Statins in High Cardiovascular Risk Patients

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Atherosclerotic cardiovascular disease (ASCVD) morbidity and mortality are decreasing in high-income countries, but ASCVD remains the leading cause of morbidity and mortality in high-income countries. Over the past few decades, major risk factors for ASCVD, including LDL cholesterol (LDL-C), have been identified. Statins are the drug of choice for patients at increased risk of ASCVD and remain one of the most commonly used and effective drugs for reducing LDL cholesterol and the risk of mortality and coronary artery disease in high-risk groups. Unfortunately, doctors tend to under-prescribe or under-dose these drugs, mostly out of fear of side effects. The latest guidelines emphasize that treatment intensity should increase with increasing cardiovascular risk and that the decision to initiate intervention remains a matter of individual consideration and shared decision-making.

statin cardiovascular disease atherosclerosis LDL-cholesterol

1. Introduction

Statins are commonly used drugs in patients at high cardiovascular risk. These drugs reduce serum low-density lipoprotein cholesterol (LDL-C), which is involved in the pathogenesis of cardiovascular disease [1]. Proper treatment of patients with hypercholesterolemia begins with the notion that not all patients are the same and that treatment must be individualized. The first step is to determine the patient's overall cardiovascular risk [2] (**Figure 1**). Depending on each patient's specific risk category, specific therapeutic targets for LDL cholesterol need to be achieved [2]. In addition to cardiovascular risk, individual patient characteristics and possible adverse effects of drugs in specific patient categories must also be considered (**Figure 1**). In addition, statins vary in their chemical composition (**Figure 2**), pharmacokinetics, and potency of lowering LDL cholesterol [3].

