**ABSTRACT**

**Introduction:** Statins are remarkably safe and efficient medications that are the mainstay of hypercholesterolemia treatment and have proven to be an invaluable tool to lower the risk of acute cardiovascular events. These compounds are inhibitors of 3-hydroxy-methylglutaryl CoA reductase (HMG-R), the rate-limiting enzyme in cholesterol biosynthesis. In spite of their success, they present undesirable side effects and are now losing patent protection, which provides a great opportunity for the development of new and improved statins.

**Areas covered:** This review summarizes the new patents for HMG-R inhibitors for the 2011–2015 period. Combinations of existing statins with other drugs are also addressed, as well as novel applications of existing statins.

**Expert opinion:** Recent efforts for the discovery of HMG-CoA-R inhibitors has resulted in several new molecules. Most of these are based on commercially available statins, including sterol and terpenoid derivatives. A few peptides have also been patented. However, the origin of the side effects caused by previous statins continues to be, to a large extent, unknown. Although the patents published in the past 5 years are promising, and might result in new drugs, there is still no way to know if they will present reduced toxicity. Only future clinical trials will answer this question.

1. Introduction

The World Health Organization identifies cardiovascular diseases (CVDs) as the number one cause of death globally, accounting for 31% of all global deaths. The main group of CVDs, responsible for 42% of these diseases, is coronary heart diseases (CHDs), which include myocardial infarction, angina, and coronary insufficiency.

Several risk factors for CHD have been identified but prospective studies have shown that hypercholesterolemia, in particular, high serum concentrations of low-density lipoprotein cholesterol (LDL-C) are among the major risk factors. Up to now, the standard lipid-lowering therapies have been targeting the inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-R), the rate-limiting step of hepatic cholesterol biosynthesis. In fact, the mechanism by which inhibitors of HMG-R lower LDL-C is considerably more complex than simple HMG-R inhibition. Inhibition of HMG-R lowers the synthesis of mevalonate and consequently reduces the regulatory sterol pool. The response is an upregulation of enzymes participating in cholesterol biosynthesis, in particular HMG-R, and, more crucially, upregulation of the LDL receptors. Hence, the primary mechanism of action of statins is increasing the uptake of LDL.

The family of clinical inhibitors that target HMG-R is generally termed as statins. The development of statins started in the 1970s with the discovery by Akira Endo of a compound isolated from *Penicillium citrinum* fermentation broth with a powerful inhibitory effect on HMG-R [1]. Development of this compound, ML-236B (compactin or mevastatin), was interrupted in September 1980 during the clinical trials for undisclosed reasons, but believed to be related to the toxicity of the compound. Therefore, the first commercial available statin was lovastatin (1987, Merck) [2], a natural compound with close structure similarity to compactin. In 1988 and 1991 two other statins (fluvasstatin and pravastatin) were introduced in the market and all the three represent the first generation of natural products targeting HMG-R [3]. Since their introduction, these drugs have emerged as one of the world’s best-selling medication classes to date, with numerous trials demonstrating powerful efficacy in preventing CHDs. Facing these encouraging results, they became the first-line treatment in all guidelines, in every country, for primary and secondary prevention of CHDs since 1990 [4,5].

A second generation of statins was developed shortly after. All of these compounds are synthetic and are more potent than the ones from the first generation. They include simvasstatin, atorvastatin, cerivastatin, rosuvastatin, and pitavastatin [3].
Statins are usually well tolerated and have a good safety profile but was withdrawn from the market of cerivastatin in 2001 due to 52 deaths from rhabdomyolysis brought special attention to statins’ safety profile [6,7]. Most of the adverse effects of statins available in the market are muscle related and 10–15% of patients might be affected by muscle aches (myalgia), weakness, stiffness, and cramps [8]. Nevertheless, the prevalence of serious side effects is considerably lower, with 3–5% of patients suffering from myalgia, 0.1–0.2% myopathy while rhabdomyolysis might occur in 0.01% of patients [9]. The mechanism by which statins cause myopathies remains elusive but the risk is clearly lower for more hydrophilic statins (pravastatin and fluvastatin) when compared to synthetic, more potent and more lipophilic statins [10]. Treatments with higher potency statins, in particularatorvastatin and simvastatin, might also be associated with an increased risk of new onset diabetes [11]. Cholesterol-independent or ‘pleiotropic’ effects of statins, such as improved endothelial function, reduced inflammation, and reduced thrombus formation, were also described. Many of these pleiotropic effects result from the inhibition of isoprenoid synthesis, which serve as important lipid attachments for intracellular signaling molecules, but some of the pleiotropic effects might be independent of mevalonate synthesis. For instance, statins reportedly bind to leukocyte function antigen-1 (LFA-1) and inhibit LFA-1/intercellular adhesion molecule-1 (ICAM-1) interaction, important for T cell activation [12–14].

