. INTRODUCTION

Coronary artery disease is a public health problem, as cardiovascular diseases represent the most common cause of death worldwide and coronary artery disease is the most frequent cardiovascular disease. Therefore, analyzing this complex subject is not a waste of time, but it is fully justified. Dyslipidemia plays a central role among the risk factors involved in the pathogenesis of coronary artery disease and deserves a careful analysis of the most recent and relevant data from the literature.

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The latest review on the impact of lipid metabolism parameters on coronary artery disease pathogenesis occurred in June 2016 [1]. The present review discusses recent advances in better understanding the mechanisms of dyslipidemia involvement in the pathogenesis of coronary artery disease, including the results of recent genetic studies. It also presents the methods used for estimating the atherogenic risk. Recent studies on therapeutic advances, including a large meta analysis on the use of Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have established the best way to treat atherogenic dyslipidemia today.

Low HDL-cholesterol, high triglycerides/HDL-cholesterol ratio, and high total cholesterol/HDL-cholesterol are biomarkers that have been associated with an increased risk of coronary heart disease in a cohort of 51,462 Mediterranean subjects aged over 30 years without cardiovascular

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disease but with dyslipidemia, hypertension or diabetes [2]. Dyslipidemia was observed in 26.1% of 624 consecutive Kashmiri patients undergoing percutaneous coronary interventions [3]. There is a relationship between low serum levels of vitamin D and dyslipidemia, that explains why the deficiency of this vitamin is associated with an increased risk of cardiovascular disease occurrence [4]. Blood group "A" is associated with coronary artery calcification [5], unlike blood group "O".

Hypercholesterolemia is known to be a major cause of coronary artery disease in Western countries. But the prevalence of hypercholesterolemia has also increased in Asia in the last 50 years and is associated with the risk of myocardial infarction [6]. In addition, any increase of 10.8 mg/dL of serum LDL-cholesterol variability in patients who have had a myocardial infarction in their history resulted in a higher risk of any coronary event compared to patients without such variations [7]. Serum total cholesterol level is associated with higher myocardial infarction risk to a greater extent in men than in women [8].

A linear dose-response relationship was found between cumulative total cholesterol and the incidence of cardiovascular death, episodes of angina pectoris or nonfatal myocardial infarction in patients with homozygous familial hypercholesterolemia (FH) [9]. Serum low-density lipoprotein and total cholesterol levels are increased by tocilizumab, an antitumor necrosis factor α drug, which appears to improve endothelial function [10].

Although hypercholesterolemia is the main atherogenic risk factor, the role of triglycerides can not be neglected. Thus, the atherogenic index of plasma, calculated as the logarithm of the ratio of the molar concentrations of triglycerides to HDL-cholesterol, was the lipid parameter most strongly associated with coronary artery disease and an independent risk factor for this pathology in the Chinese Han population [11].

The research strategy is aimed at analyzing new data on the pathophysiology of dyslipidemia involvement in coronary artery disease, the modalities of atherogenic risk estimation and therapeutic advances in this field. Scientific articles published in PubMed from January 2017 to February 2018 were searched using the terms "dyslipidemia" and "ischemic heart disease".

2. PATHOPHYSIOLOGY

The more thorough the study of ischemic heart disease, the more complex data is found on its pathogenesis whereas dyslipidemia is just one of the many factors involved.

As research is diversifying and progressing, new findings highlight the variety and complexity of the mechanisms involved in the pathogenesis of dyslipidemia. The fact that dyslipidemia is an important risk factor involved in the pathogenesis of atherosclerotic vascular disease is unanimously accepted today [12]. Recent studies on genetic polymorphisms associated with dyslipidemia in the pathway of coronary artery disease are presented in Table **1**.

Table 1. Genetic polymorphisms involved concomitant with dyslipidemia in the pathway of coronary artery disease.