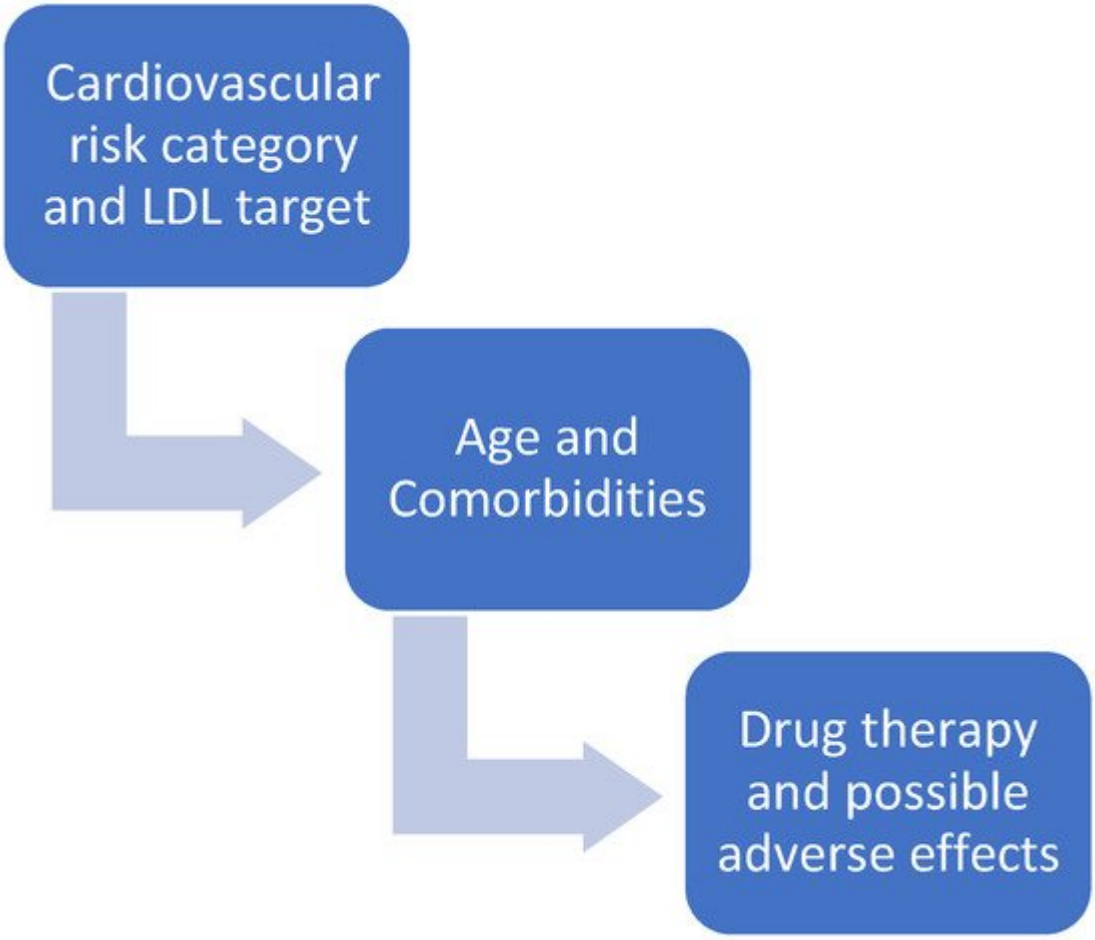

Figure 1. How to decide which statin and what dosage.

Lipophilic statins	Hydrophilic statins
simvastatin	rosuvastatin
fluvastatin	pravastatin
pitavastatin	
lovastatin	
atorvastatin	

Figure 2. Hydrophilic and lipophilic statins.

1.1. Are Statins All the Same?

Statins are the drug of choice for the treatment of hypercholesterolemia to lower LDL cholesterol. They act principally in the liver by competitively inhibiting 3-hydroxy-3-methylglutaryl-CoA reductase activity. The pharmacological activity determines the decrease in intracellular cholesterol concentration, which leads to an increase in the expression of LDL receptors on the surfaces of hepatocytes. Increased LDL receptor expression leads to increased uptake of LDL-C in the blood, resulting in lower plasma concentrations of LDL-C and other apolipoprotein B-containing lipoproteins, including triglyceride-rich particles [1]. Although all statins act by the same mechanism of action, they differ in chemical composition and pharmacokinetics, affecting treatment and adverse

effects. Lovastatin, pravastatin, and simvastatin are fungal-derived 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, while atorvastatin, cerivastatin, fluvastatin, pravastatin, pitavastatin, and rosuvastatin are fully synthetic compounds [4]. Atorvastatin, fluvastatin, lovastatin, and simvastatin are relatively lipophilic compounds, while pravastatin and rosuvastatin are more hydrophilic (**Figure 3**) [5]. Lipophilic drugs are more susceptible to oxidative metabolism by the CYP450 system (cytochrome P450) [6]. Due to the risk of drug interactions that inhibit CYP450, statins metabolized by the CYP450 system are more likely to cause muscle damage; this leads to increased blood statin levels, which lead to an increased risk of toxic effects [7]. Several studies have compared lipophilic and hydrophilic statins in the clinical setting [8][9]. Lipophilic statins reduce adenosine triphosphate (ATP) production, which theoretically increases myocardial stunning after ischemia and worsens myocardial function after reperfusion [10]. This was demonstrated in an animal study in which lipophilic statins exacerbated myocardial shock and decreased tissue ATP following coronary reperfusion, whereas hydrophilic statins did not show these effects. A meta-analysis concluded that lipophilic statins have risks of major adverse cardiovascular events, myocardial infarction, and all-cause mortality comparable with hydrophilic statins [11].

The degree of LDL-C reduction is dose dependent and varies between the different statins.

High intensity (average LDL-C reduction ≥50%)	Moderate intensity (30 to <50% reduction)	Low intensity (<30% reduction)
Atorvastatin 40–80 mg	Atorvastatin 10–20 mg	Simvastatin 10 mg
Rosuvastatin 20–40 mg	Rosuvastatin 5–10 mg	Pravastatin 10–20 mg
Simvastatin 80 mg	Simvastatin 20–40 mg	Lovastatin 20 mg
	Pravastatin 40–80 mg	Fluvastatin 20–40 mg once daily
	Lovastatin 40 mg	Pitavastatin 1 mg daily
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg PO BID	
	Pitavastatin 2–4 mg	

Figure 3. Intensity of statin therapy [12].