In spite of some statins’ side effects, these drugs are currently widely used to treat CHDs. The latest report issued by the American College of Cardiology (ACC) foundation and the American Heart Association (AHA) [5], which substitutes previous guidelines for statin therapy for primary CHD (Expert Panel on Detection, Evaluation 2001) [15], increases considerably the number of patients who qualify for statin therapy. The most notable change of this guideline was to extend the statin therapy recommendation for individuals with 10-year atherosclerotic CVD risk higher than 7.5%, from the previous risk of 20%. Consequently, the number of patients eligible for statin therapy might even double [16]. In a similar trend, other studies such as the study from the Cholesterol Treatment Trialists indicate that the benefits of LDL cholesterol reduction with statins are similar even for people with lower risk of a major cardiovascular event and largely uncorrelated to the baseline LDL cholesterol levels [17]. The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study, which included individuals with cholesterol levels below traditional treatment thresholds but with elevated high-sensitivity C-reactive protein (hsCRP), found great reduction of cardiovascular events for individuals who achieved either a LDL-C <70 mg/dL or hsCRP <2 mg/L and even greater risk reduction for individuals who achieved both goals [18].

These studies support a broader and more intensive statin therapy. Consequently, most clinical practice guidelines are lowering the recommended LDL-C thresholds and the benefits of prophylactic statin therapy for low-risk populations are being considered. As statin therapy is extended to a larger population and an earlier onset on the primary prevention of high-risk individuals is advised, the milder nonspecific secondary effects of statins gain relevance and must be addressed.

Today, statins represent a multibillion dollar product. However, all the approved statins have already lost, or will lose in 2016, patent protection. This has prompted the pharmaceutical industries to seek for new chemical entities or statin derivatives capable of offering new ways to inhibit HMG-R [19]. At the same time, statins are also being studied for other therapeutic guidelines, which makes the appeal for the development of new statins still stronger. In the following sections, we will review the patent publications from 2011 to 2015, retrieved from the European Patent Office – Espacenet, on novel statins targeting HMG-R for the treatment of CHDs. In addition, novel uses of statins in the treatment of other diseases will also be discussed.

2. Statins with novel chemical entities

HMG-R is a transmembrane protein that is formed by four identical monomers, which forms two dimers that coil around each other in an intricate way. The enzyme contains four active sites, two in each dimer. Each active site is located at the interface of both monomers, being one of the monomers responsible for the binding of the nicotinamide dinucleotide cofactor and a second monomer of the binding of HMG-CoA. The essential structural components of all commercial statins are a dihydroxyheptanoic acid unit (structurally similar to the natural substrate) and a ring system (Figure 1). These similarities allow statins to bind to the active site of HMG-R and compete with the natural substrate (HMG-CoA), inhibiting the enzyme.

One of the lines of development of new statins continues to follow the same general recipe, but with new variations. The idea is to introduce new and different chemical components either at the hydroxyglutaric acid component or/and in the ring system positions in order to improve the inhibitory activity. These inhibitors are termed derivatives of existing derivatives. Other lines try to use different chemical entities to inhibit HMG-R. Recent examples include the use of sterol derivatives or even small peptides. The specific region where these compounds interact with HMG-R is still not fully understood but it cannot be disclosed the possibility that they interfere with the association of the dimers of HMG-R, which ultimately leads to its inhibition [20].
2.1. Derivatives of existent statins

All novel compounds displaying inhibition constants in the low nanomolar range are derivatives of existent statins. Even though the claimed chemical space includes substituent groups that may potentially lead to molecules very distinct from commercial statins, the most potent compounds resemble already known statins.

2.1.1. Atorvastatin derivatives

A series of patents by RedX Pharma and Bradford Pharma disclose activity of atorvastatin and rosuvastatin lactoles [21,22]. This is interesting because the closed lactol form is described in the literature as being inactive, and only the open hydroxy acid chain is considered active [23]. However, these patents report that atorvastatin lactol is actually slightly more potent than atorvastatin in an in vitro inhibition assay. Other study confirms the activity of atorvastatin lactol in the low nanomolar range [24]. It is unclear if other statins, such as lovastatin, are active in the closed lactol form. The most potent compounds in these series have substituents in the lactol ring, making it more bulky, and can inhibit HMG-R in vitro with IC_{50} in the high picomolar range. Figure 2 shows the most potent compound and Figure 3 illustrates the claimed chemical space.