Polymorphisms	Studied Population	Frequency in Studied Patiens	Refs.
D allele of angiotensin-converting enzyme gene and its DD genotype	145 symptomatic Tunisian patients with CAD	OR 5.2 and 6.8, respectively	[13]
Matrix metalloproteinase-3 5A/6A and angiotensin-converting enzyme gene I/D	533 patients with acute coronary syndromes	OR 1.5 and 1.7, respectively in combination with classical risk factors, including dyslipidemia (OR 2.1), increase the risk of ST segment elevation myocardial infarction	[14]
HMG-CoA *rs3846662* GG genotype	1622 subjects, of which 183 under statin treatment	More often found in hypercholesterolemic patients ($p = 0.03$); is associated with the blood level of LDL-cholesterol and total triglycerides	[15]
Pro-platelet basic protein (*PPBP*), α-defensin (*DEFA1/DEFA3*), and beta and alpha2 hemoglobin mRNA expression	45 patients (24 with hypercholesterolemia and 21 with coronary heart disease)	Their expression was higher in both groups of patients, but only PPBP and α-defensin 1-3 proteins had higher values ($p = 0.034$, and $p = 0.003$, respectively) in their plasma	[16]
ADRA2B D/I and ADRB1 Ser49Arg (of adrenergic receptor-encoding genes)	717 patients with myocardial infarction and 612 controls	They are responsible for an altered genetic susceptibility to myocardial infarction and have impact on plasma lipid changes	[17]
APOA5 -1131T>C	599 hypertriglyceridemic patients and 1,549 subjects with normal triglyceridemia	Higher atherogenic LDL levels and arterial stiffness – a probable effect of apoA5 concentrations	[18]
APOA5 1131 CC genotype	17,692 Asian patients with cardiovascular diseases and 23,566 controls	Higher risks for dyslipidemia and myocardial infarction (RR > 2.00), and coronary artery disease (RR > 1.00)	[19]
rs16944 (IL-1β)	1837 Caucasian patients, of which 818 with and 1019 without a history of myocardial infarction	Associated with both hypercholesterolemia and myocardial infarction - an independent effect without other environmental or genetic factors	[20]

(Table 1) Contd…

Polymorphisms	Studied Population	Frequency in Studied Patiens	Refs.
SNP rs1558861 residing at the apolipoprotein A-I / A-5 locus, rs780094 found at the glucokinase regulatory protein locus, and rs10911205 placed at the laminin subunit gamma-1 locus	5501 Saudi Arab subjects	Were associated with hypertriglyceridemia, which is known as a risk factor for coronary artery disease	[21]
The C allele of the rs11053646 variant of oxidized low-density lipoprotein receptor 1	665 heterozygous adult patients with familial hypercholesterolemia	Is associated with a higher risk of coronary artery disease (40.7% of GC carriers had a coronary artery disease, compared to only 29.0% of GG carriers)	[22]
TT genotype of CDKN2A-rs10811661	1165 subjects from the Mashhad-Stroke and Heart-Atherosclerotic-Disorders cohort	Leads to higher triglycerides plasma level and triglycerides/HDL ratio, and a higher risk for hypercholesterolemia and cardiovascular disease	[23]

Legend: APOA5 = apolipoprotein A5; CAD = coronary artery disease; OR = odds ratio; SNP = single nucleotide polymorphisms.

Increased serum LDL-cholesterol and/or lipoprotein (a) levels are the main factors involved in the pathogenesis of ischemic heart disease [24]. A linear relationship was found between the plasma concentration of LDL-cholesterol and coronary events [25]. Almost one-third of patients with stable ischemic heart disease have an elevated lipoprotein (a) level [26].

2.1. Familial Hypercholesterolemia

FH is due to the occurrence of mutations in the genes encoding: PCSK9, LDL receptor, and apolipoprotein B [27]. The biomarkers associated with atherogenesis are increased in FH. In addition, the biomarkers of oxidative stress and endothelial activation, which are involved in the pathogenesis of ischemic heart disease, can be predicted by FH [28]. Lipoprotein (a) and FH (diagnosed according to the Dutch Lipid Clinic Network criteria) have a synergistic role in estimating the risk of early onset and severity of coronary atherosclerosis [29]. Indeed, a value of lipoprotein (a) $\geq$10 mg/dL is a predictive risk factor for acute coronary syndrome [30].

2.2. The Role of Proprotein Convertase Subtilisin/Kexin Type 9

PCSK9 contributes to the increase in serum levels of both LDL-cholesterol and lipoprotein (a) [24]. A correlation has been found between PCSK9, determined by the ELISA technique, and lipoprotein (a) levels established by the immunoturbidimetric method, in patients diagnosed with FH, including those with probable or definite FH, with coronary artery disease or not, with or without statin treatment [31]. This interaction requires further pathogenetic studies.

Fig. (**1**) shows how PCSK9 can influence lipid metabolism regulation [32-39]. A gain-of-function mutation for PCSK9 was found in families with FH [40].

The value of mature PCSK9 was associated with atheroma volume and vascular remodeling in heterozygous FH patients with coronary atherosclerosis [41]. Not only the level of circulating PCSK9 is increased in patients with coronary artery disease, but also the level of sortilin, which is another regulating factor of lipoprotein metabolism. The use of statin affects the correlation between PCSK9 and sortilin [42].

2.3. Hypercholesterolemia

Hypercholesterolemia is involved not only in the onset and progression of atherosclerosis, including its coronary location, but also has direct effects on the myocardium. By changing the global cardiac gene expression profile, hypercholesterolemia is involved in increasing oxidative stress, mitochondrial dysfunction, and apoptosis initiated by inflammation. The result is a myocardial dysfunction and predisposition to myocardial infarction [43]. Hypercholesterolemia diminished myocardial cell membrane fluidity in an experimental study on rats, causing a higher susceptibility to myocardial ischemia / reperfusion. Pioglitazone, a peroxisome proliferator-activated receptor agonist, could be a therapeutic option for such patients [44].