The largest study (involving the most patients, drugs, and doses) was the CURVES study [13], which compared doses of atorvastatin (10, 20, 40, and 80 mg), simvastatin (10, 20, and 40 mg), pravastatin (10, 20 and 40 mg), fluvastatin (20 and 40 mg) and lovastatin (20, 40 and 80 mg). This was a multicenter, randomized, open-label, 8-week, parallel-group study of 534 hypercholesterolemic patients with LDL values above 160 mg/dL and triglycerides above 400 mg/dL. Atorvastatin 10, 20, and 40 mg resulted in greater LDL-C lowering than equivalent doses of simvastatin, pravastatin, lovastatin, and fluvastatin (238%, 246%, and 251%). Atorvastatin 10 mg produced LDL-C lowering comparable to simvastatin 10, 20 and 40 mg, pravastatin 10, 20 and 40 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg. Atorvastatin 10, 20, and 40 mg resulted in greater reductions in total cholesterol compared to mg-equivalent doses of simvastatin, pravastatin, lovastatin, and fluvastatin. All reductase inhibitors tested were similarly tolerated.

1.2. Cardiovascular Risk Category and LDL-C Target

Treatment goals have been defined according to different risk categories (they apply to primary and secondary prevention; treatment must always be combined with lifestyle changes) [2] (**Table 1**).

Table 1. LDL-C target according to cardiovascular risk.

RISK CATEGORY.	WHICH PATIENT?	LDL-C TARGET
Very high-risk patients (10-year risk of cardiovascular mortality > 10%)	Atherosclerotic cardiovascular disease (ASCVD) documented clinically or by imaging (acute coronary syndrome, stable angina, coronary revascularization, stroke or transient ischemic attack, peripheral arterial disease). Imaging documented ASCVD, including findings known to be relevant to the development of future clinical events, such as Diabetes mellitus (DM) with end-organ damage (microalbuminuria, retinopathy, and neuropathy) or at least 3 CV (cardiovascular) risk factors or early-onset type 1 diabetes that has been present for more than 20 years. Severe chronic kidney disease (eGFR < 30 mL/min/1.73 m^2).	LDL < 55 mg/dL or reduce LDL by at least 50% compared to baseline levels
Very very high-risk patients	Very high-risk patients who experience a second vascular event within 2 years of the first during therapy with statins at the highest tolerable dosage.	LDL < 40 mg/dL
High-risk patients (10-year risk of cardiovascular mortality 5–10%)	Particularly high individual risk factors, such as total cholesterol > 310 mg/dL (>8 mmol/L), LDL-C > 190 mg/dL (>4.9 mmol/L) or blood pressure ≥ 180/110 mmHg. Familial hypercholesterolemia without other CV risk	LDL < 70 mg/dL or reduce LDL values by at least 50% compared to the initial ones

RISK CATEGORY.	WHICH PATIENT?	LDL-C TARGET
	factors. Diabetes mellitus without end organ damage, but present for at least 10 years or in conjunction with another CV risk factor. Chronic moderate kidney disease (eGFR 30–59 mL/min/1.73 m^2).	
Moderate risk patients (10-year risk of cardiovascular mortality > 1% <5%)	Diabetes in young subjects (T1DM < 35 years, T2DM < 50 years), present for less than 10 years and in absence of other risk factors	LDL < 100 mg/dL
Low-risk patients (risk of cardiovascular mortality at 10 years < 1%)		LDL < 116 mg/dL

2.1. Acute Coronary Syndrome (ACS)

Randomized clinical trials have demonstrated the efficacy and safety of statins for the primary and secondary prevention of cardiovascular disease [14]. In the context of acute coronary syndrome, other studies have shown that loading doses of statins can attenuate the inflammatory cascade and promote coronary artery vulnerability [15][16] by reducing macrophage and cholesteryl ester levels and increasing collagen and smooth muscle cells [17][18]. Plaque rupture activates the thrombotic cascade: statins mitigate this event by inhibiting platelet aggregation and maintaining a balance between prothrombotic and fibrinolytic mechanisms [17][19][20]. These non-lipid properties of statins may explain the early and significant reduction in cardiovascular events reported in several clinical trials. Several studies and systematic reviews have examined the effect of loading doses of statins before and after percutaneous coronary intervention (PCI) [21][22][23][24][25]. These studies suggest that perioperative myocardial infarction (MI) may be reduced [26]. In addition, statin pretreatment has also been shown to reduce the risk of contrast-induced acute kidney injury after coronary angiography or interventional therapy [27]. Therefore, early initiation or continuation of high-dose statin therapy is recommended for all ACS patients without contraindications or a clear history of intolerance, regardless of initial LDL-C levels [2].