The Shanghai Institute of Technology and the Shanghai Ecust Biomedicine Company in 2015 described a set of polysubstituted azoles statin lactones compounds as inhibitors of HMG-R (CN104356118A) [25]. The compounds described in this patent have the structural formula shown in Figure 4. Several of the compounds covered by this patent exhibit IC_{50} values in the range 4–20 nM.

2.1.2. Rosuvastatin derivatives

Similarly to the already described atorvastatin lactols, REDX Pharma and Bradford Pharma also developed rosuvastatin lactols [22,26]. The most potent compound, which is depicted in Figure 5, has a substituent in the lactol ring, and displays an IC_{50} value under 1 nM. Since there are no reports of activity for unsubstituted rosuvastatin lactols, it is possible that the activity of these compounds depends on the presence of substituents on the lactol ring (see Figure 6).

The Shanghai Institute of Technology and the Shanghai Ecust Biomedicine Company published a patent in 2015 covering the use of multi-substituted pyrimidine statins as inhibitors of HMG-R (patent CN104356119A) [27]. The invention protects compounds with the structural formulas presented in Figure 7. Several compounds covered by this patent exhibited IC_{50} values in inhibiting HMG-CoA activity in the range 2.0–10.0 nM.
2.1.3. Lovastatin derivatives

Lovastatin derivatives have in common a hexahydronaphthalene scaffold (Figure 8). A few molecules that resemble lovastatin are described in recent patent literature. One of such molecules is represented in Figure 9 (left), and resembles a simplified version of lovastatin because some substituents are absent. This compound was isolated from Monascus-fermented rice. The inhibition rate has been calculated in vitro at a fixed concentration and is 26.3% at 40 µg/mL. For comparison, lovastatin inhibits at 39.6% at 34 µg/mL, which means the claimed compound is less potent than lovastatin. These results are not directly comparable but since the compounds have similar molecular weights, these conclusions are credible.
A notable lovastatin derivative has been developed by the Academia Sinica, National Taiwan University, with the purpose of inhibiting both HMG-R and histone deacetylases (HDACs) \[28\], which are a target for the treatment of several cancer types. A hydroxamic acid group was attached to the hydroxy acid chain of lovastatin, creating a new molecule that is able to coordinate the catalytic zinc ion in HDACs (Figure 10). Both the patent and an academic publication \[29\] report simultaneous inhibition in the nanomolar range of both HMG-R and HDACs 1, 2, and 6. The concept of targeting both enzymes is supported by reports of synergistic effects in apoptosis of model cancer cells \[30–32\].

A patent published by the Shanghai Institute of Technology and the Shanghai Ecust Biomedicine Company in 2015 describes the use of multi-substituted phenanthrene ring statins as inhibitors of HMG-CoA (patent CN104311517A) \[33\]. Several compounds covered by this patent exhibited IC50 values in inhibiting HMG-CoA activity in the range 0.5–10.0 nM (Figure 11).

### 2.1.4. Pitavastatin derivatives

Another patent by the Shanghai Institute of Technology and the Shanghai Ecust Biomedicine Company (CN104356120A) \[34\], reported in 2015, covers a set of polysubstituted quinoline statin lactone compounds, similar to pitavastatin, with the structural formula described in Figure 12.
At least three compounds covered by this patent have been shown to have an IC_{50} below 3.0 nM in inhibiting HMG-R activity.

The Shanghai Institute of Pharmaceutical Industry submitted a patent describing a set of quinoline compounds (US2011046379A1 [35] and US8349867B2 [36]) with the structural formula presented in Figure 13(a) (published in 2011, priority date 2006). These compounds had also been protected by patents CN101210011A [37], CN101210011B [37], and WO2008077305A1 [38]. At least 15 compounds covered by this patent had reported IC_{50} values in inhibiting HMG-coA activity below 20 μM.

Another patent of the Shanghai Institute of Pharmaceutical Industry (CN101955477B [39] and CN101955477A [40]) reported a group of 2-cyclopropyl-4-substituted thiophenyl quinoline compounds represented in Figure 13(b) (concession date 2012). The patent also discloses a pharmaceutically accepted solvate, an optical isomer or polymorph, and a reaction intermediate compound. Several of the compounds covered by this patent had reported IC_{50} values in inhibiting HMG-R activity in the micromolar range (best 6.5 μM).