Data on the role of cholesterol in the pathogenesis of acute coronary syndrome is sometimes contradictory. Thus, total plasma cholesterol level was inversely related with the risk of acute coronary syndrome in a study that included patients from three countries [45].

Persistent exposure to statins leads to an important increase in the rate of cholesterol biosynthesis in the liver due to an overexpression of the hydroxyl-methyl glutaryl Co-A reductase gene and protein, while plasma cholesterol levels are lower compared to baseline. This was found both *in vitro* and *in vivo* studies. The authors have pointed out that statins induce compensatory metabolic pathways that apparently prevent excessive cholesterol storage in the body [46]. Statins also increase the number of LDL-cholesterol receptors by activating a transcription factor. In addition, they activate PCSK9, an enzyme involved in lowering the number of LDL-cholesterol receptors, which leads to a slight increase in plasma cholesterol level and partially attenuates the hypocholesterolemic effect of statins. Statins also raise the risk of type II diabetes mellitus in subjects at risk [25].

Plasma HDL-cholesterol level could be used as a predictive factor for coronary artery disease severity (as it is negatively associated with coronary artery disease severity), but it is not associated with important adverse cardiovascular events and clinical outcomes in Chinese patients with stable ischemic heart disease [47]. Hypercholesterolemia induced experimentally in pigs resulted in HDL lipidomic transformations (a loss of phosphatidylcholine-lipid species and a gain of cholesteryl esters was noted) and changes in

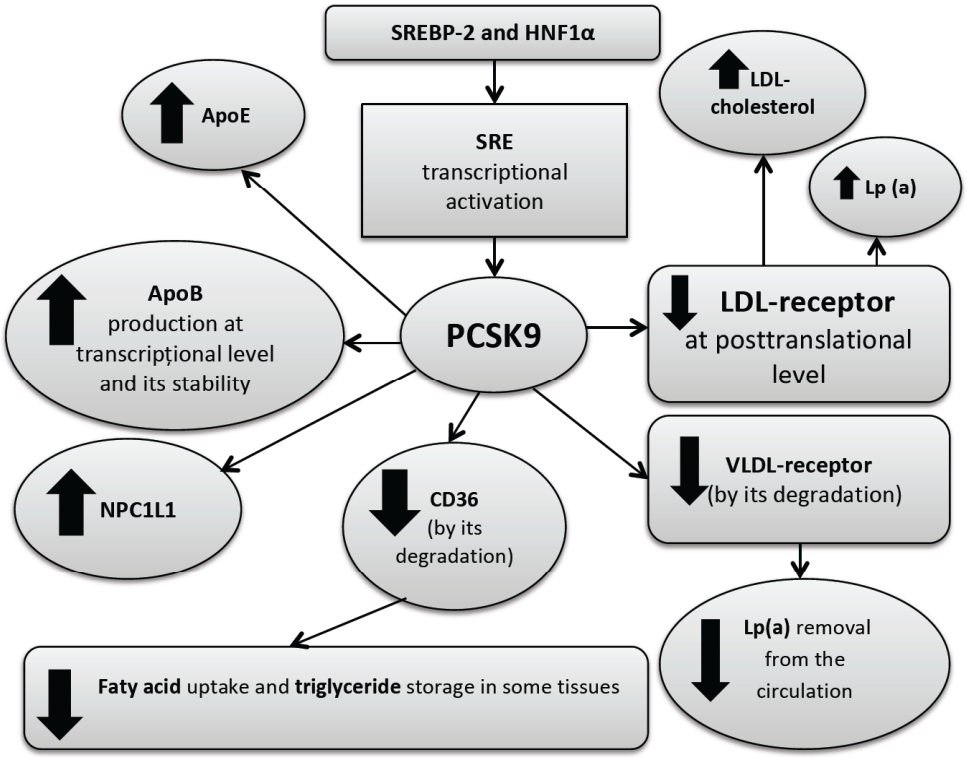

Fig. (1). PCSK9 involvement in the regulation of lipid metabolism.
Legend: ApoB = apoprotein B; ApoE = apoprotein E; HNF1α = hepatocyte nuclear factor-1α; LDL = low-density lipoprotein; Lp(a) = lipoprotein (a); NPC1L1 = epitelial cholesterol transporter; SRE = sterol-regulatory element; SREBP-2 = sterol regulatory element binding protein 2; VLDL = very low-density lipoprotein. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

proteomic structure (cardioprotective proteins were lost), which caused a decrease in the antioxidant activity and cholesterol efflux capacity [48].

2.4. The Level of Fatty Acids, Triglycerides and High-density Lipoprotein Cholesterol

A large amount of trans fatty acids in mice diet is responsible for the development of atherosclerosis by oxidative stress and inflammation [49].