Statin therapy is underused in chronic kidney disease (CKD) patients with ACS [28], although statins have been shown to be safe even in advanced CKD. CKD is associated with short- and long-term adverse events in patients with ACS [29]. In the setting of ACS with rupture, plaque instability, increased inflammatory status, and a prothrombotic environment, CKD patients should also be prescribed statin therapy regardless of their estimated glomerular filtration rate (eGFR) levels [30].

Another risk group for cardiovascular events is HIV-infected individuals, who are less likely to have lower LDL-C after ACS than non-HIV-infected individuals [31]. This may be due to chronic HIV-related infection and inflammation leading to persistent immune activation and use of antiretroviral therapy, which may lead to disturbances in lipid and glucose metabolism [32]. After the initial ACS, HIV-infected individuals are more likely to experience recurrent acute coronary events than non-HIV-infected individuals, but HIV-positive patients are often prescribed less effective or lower doses of statins. Appropriate statin strengths should be prescribed for HIV-infected individuals with attention to potential drug–drug interactions [33].

2.2. Peripheral Arterial Disease (PAD)

Patients with peripheral arterial disease, including asymptomatic patients, are at increased risk of death, myocardial infarction, and stroke [34]. In a large cohort study of Danish patients, the authors found that PAD could be considered a risk equivalent for coronary artery disease (CAD) even in the absence of diabetes. This entry showed that the combination of PAD and MI was associated with the highest cardiovascular risk [35]. Therefore, clinicians should actively assess and manage cardiovascular risk factors in patients diagnosed with PAD [36], as they do in patients with established CAD. A study by Foley and colleagues compared high-intensity (HI) and low- or moderate-intensity (LMI) statin therapy in patients with PAD undergoing peripheral angiography and/or surgery [37]. Results showed that HI statin treatment provided a mortality benefit over statin LMI treatment in patients with PAD, despite similar baseline LDL levels between groups, and a reduction in major adverse cardiovascular events (MACE) [38]. HI statin therapy has potent LDL-lowering effects and may confer additional benefits through pleiotropic mechanisms associated with regression and plaque stabilization [39][40]. In addition, high-intensity statin use at PAD diagnosis was associated with significantly lower limb loss and mortality compared with low-intensity statin users and patients receiving antiplatelet therapy alone [41]. Therefore, patients with PAD are at very high risk and should be treated according to the recommendations of the European Society of Cardiology (ESC) guideline [2] to ensure aggressive secondary prevention.

2.3. Heart Failure

Several observations suggest that statins may be an effective treatment for heart failure (HF) [42]. Small studies have shown that statins improve endothelial function [27] and reduce plasma proinflammatory cytokine levels [28] in patients with CAD and hyperlipidemia. Statins can directly exert antioxidant [43], anti-hypertrophic [44], and anti-fibrotic effects on the myocardium and alter immune function [45], macrophage metabolism, and cell proliferation, in contrast to changes in low-density lipoprotein cholesterol concentrations [46]. Experimental evidence also suggests that statins counteract sympathetic upregulation in acute and chronic heart failure by reducing plasma norepinephrine levels and reducing renal sympathetic nervous system activity [47].

A study by Khush and colleagues showed that high-dose statins not only reduced the rate of major cardiovascular events in high-risk patients, but also hospitalizations in patients with stable coronary artery disease [48]. Statins appear to reduce the development of heart failure, at least in part, by lowering blood lipids and other anti-atherothrombotic mechanisms; in fact, heart failure progression is strongly associated with recurrent ischemic events, and statins can promote stabilization of sclerotic plaques, reducing myocardial necrosis, maintaining myocardial viability and improving ventricular function [49].