The Shanghai Institute of Pharmaceutical Industry published another patent (CN101967123B [41] and CN101967123A [42]) covering a set of molecules based on...
2-cyclopropyl-4-(N-methyl substituted anilino) quinolones (Figure 13(c)) (concession 2012, priority date 2009). Among the molecules reported in this patent are four compounds with IC_{50} values below 10 μM in inhibiting HMG-R activity.

Another patent submitted by the Shanghai Institute of Pharmaceutical Industry (CN102442997A [43] and CN102442997B [44]) describes a set of quinoline derivatives with the structural formula presented in Figure 13(d). In this structure, X represents O, S or N (CH3), R1 is OCH3 or halogen, R2 is H or F, and R is H or halogen or alkyl or alkoxy. The patent covers both the preparation method and its application. Among the compounds covered by this patent are three molecules with IC_{50} values in the range 0.87–2.33 μM.

The Shanghai Institute of Pharmaceutical Industry published another patent (CN102477032A [45] and CN102477032B [46]) disclosing a class of 2-cyclopropyl-4-substituted-phenoxy-quinoline derivatives, with the structural formula represented in Figure 13(e). Ten compounds covered by this patent with IC_{50} values below 10 μM in inhibiting HMG-CoA reductase activity have been presented.

The Shanghai Institute of Pharmaceutical Industry published a patent in 2012 (CN102816203A [47] and CN102816203B [48]) protecting the substituted quinoline compounds is represented in Figure 13(f). The patent also covers a pharmaceutically acceptable salt of the same compounds (i.e. a sodium, potassium, calcium, or hydrochloride salt), and their preparation, medicine combination, and resulting application. These compounds were first found to be in vivo metabolites of a blood-fat-reducing compound and had a reported IC_{50} value of 12.5 μM.

2.1.5. Pravastatin derivatives

Modification of pravastatin resulted in a different scaffold that contains a fully saturated naphthalene backbone and inverted stereochemistry in one of the hydroxyl groups (see Figure 14) [49]. Both the open hydroxyl acid and cyclized lactone form are described, and the IC_{50} values are 69.8 and 25.8 nM, respectively. Animal testing with rabbits provided further indication for the possible use of these compounds for treatment of CVD.

2.1.6. Fluvastatin derivatives

The Shanghai Institute of Technology together with the East China University of Science and Technology reported a patent in 2011 of 4-substituted 3,5-dihydroxy carboxylic acid compounds as inhibitors for HMG-R activity (patent CN102153463A [50]), similar to fluvastatin. The patent also covers their preparation method. One of the compounds covered by the patent -(E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-benzpyrole-2-yl]-3,5-dihydroxy-4,4-difluoro-6-sodium heptanoate – had a reported IC_{50} for HMG-R of 40 nM (Figure 15(a)).

The Shanghai Institute of Technology published another patent in 2011 describing 5-fluorine-substituted-4-hydroxy-3,4,5,6-tetrahydro-2H-pyrane-2-ketone compounds and their preparation (Figure 15(b)) [51]. One of the compounds has a reported IC_{50} of 60 nM for HMG-R activity.

The Shanghai Institute of Technology and the Shanghai Ecust Biomedicine Company also published a patent in 2015 describing a set of polysubstituted indole statin lactone dehydrated compounds (CN104327057A [52]), with the structural formula displayed in Figure 15(c). One of the compounds covered by this patent had a reported IC_{50} of 1.6 nM in inhibiting HMG-R activity, while several displayed IC_{50} below 10 nM.
2.2. Sterol and terpenoid derivatives

A series of sterol derivatives have been patented by the Beijing Peking University WBL Biotech Co., Ltd [53, 54]. These compounds were isolated from Monascus fermented rice, which has been used in Traditional Chinese Medicine. The three distinct molecular scaffolds are summarized in Figure 16. The first scaffolds, shown in figure 16, differ from the third by the presence of a cyclic penthane. The second scaffold differs from the first by the linking carbons 5 and 8 with a peroxide group. The first two compounds have been compared to lovastatin in an in vitro inhibition assay, but values are reported for a single concentration that differs from the concentration used for lovastatin. It is difficult to compare the potency of these inhibitors with other compounds characterized by different experimental setups.