Achieving the target levels of LDL-cholesterol is not always sufficient to exclude cardio-vascular complications. Some patients optimally treated with statins continue to have an increased residual risk of cardio-vascular events, particularly if they have elevated triglyceride levels or low high-density lipoprotein (HDL) cholesterol values [50]. It was found that high triglyceride and low HDL plasma levels are associated with the risk of coronary heart disease compared to those who had normal values, in a prospective study on 3,216 American Indians, during a 17.7 year median follow-up, with no cardiovascular disease at baseline [51].

Triglycerides and, in particular, triglyceride-rich lipoproteins and remnants are involved in the occurrence of cardiovascular disease by the following possible mechanisms: increased release of free acids, higher production of proinflammatory cytokines and coagulation factors and a disruption of fibrinolysis [52]. Autosomal dominant mutations appeared in the apolipoprotein E genes involved in the pathogenesis of familial dysbetalipoproteinemia, which predisposes to premature cardiovascular disease [53].

2.5. Coronary Artery Calcifications

Coronary artery calcifications are more commonly present in patients with higher total cholesterol burden who are aged <45 years and with heterozygous FH. These patients, even asymptomatic, present early coronary atherosclerosis, as it is directly associated with total cholesterol burden (calculated as total cholesterol multiplied by age at the time of diagnosis plus annual total plasma cholesterol level) [54].

Tissue-nonspecific alkaline phosphatase can be overexpressed in vascular endothelial cells and is involved in arterial calcification, followed by lipid deposition and the development of coronary atherosclerotic lesions in mice. This mechanism requires additional studies in human [55].

2.6. The Link Between Inflammation and Atherogenesis

Tumor necrosis factor superfamily member 14 LIGHT decreases the expression of lipolytic genes and increases that of lipogenic genes in oxidized LDL-induced THP-1 macrophages (a human monocytic cell line), contributing to lipid accumulation. Nuclear factor-kappa B activated by LIGHT is also involved in the pro-lipogenic process. This is a confirmation of inflammation being involved in the progression of hyperlipidemia [56]. Fatty acid desaturase is involved in the last step of eicosapentaenoic acid and arachidonic acid formation. Loss of function of Δ-5 fatty acid desaturase 1 has a proinflammatory effect in the liver and promotes atherosclerosis [57]. This is an additional link between inflammation and atherogenesis.

A high value of resting heart rate is associated with increased serum levels of non-HDL-cholesterol, total cholesterol, triglycerides, and apolipoprotein B. This could be an explanation for the association between raised resting heart rate and ischemic heart disease [58].

2.7. The Role of Angiopoietin-like Protein Family

Angiopoietin-like 3, 4, and 8 are involved in the regulation of plasma lipoprotein levels by lipoprotein lipase inhibition. Angiopoietin-like 8 activates angiopoietin-like 3 (produced only in the liver), which inhibits lipoprotein lipase in the cardiac muscle [59]. Patients with homozygous or heterozygous loss-of-function angiopoietin-like 3 gene have lower plasma levels of LDL-cholesterol, triglycerides, and HDL-cholesterol [59, 60]. Also, studies have shown that treatment with evinacumab (a human monoclonal anti-Angiopoietin-like 3 antibody) was able to reduce plasma triglyceride levels up to 76% and cholesterol levels of up to 23%. This gene mutation and the pharmacological inhibition of Angiopoietin-like 3 can reduce the risk of atherosclerotic cardiovascular disease [60]. Heterozygous carriers of Angiopoietin-like 3 mutated gene have a lower risk for ischemic heart disease occurrence [59].

2.8. Other Disorders of Lipid Metabolism Involved in the Pathogenesis of Coronary Artery Disease

A high level of high prebeta-1 HDL is associated with ischemic heart disease, which can indicate functional impairment of cholesterol efflux from the artery wall. Statins are able to reduce the levels of prebeta-1 HDL, a process associated with the decrease of triglycerides levels [61].

The study of dyslipidemia can not make abstraction of non-cholesterol sterols or lipoprotein subclasses. Studies have shown that the size of low-density lipoproteins is inversely associated with the markers of cholesterol-synthesis. LDL I fraction is higher in poor synthetizer/poor absorber patients. A high level of LDL IVB can be found in statin-treated patients with high cholesterol absorption [62]. Paraoxonase 1 (PON1) is involved in the oxidation of low density lipoprotein (LDL) and in the prevention of coronary atherogenesis development, but PON1 Q192R genotypes can not modify the risk of the occurrence of a new acute coronary event during a medium-term follow-up [63].

Epigenetic changes can influence blood lipid concentrations. So, plasma lipid levels (total cholesterol, HDL-cholesterol and triglycerides) and coronary heart disease are associated with an important cis-methylation in loci at 64% of the 193 cytosine-guanine dinucleotides in whole blood [64].