A meta-analysis of unpublished data from major randomized trials showed that statins modestly reduced the risks of non-fatal HF hospitalization and a composite of non-fatal HF hospitalization and HF death with no demonstrable difference in risk reduction between those who suffered an MI or not [50]. However, according to the 2019 ESC/European Atherosclerosis Society (EAS) Dyslipidemia Guidelines [2], statins are not recommended for cholesterol-lowering therapy in patients with moderate to severe symptomatic heart failure (New York Heart

Association (NYHA) Class III-IV). However, for those already taking statins to prevent CAD [35], continued use may be considered. These recommendations are based primarily on results from two large outcome studies, Controlled Rosuvastatin Multinational Trial in Heart Failure CORONA [51] and the GISSI-HF trial [52]: in both studies, no significant reduction in the primary combined mortality/morbidity endpoint was observed in actively treated patients.

In conclusion, statins reduce the risk of new-onset heart failure in the medium to long term, albeit modestly, well below the comparable benefit on CAD outcomes [53]. Therefore, statins should be continued in heart failure with reduced ejection fraction (HFrEF) patients already receiving statins for coronary artery disease or hyperlipidemia, whereas initiation of statins is not recommended for most patients with chronic heart failure.

2.4. Cardiac Valvulopathies

Calcified aortic stenosis (AS) is mediated by a chronic inflammatory process that shares many similarities with atherosclerosis [54][55], given its clinical association with hypercholesterolemia and coronary artery disease and its association with atherosclerosis. Histological similarities have suggested that cessation of statin therapy or even progression induces regression of calcified aortic stenosis [56]. However, randomized clinical trials have not demonstrated that lipid lowering prevents AS progression [57]. In fact, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) [58], Scottish Aortic Stenosis and Lipid Lowering (SALTIRE) [59] and the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) [60] trial studies concluded that lipid lowering may be a treatment to slow AS progression. A review by Thiago and colleagues suggests that the effect of statins on aortic stenosis is uncertain [61]. Therefore, lipid lowering can only have a significant effect in patients with primary or secondary hyperlipidemia; in this case, LDL would be the main driver of disease progression. Valve lesions in the early stages of AS have been shown to resemble lipid-laden atheromatous plaques, leading to irreversible mineralized osteogenic bone formation in later stages, followed by the differentiation of interstitial valve cells into osteoblasts [62]. Experimental models suggest that statin treatment slows the differentiation of interstitial valve cells into bone [63]. A study by Greve and colleagues [55] suggests that lowering blood lipids before osteoblast formation may be the best treatment for altering the natural history of AS. They showed that targeting hyperlipidemia early in the disease prevented AS progression [55]. Therefore, statins may be more useful in the early stages of aortic stenosis than during moderate or severe stenosis. Under no circumstances is it recommended to initiate lipid-lowering therapy to slow progression of aortic stenosis in patients with non-CAD aortic stenosis without other indications for use [2].

2.5. Stroke

The use of statins in patients with ischemic stroke improves post-stroke outcomes [64][65], reduces the risk of recurrent ischemic stroke [66] and is, therefore, recommended for patients with a history of ischemic stroke [67] or transient ischemic attack (TIA) [2]. There are conflicting data on the effect of statins on the risk of intracerebral hemorrhage (ICH). A systematic review and meta-analysis of data from 23 randomized trials and 19 observational studies [68] and a further meta-analysis of 31 randomized controlled trials [69] suggest that outpatient statin use does not increase the risk of bleeding. On the other hand, in the SPARCL study (a prospective, randomized,

double-blind clinical trial), treatment with atorvastatin (80 mg/day) reduced bleeding in patients with a history of transient ischemic attack (TIA) or recent stroke [70], but a post hoc analysis showed an increase in the number of stroke-bleeding patients receiving treatment (55 in the atorvastatin group and 33 in the placebo group) [70]. A secondary analysis found that statin therapy, increasing age, and ICH as eligible strokes for included studies were factors associated with late-onset ICH. This has led many clinicians to be cautious about prescribing statins to patients with ICH following these findings. Markov analysis concluded that statin avoidance should be considered in patients with a history of ICH, especially in the setting of lobar localization [71]. The association between statin therapy and increased presence and number of microbleeds (MB), which are frequently observed in cerebral amyloid angiopathy (particularly cortico-subcortical microbleeds), was investigated, with the conclusion that statin use in patients with ICH is independently associated with MB, especially csMB [72]. It is unclear whether statin use should be continued in patients with ICH, but a retrospective study suggests that continued statin use after ICH may be associated with early neurological improvement and may reduce mortality within 6 months, which may be due to immunomodulation as a pleiotropic effect of statins [72]. There are no data to suggest that susceptibility to ICH is dose-dependent.