A series of three patents claim a small set of pentacyclic triterpene natural products that can be extracted from plants. A range of extraction methods, plants, and possible food preparations are described, suggesting a possible nutraceutical application for the compounds.

The claimed chemical space is well defined and counts with only two substituents, H and OH, in two positions, X and Y, depicted in Figure 17.

In vivo tests assessed the efficacy of an extract from Amelanchier alnifolia berries in lowering plasma cholesterol and in decreasing LDL. This extract contained about 4% of euscaphic acid and was administered at 100 mg/kg. Hamsters fed with a cholesterol-rich diet were subject to a positive control with ezetimibe, which had a pronounced effect, and to the extract, which had a small but significant effect after 29 days.

2.3. Peptide inhibitors

Several companies are also developing small peptides derived from plant proteins that show promising hypocholesterolemic effects. These compounds started to be developed based on the observation that Asian populations, who consume soy foods as a dietary staple, have a lower incidence of CVDs than those who consume a typical Western diet [55]. Several animal and human clinical studies revealed that the proteins present in soybeans are capable of decreasing LDL-C, without affecting the high-density lipoprotein (HDL) cholesterol (the ‘good’ cholesterol) [56–58]. Interestingly, it was also reported that the consumption of soybeans does not appear to have a hypocholesterolemic effect in adults with low or normal cholesterol levels [59].

The mechanism that is responsible for the hypocholesterolemic effect has however not yet been fully clarified. Some studies indicate that when soybean protein is consumed, cholesterol absorption and/or bile acid reabsorption is impaired. Others propose that it produces some changes in the endocrine status and thyroid hormone concentrations. In any of the cases, it leads to a metabolic change on the organisms that includes decreased cholesterol synthesis, increased bile acid synthesis (or fecal bile acid excretion), increased apolipoprotein B or E receptor activity, and decreased hepatic lipoprotein secretion and cholesterol
content (which are associated with an increased clearance of cholesterol from the blood).

The active components of soybeans that promote the hypocholesterolemic effect are not fully identified. So far, it is known that soybeans contain a mixture of isoflavones, saponins, and proteins. The proteins available on soybeans (mainly β-conglycinin and glycinin) are believed to be mainly responsible for the cholesterol-lowering effect of soybeans. However, the active compounds are only small peptides that result from the degradation of these proteins after digestion [60,61]. For example, Lovati and coworkers were able to isolate the peptide LRVPAGTTFFYVVNPDNSLRLMIA that was obtained after the digestion of soybean β-conglycinin. This compound was shown to increase LDL uptake in human HepG2 cells by 41% [62].

Lammi and coworkers have also shown that the peptides YVVNPDNSI and YVVNPDNSIN can be competitive inhibitors of HMG-R activity with a statin-like mechanism [63]. The same authors have also identified several small peptides from soybean glycinin, such as AVPGEVA, IAVPTGVA, and LPYP that are capable of altering cholesterol metabolism in HepG2 cells through activation of the LDL receptor (LDL-R) sterol regulatory-element-binding protein 2 and inhibition of HMG-R [64].

Lunasin is another soy-derived bioactive small peptide composed by 43 amino acids residues (SKWQHQQDSCRRKQ-KQGVNLTPCEKHIKEIQG-RGD-DDDDDDDD) that has been shown to reduce the serum LDL cholesterol levels by two pathways [65,66]. First, it selectively inhibits the expression of HMG-R gene and makes it unavailable for the liver to conduct cholesterol synthesis. Second, it increases expression of the LDL-R gene, which increases the quantity of receptors to clear LDL-C from the bloodstream. This compound has been patented by Galvez et al. as a product and method to lower total and LDL-C levels using soy peptides [61,67–69].

A set of small peptides have also been isolated and identified as promising targets to inhibit HMG-R. Some examples of recent patents include the dipeptides DI [70], SD [71], QD [72], ST [73], and DL [74].

Other groups have also generated new peptides that mimic the bioactive conformation of statins and inhibit HMG-R [75]. These compounds were generated by theoretical means, and based on a method that correlates the structural similarity between the binding sites of statins and other peptide molecules that are known to be HMG-R inhibitors. The top scored compounds, IAIVP, IAVE, YAVE, IVAE, and YVAE were subsequently synthesized and their activity measured in vitro. These assays have shown that among all peptides, YVAE showed the highest ability to inhibit HMG-R. A kinetic analysis revealed that this peptide is a competitive inhibitor of HMG-R with an inhibition constant of 15.2 ± 1.4 μM.