3. METHODS OF ESTIMATING ATHEROGENIC RISK

3.1. The Detection of Familial Hypercholesterolemia and the Risk of Coronary Artery Disease

Patients with thickened Achilles tendon measured radiologically over 9 mm have significantly higher LDL-cholesterol levels. This tendon thickening contributes to the identification of those with heterozygous FH - an important risk factor for the premature occurrence of coronary artery disease [65].

The detection of FH is not easy. Clinical criteria are not always useful. For instance, it was detected in 8.7% of 103 patients with acute coronary syndrome, aged ≤65 years, and with LDL-cholesterol levels over 160 mg/dL; the diagnosis was confirmed by molecular biology [testing the following genes: LDL-receptor, apolipoprotein B, PCSK9, apolipoprotein E, signal transducing adaptor family member 1 (STAP1), low-density lipoprotein receptor adaptor protein 1 (LDLRAP1), and LIPA gene that encodes lysosomal acid lipase]. Clinical algorithms Simon Broome and Dutch Lipid Clinic found FH (probable or definite) in only under 30% of affected patients [66].

Patients with heterozygous FH have a variable risk of developing coronary artery disease. Six protein biomarkers are associated with severe atherosclerotic disease and adverse coronary events, between which histidine-rich glycoprotein has a strong association with coronary artery disease [67]. Patients with heterozygous FH may develop atherosclerotic disease of the carotid arteries at 17 years of age in male and 26 years in female [68].

3.2. The Coronary Artery Calcium

Patients with coronary artery calcium score over 0 have more often cardiovascular risk factors, including dyslipidemia. They also have a higher 5-year mortality rate than patients with artery calcium score 0, even in the absence of coronary luminal narrowing. The risk of death has been similar for patients with score ≥100 and without coronary luminal narrowing and those with non-obstructive coronary artery disease [69]. The calcium-volume score (%) was higher in dyslipidemic patients compared to nondyslipidemic subjects, but it was similar in nondyslipidemic subjects and those with dyslipidemia treated with statins. There were no significant gender differences [70]. Coronary artery calcification score, in addition to the clinical guidelines, may contribute to a better stratification of patients regarding the risk of coronary events, according to a study that included 3,745 subjects without cardiovascular disease diagnosis or lipid-lowering treatment at baseline [71].

3.3. The Arterial Stiffness

High arterial stiffness increases the risk of cardiovascular disease. Total plasma cholesterol level is associated with the risk of increased arterial stiffness in a population of Brazilian men, while both HDL-C and non-HDL-C plasma values are indicators of the risk of high arterial stiffness in postmenopausal women of the same population [72].

Calculating the cardio-ankle vascular index is a method of noninvasive estimation of arterial stiffness and it correlates with subclinical coronary atherosclerosis, mainly with plaque burden score and plaque extent, but not stenosis severity [73].

3.4. The Role of Carotide Plaques

Ultrasonography can detect various systemic atherosclerotic lesions, including carotid artery atherosclerotic lesions

[74]. The severity of corotid atherosclerosis can also be appreciated by using ultrasonography. Intima-media thickness and carotid plaque can independently predict ischemic heart disease. The presence of plaque surface irregularity and calcification length at the carotid level are independently associated with major adverse cardiovascular events. This finding is the result of the frequent association of the two locations of the atherosclerosis process [74].

Carotid plaque score (the sum of the maximum thickness of each carotid artery plaque) is superior to carotid intima-media thickness for risk stratification in patients with familial hypercholesterolemia [68].

3.5. The Residual Risk for Atherosclerotic Cardiovascular Disease of Patients Treated with Statins

Patients free of atherosclerotic cardiovascular disease and those under statin therapy have a residual risk for this disease. Atherosclerosis can be predicted by the following risk factors: family history, smoking habit, presence of diabetes, high level of high-sensitivity C-reactive protein, high number of low-density lipoprotein particles, increased intimal medial thickness, and high coronary artery calcium score [75].

3.6. The Role of Apolipoprotein A1

It has been demonstrated that higher levels of apolipoprotein A1 (the major component of HDL particles) are associated with a reduced risk of ischemic cardiovascular outcomes in patients with atrial fibrillation treated with apixaban [76].

3.7. Other Methods of Estimating Atherogenic Risk

Patients with HDL-cholesterol under 1.25 mmol/L, lipoprotein (a) over 0.09 g/L, and a genetic risk score (based on a combination of 25 single nucleotide polymorphisms associated with ischemic heart disease) over 20.9 had a higher risk of myocardial infarction [77].

Patients with chronic kidney disease in stages 3-4 have higher plasma triglyceride level, VLDL, and low LDL particles, and lower plasma HDL particles level - lipid-related changes associated with the risk of ischemic heart disease [78].