3. Statins in Special Populations

3.1. Statins and Elderly People

Biologically, people over the age of 75 are a very heterogeneous group, often with disabilities, comorbidities, and multiple concomitant medications. In primary prevention, a person's life expectancy must be considered. Prevention may be useless if started too late, as in patients with dementia [73] or advanced heart [52] or renal failure [74]. Results of randomized controlled trials and observational studies in younger patients and more than 75 year-aged subgroups support the treatment of secondary prevention of ASCVD. According to a meta-analysis of randomized statin trials involving 14,483 participants over the age of 75, statin therapy was associated with a 15% reduction in the rate of major vascular events [75]. Conversely, the evidence from primary prevention studies is less clear [76][77]. A systematic review by Ravnskov and colleagues showed that low cholesterol is associated with poorer outcomes in older age [78], raising concerns and criticism about the importance of statins in older adults. In the frail elderly, low serum cholesterol may be an indicator of changes in cholesterol metabolism [75], a marker of terminal decline [75], or a marker of subclinical diseases such as cancer [75]. Frail people with comorbidities and polytherapy may also be more prone to adverse effects and drug interactions: adverse muscle effects could promote sarcopenia and predispose to frailty, falls and morbidity, but there is no hard evidence of this in the available studies [79], and there is no evidence that very low cholesterol could be associated with cognitive impairment [80]. In conclusion, statin therapy is generally safe and well-tolerated in these patients, and therapy should be continued for those aged more than 75 years. If a patient is considered to be at increased risk of developing ASCVD, then primary prevention therapy needs to be initiated in older age [76]. Finally, the recent ESC 2021 cardiovascular disease prevention guidelines provide a single cut-off point for identifying "elderly" as 70+ rather than 75, but also emphasize that all of these age intervals are relatively arbitrary, and biological age affects this threshold in clinical practice. In addition, according to the latest ESC guidelines, starting statin therapy for

primary prevention at age 70 in patients at very high cardiovascular risk may be considered, subject to other factors such as risk modifiers, frailty, estimated benefit over the life course, comorbidities and patient preferences. Regarding LDL-C targets, there is insufficient evidence to support primary prevention targets in elderly patients, but if there is significant renal impairment and/or the possibility of drug–drug interactions, it is recommended to start with low-dose statins [81].

3.2. Statins and Young People

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) blood cholesterol management guidelines recommend statin therapy for primary prevention of ASCVD in individuals ≥ 21 years of age with LDL-C ≥ 190 mg/dL. Statins may be considered in patients up to 75 years of age with diabetes or an estimated 10-year ASCVD risk of ≥7.5%, and in those with an estimated 10-year risk of 5% to 7.5% [81]. Due to the lack of evidence from RCTs, this guideline does not recommend statin therapy for adults younger than 40 years with LDL-C < 190 mg/dL. Recently, the AHA, ACC, and several other health organizations collaborated on the 2018 cholesterol guidelines [82]. These guidelines are consistent with the previous 2013 ACC/AHA guideline; in addition, for individuals 20 to 39 years of age with LDL-C < 190 mg/dL, a lifetime risk assessment is recommended, with particular attention to lifestyle modifications to consider the risk of premature ASCVD. Individuals with a family history and LDL-C > 160 mg/dL receive statin therapy to reduce ASCVD risk. A novelty of the 2018 guidelines is the recommendation to test the coronary artery calcium score (CAC) in persons at intermediate risk (10-year risk ≥ 7.5% ≤20%) when uncertain about the decision to initiate statin therapy [12]. The development of coronary atherosclerosis is a lifelong process with atherosclerotic changes evident in early adulthood [83], and statin therapy has been shown to reverse coronary atherosclerosis [84]. There is concern about starting statin use because of the side effects associated with myalgia and arthralgia; in addition, there has been a reported risk of developing diabetes with statin use, although the risk is small and the potential benefit appears to be significantly greater [85]. Additionally, it is unclear whether long-term statin use leads to an increased risk of diabetes. Randomized trials have also failed to demonstrate cognitive impairment problems associated with statin use [86]. On the other hand, women wishing to have children should avoid statins due to their possible teratogenic effects. To improve risk stratification to help decide when and whether to start statin use in young adults, researchers are trying to identify risk markers such as CAC [87]. A recent analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) study showed that CAC is a strong predictor of future CAD in young adults. Among 3043 CARDIA participants aged 32 to 46 years (mean age 40.3 years), 10.2% had CAC at baseline, and those with any CAC had a 5-fold and 3-fold increase in coronary heart disease events and cardiovascular deaths, respectively, after adjustment for demographics, risk factors, and cardiovascular medications [88]. Although not yet clinically available, polygenic risk assessments for ASCVD outcomes have been developed and show promise for improved risk stratification [89]. Further studies are needed to assess the effectiveness of the use of polygenic risk scores and CACs in the decision to introduce statins. In conclusion, for patients in their 20s with increased lifetime risk, the focus should be on a healthy lifestyle, and statin use should be limited to those with familial hypercholesterolemia. For individuals in their 30s at increased lifetime risk, low- to moderate-intensity statin therapy may be offered to patients who place a high priority on reducing future ASCVD risk. In addition, CAC testing can be performed in

selected individuals (mainly men in their 30s), although the results should be interpreted with caution given the low prevalence of CAC in this age group.

3.3. Statins and Familial Dyslipidemias

Familial hypercholesterolemia (FH), the most common and severe form of congenital hypercholesterolemia, significantly accelerates the onset of ASCVD, primarily coronary artery disease [90]. Statins are first-line therapy for LDL cholesterol in FH, especially in heterozygous patients [91]. FH is undertreated, with more than 80% of FH patients receiving statins failing to achieve LDL-cholesterol goals. This may be related to adherence, genetic differences and tolerance to statins. Current guidelines recommend that children homozygous for FH should be treated as early as possible at the time of diagnosis. Treatment for children who are heterozygous for FH should be initiated at the lowest recommended dose (such as pravastatin 20 mg, atorvastatin 10 mg, and rosuvastatin 5 mg) and up-titrated according to the LDL cholesterol-lowering response and tolerability from 8 to 10 years of age [2][92]. In general, it is recommended to consider FH patients with ASCVD or other major risk factors as very high-risk patients, and patients without previous ASCVD or other risk factors as high-risk patients.

3.4. Statins and Cognitive Impairment

Some cases have linked statin use to cognitive impairments, such as short- and long-term memory loss [93], behavioral changes, concentration and attention problems, anxiety, and paranoia [94]. The statins involved are simvastatin, atorvastatin, and rosuvastatin. The underlying mechanism of cognitive impairment is based on the relationship between cholesterol and myelin; myelin is composed of cholesterol, and statins reduce the de novo synthesis of cholesterol [95]. Changes in myelination can also lead to changes in nerve signaling pathways that can lead to cognitive decline. Another mechanism may involve oxidative stress and mitochondrial function [96]. Statins lower coenzyme Q10 levels by inhibiting mevalonate synthesis. In turn, coenzyme Q10 is responsible for the correct function of mitochondria, is involved in the production of adenosine triphosphate and has antioxidant functions. Therefore, statins will determine changes in mitochondrial function, increased oxidative stress, and thus cognitive deterioration. On the other hand, high cholesterol levels are associated with an increased risk of Alzheimer's disease [97][98]. In this case, the protective effect of statins would be attributed to the pleiotropic effects of these drugs (reduced endothelial dysfunction, increased endothelial nitric oxide production, anti-inflammatory, antioxidant, and antithrombotic properties, vascular generation and other angioprotective properties) [99][100].

If patients at high cardiovascular risk develop cognitive impairment due to statin use and require continued lipid-lowering therapy, the use of less lipophilic statins that cannot cross the blood–brain barrier, such as pravastatin and rosuvastatin, should be considered [101]. Despite a 2012 U.S. Food and Drug Administration (FDA) warning about the potential adverse effects of statins on cognition, a systematic review and meta-analysis of randomized controlled trials found that statin therapy had no significant effect on cognitive function [86]. Therefore, these results call into question the aforementioned FDA warning that statins may have negative effects on cognition.

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