Monogenic predisposition for the occurrence of atherosclerosis can be investigated today using next-generation sequencing, although there is still no methodology for identifying patients at this risk. This could be a way for personalized medicine to be applied in order to prevent atherosclerotic lesions [79].

Plasma miR-130a-3p level, from microvesicles with origin in human coronary artery smooth muscle cells, decreased after exposure to atherogenic lipoproteins in FH patients. In addition, this microRNA was inversely related with coronary atherosclerosis and, therefore, could be a biomarker for coronary atherosclerosis [80].

4. THERAPEUTIC ASPECTS

Hyperlipidemia control is required in the existence of any atherosclerotic cardiovascular disease. It may also be due to patients with FH, chronic kidney disease or diabetes mellitus who are predisposed to develop atherosclerotic cardiovascular disease [27].

Lipid phenotype and the presence of other cardiovascular risk factors must be considered in choosing the best therapy for patients with atherosclerosis [12], which needs to be personalized. Lifestyle modifications should be recommended to any dyslipidemic patient [27].

The recommended serum low density lipoprotein cholesterol level target value is under 100 mg/dL in high-risk patients, and under 70 mg/dL in very high-risk patients [81]. A target value below 70 mg/dL must be obtained in patients with stable ischemic heart disease and acute coronary syndrome and below 55 mg/dL in those with acute coronary syndrome and diabetes mellitus [27].

4.1. The Use of Statins

Cardiovascular endpoints can be significantly reduced using statins; their effects are proportional to the decrease of serum cholesterol levels [81]. In fact, statins are the most commonly used lipid-lowering drugs. About half of the French patients achieved the LDL-cholesterol goal at 120-day follow-up (under 70mg/dL) [82]. The primary prevention of coronary heart disease in subjects without any vascular disease at baseline and with LDL-cholesterol ≥190 mg/dL can be achieved using pravastatin 40 mg/day; thus, the risk of coronary heart disease and major adverse cardiovascular events was reduced in a large trial that included 5529 participants in short- and long-term follow up [83].

A decrease in coronary plaque burden score can be obtained with statins either alone or in combination with ezetimibe, according to a recent study on patients with acute coronary syndrome [84]. A follow-up of 147 patients with detectable atherosclerotic coronary plaques performed by computed tomography angiography found a decrease in plaque progression in those with plasma LDL-cholesterol levels below 70 mg/dL [85].

Results of dyslipidemia treatment are far from ideal. For instance, only about 55% of 61,839 high-cardiovascular-risk patients treated with lipid-modifying therapy achieved an LDL-C target of under 100 mg/dL in the Netherlands. The suboptimal control of low-density lipoprotein cholesterol (LDL-C) levels can be explained by an underuse and subtherapeutical use of this class of medicines (usually inadequate statine dose - too low) [86, 87]; these are the main causes that explain the current situation [87]. Other causes are the presence of statin adverse effects, low treatment compliance of patients, and consumption of under three fish meals per week [86]. In addition, statins have various mechanisms of action, therefore their efficiency is not identical. For example, atorvastatin increases trans-intestinal and biliary excretion of cholesterol in mice [46], unlike rosuvastatin and lovastatin, which increase only biliary excretion of cholesterol.

4.2. Utility of Ezetimibe

Ezetimibe can can reduce atherosclerotic cardiovascular disease risk in patients who have had an acute coronary syn-

drome and whose plasma cholesterol levels have been lowered below 70 mg/dL [88].

In a long-term follow-up study on 200 hypercholesterolemic patients, less than a quarter of the patients with autosomal recessive hypercholesterolemia reached LDL-C levels <100 mg/dL under high dose statin treatment and ezetimibe and even in combination with lipoprotein apheresis in a long-term follow-up study [89]. The RosEze trial is underway and studies whether the administration of rosuvastatin and ezetimibe in the morning or evening is more effective in lowering cholesterol levels in 200 hypercholesterolemic patients [90].

Decreasing cholesterol level is not necessarily reflected in better clinical outcome, although it seems to be paradoxical. Although the therapy with pitavastatin plus ezetimibe in 1734 Japanese patients managed to decrease LDL-cholesterol level and obtain a mean value under the target and lower than that obtained with pitavastatin alone (which also was below the target), it failed to reduce overall mortality, acute non-fatal coronary syndromes or ischaemia-driven revascularization. The combination therapy: pitavastatin + ezetimibe may be more efficient in patients with increased pre-treatment sitosterol, which is an expression of higher cholesterol absorption [91].

4.3. Are Bile Acid Sequestrants Still Used Today?

Apart from ezetimibe, the combination of bile acid sequestrants and PCSK9 inhibitor may be an effective therapeutic alternative in patients on the maximally tolerated dose of statin [88]. Bile acid sequestrants are indicated nowadays only as a second treatment option in patients with intolerance to ezetimibe [92].

4.4. Benefits of Using PCSK9 Inhibitors

Patients with familial hypercholesterolemia and those who do not reach LDL-cholesterol target levels under maximally tolerated statin therapy can be treated with alirocumab or evolocumab (PCSK9 inhibitors), which reduce LDL-cholesterol level 50-65% more than that obtained with the maximally tolerated statin dose. In addition, evolocumab associated with statin treatment reduced cardiovascular risk in primary prevention with 15% and in secondary prevention with 20% during a 2.2 year treatment period. Moreover, an important regression of atherosclerosis plaque volume was observed after 76 weeks of evolocumab treatment in about two-thirds of patients [40]. Patients with statin treatment, as previously lipid-lowering therapy, who failed to reach the therapeutic targets, were later given 75 mg of alirocumab every two weeks in association with a statin. Nearly three-quarters of these patients obtained LDL-cholesterol levels lower than 70 mg/dL or lower than 100 mg/dL by week 8. About 61% of the rest achieved the LDL-cholesterol target level by week 24 with a double dose of alirocumab [93].

A large meta-analysis that included 62,776 patients from 6 randomized clinical trials found that treatment with PCSK9 inhibitors was associated with a lower number of major adverse cardiovascular events, coronary revascularization, and myocardial infarction, but had no effect on mortality. These are arguments for their use in patients with a high risk of ischemic heart disease [94]. A highly durable RNA interference therapeutic inhibitor of PCSK9 synthesis is being tested. It can maintain a 75% reduction in PCSK9 levels and a 50% decrease in LDL-cholesterol levels after a single dose [40].

4.5. Other Means of Lowering Plasma LDL-cholesterol Level

Mipomersen targets mRNA encoding apolipoprotein B-100 and mRNA is degraded by ribonuclease H; subsequently, mipomersen might be an alternative method of reducing the plasma LDL-cholesterol level in FH patients [27].

Patients treated with lomitapide (an inhibitor of microsomal triglyceride transfer protein, involved in very low-density lipoprotein assembly and secretion) had lower values of LDL-cholesterol [27, 95].

4.6. How to Treat Atherogenic Dyslipidemia?

Over one-third of Chinese outpatients optimally treated with statins in monotherapy (with normalized low-density lipoprotein cholesterol values) had atherogenic dyslipidemia (hypertriglyceridemia and / or hypo-HDL-cholesterol levels). Atherogenic dyslipidemia was associated with age, body mass index, male gender, sedentary condition, diabetes mellitus or increased fasting plasma glucose, ischemic cerebrovascular and cardiovascular disease, and hyperuricemia. It should be emphasized that the prevalence of atherogenic dyslipidemia was not influenced by a higher dose of statin [95]. Atherogenic dyslipidemia is a common disease throughout the world today.

After the effective reduction of plasma LDL-cholesterol level and reaching the target value, patients with triglycerides over 200 mg/dL have additional indications for achieving a non-HDL-cholesterol target below 100 mg/dL if they have ischemic heart disease, including acute coronary syndrome [27].

High triglyceride levels can be reduced with lifestyle modifications [52] like daily physical exercise, reducing body weight and lowering ethanol consumption [27] and add-on therapy with fibrates and omega-3 fatty acids [52]. New drugs, like pemafibrate or volanesorsen (which targets apolipoprotein C-III) complete the range of therapeutic possibilities [52].

The antisense oligonucleotide therapy against the gene encoding angiopoietin-like 3 has been able to decrease plasma levels of atherogenic lipoproteins, not only in mice but also in humans [96]. Antisense oligonucleotides and monoclonal antibodies against angiopoietin-like 3 are currently being studied in human clinical trials as a treatment for both dyslipidemia and atherosclerosis [59].

The best treatment for patients with lipoprotein(a)-hyperlipoproteinemia is long-term weekly lipid apheresis, which also significantly reduces the plasma LDL-cholesterol level. [97] This is an effective method to reduce the incidence of major adverse cardiac events in these patients [98]. Lipoprotein (a) thresholds for these patients

were established to be 120 nmol/L or 60 mg/dL, according to the German LA guideline [98]. This procedure could reduce the number of percutaneous coronary interventions by 71.43% in a group of 23 patients, during a median period of 51 months [97].

4.7. The Lipid Management Post-coronary Revascularization

Patients treated for coronary artery disease commonly evolve towards restenosis through a rapid atherosclerosis process and intimal hyperplasia [99]. An explanation for this outcome can be the inflammatory response and plaque vulnerability that can be observed either in damaged coronary arteries or whole vessels in patients with an acute coronary event [84]. Inflammation is involved in the progression of atherosclerotic lesions, as it was noted in the pathology section. A lipoprotein (a) level over 30 mg/dL was associated with a three-fold increased risk of venous graft occlusion during the first year after coronary artery bypass grafting. The frequency of these occlusions was 14.3% in the group treated weekly with lipoprotein apheresis and atorvastatin for over a year compared to 27.4% in the control group [100]. Drug-eluting stent use and the patient's history of dyslipidemia were associated with a favorable outcome in a cohort of high-risk patients included in the Melbourne Interventional Group Registry who underwent 19,858 procedures of percutaneous coronary intervention [101]. The use of gene silencing oligonucleotides-495 in a mouse model with intimal hyperplasia and hypercholesterolemia led to regression of atherosclerotic plaque development by over 50% and a 32% reduction of intimal hyperplasia, as microRNA miR-495 is involved in the atherosclerotic process and 14q32 microRNAs inhibit post-ischemic neovascularization [99].

CONCLUSION

Inflammation is involved in the progression of hyperlipidemia [56] and promotes atherosclerosis [57]. PCSK9 contributes to the increase in serum levels of both LDL-cholesterol and lipoprotein (a) [24]. Hypercholesterolemia changes the global cardiac gene expression profile and is thus involved in the increase of oxidative stress, mitochondrial dysfunction, and apoptosis initiated by inflammation [43].

Hypercholesterolemia induced experimentally in pigs, determined in HDL lipidomic transformations and changes in proteomic structure (cardioprotective proteins were lost), reduced the antioxidant activity and cholesterol efflux capacity [48].

Coronary artery calcification score, in addition to the guidelines, may contribute to a better stratification of patients regarding the risk of coronary events [70]. A high arterial stiffness increases the risk of cardiovascular disease [72]. Cardio-ankle vascular index is a method of noninvasive estimation of arterial stiffness and it correlates with subclinical coronary atherosclerosis [73]. Carotid intima-media thickness and carotid plaque can independently predict ischemic heart disease [74]. Carotid plaque score is superior to carotid intima-media thickness in risk stratification of patients with FH [68]. Lipoprotein (a) and FH have a synergistic role in predicting the risk of early onset and severity of coronary atherosclerosis [29]. Monogenic predisposition for atherosclerosis occurrence can be investigated today using next-generation sequencing [79].

A decrease in atherosclerotic coronary plaque progression can be obtained in patients with plasma LDL-cholesterol levels below 70 mg/dL [85]. Patients with FH and those who do not reach LDL-cholesterol target levels under maximally tolerated statin therapy can be treated with alirocumab or evolocumab, which can reduce LDL-cholesterol level 50-65% more than that obtained with the maximally tolerated statin dose. Moreover, an important regression of atheroma plaque volume was observed after 76 weeks of evolocumab treatment in about 2/3 of patients [40]. The treatment with PCSK9 inhibitors was associated with a lower number of major adverse cardiovascular events, coronary revascularization, and myocardial infarction, but had no effect on mortality [94]. A highly durable RNA interference therapeutic inhibitor of PCSK9 synthesis is being tested. It can maintain a 75% reduction in PCSK9 levels and a 50% decrease in LDL-cholesterol levels after a single dose [40].

Some patients optimally treated with statins continue to have an increased residual risk of cardio-vascular events, particularly if they have elevated triglyceride levels or low HDL-cholesterol values [50]. Triglycerides and, particularly, triglyceride-rich lipoproteins and their remnants are involved in cardiovascular disease occurrence by the following possible mechanisms: increased free acid release, higher production of proinflammatory cytokines and coagulation factors and a disruption of fibrinolysis [52].

After the effective reduction of plasma LDL-cholesterol level and reaching the target value, patients with triglycerides over 200 mg/dL have additional indications for achieving a non-HDL-cholesterol target level below 100 mg/dL if they have ischemic heart disease, including acute coronary syndrome [27]. Antisense oligonucleotide and monoclonal antibodies against angiopoietin-like 3 are currently being studied in human clinical trials as a treatment for both dyslipidemia and atherosclerosis [59]. The best treatment for patients with lipoprotein(a)-hyperlipoproteinemia is long-term weekly lipid apheresis, which also significantly reduces the plasma LDL-cholesterol level. [97] This is an effective method to reduce the incidence of major adverse cardiac events in these patients [98].

Patients treated for coronary artery disease commonly evolve towards restenosis through a rapid atherosclerosis process and intimal hyperplasia [99], as a result of an inflammatory response and plaque vulnerability [84]. A lipoprotein (a) level over 30 mg/dL was associated with a three-fold increased risk of venous graft occlusion during the first year after coronary artery bypass grafting. Solutions to prevent coronary restenosis are: lipoprotein apheresis and treatment with atorvastatin [84], the use of a drug-eluting stent [101] or perhaps, in the near future, the use of gene silencing oligonucleotides-495, which may reduce atherosclerotic plaque development and intimal hyperplasia, as it was observed in a mouse model with intimal hyperplasia and hypercholesterolemia [99].

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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