In Table 1 are listed the most promising HMG-CoA Reductase peptide inhibitors that were discussed in this section.

3. Combination of statins with other drugs for CVD

Even though statins are very effective at lowering cholesterol levels, CVD has a complex set of risk factors and causes and, as such, it should be mitigated in several fronts, for example decreasing of triglycerides levels, inhibition of cholesterol absorption in the intestine, and lowering the blood pressure. This multi-target therapeutic approach has already been proven beneficial in the past for CVDs (combination of atorvastatin and amlodipine, a calcium channel blocker, for example), and other diseases like type 2 diabetes, viral infection, and cancer [76]. The tendency for multi-target therapies over traditional one drug/target approach was also manifest in our patent search: we found 147 patents describing compositions that combine statins with other drugs with the objective of fighting CVDs.

The following sections focus on the medications that were the subject of a larger number of patents. The list is not exhaustive, many other molecules are presented in these patents in combination with statins: calcium channel blockers, fibrates, ubiquinone, emulsifiers of atherosclerotic plaque, cholesterylester transfer protein (CETP) inhibitors, tocotrienol, microsomal triglyceride transfer protein (MTP) inhibitors, among others (see full list of patents in Supplemental data).

### 3.1. Omega-3 fatty acids

Omega-3 fatty acids, in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce the levels of triglycerides in the blood. They are currently used for treating hypertriglyceridemia (HTG), and they have other benefits for CVD, including reduction of blood pressure, atherogenic cholesterol, remnant lipoproteins, inflammation, atherosclerosis progression, arrhythmia risk, and thrombosis risk [77,78]. The mechanisms of action of omega-3 fatty acids are not completely understood, but may include the inhibition of diacylglycerol acyltransferase-2 (DGAT2) and subsequent decreased lipogenesis in the liver, as well as increased plasma lipoprotein lipase activity and B-oxidation [78].

Coadministration of omega-3 drugs and statins improves the circulating lipoprotein lipid profile in comparison with sole administration of statins [79]. In the last 5 years, 37 patents have been published (IDs 31–67 in Table 1 of the Supplemental data) referring to mixed formulations of statin and omega-3 fatty acids, namely EPA and DHA.

### 3.2. Niacin

Niacin (nicotinic acid or vitamin B3) main target is also the DGAT2 enzyme in hepatocytes, which is involved in the synthesis of triglycerides. Synergetic effects on other tissue cells
(adipocyte, endothelium, macrophages) contribute further to the niacin beneficial profile [80]. Niacin, when taken alone, reduces LDL cholesterol and the level of triglycerides, while increasing the levels of HDL cholesterol. All these effects are associated with lower risk of CVD [81].

A recent review, however, found that the administration of niacin together with statins does not contribute further to reducing all-cause mortality, CHD mortality, myocardial infarction, or stroke [82]. Even so, there are eight patents (IDs 25–30 in Table 1 of the Supplemental data) about mixed compositions of niacin with statins.

3.3. Renin–angiotensin system

The Renin–angiotensin system (RAS) mediates several processes that control blood pressure. Its main biochemical components are the enzymes renin and ACE (angiotensin-converting enzyme), which convert angiotensinogen to angiotensin I and then to angiotensin II, respectively. Angiotensin II acts on several tissues and has the overall effect of inducing vasoconstriction and thus increasing blood pressure. Inhibitors of renin and ACE, as well as antagonists of angiotensin II are clinically used to treat hypertension [83].

Concomitant therapy of statins and antihypertensive medication is very effective at reducing CVD risk [84,85]. Formulations with both active principles would increase patient compliance, and possibly diminish adverse interactions. Over the last 5 years, 40 patents (IDs 121–136 in Table 1 of the Supplemental data) were published with compositions that include statins and drugs that target RAS.

3.4. Bile acids sequestrants and cholesterol intestinal absorption inhibitors

Bile (composed mainly by bile acids and cholesterol) is released in the duodenum to help in the digestion of lipids, and is then reabsorbed in the ileum. About half of the cholesterol produced by the body daily is used for bile acid synthesis. Inhibition of cholesterol reabsorption or bile acids sequestration in the intestine are then effective and complementary ways of lowering circulating cholesterol [86].

A particular combination of simvastatin with ezetimibe, a cholesterol absorption inhibitor, has been on the market since 2004, under the name of Vytorin. On our search, we found 11 patents (IDs 137–147 in Table 1 of the Supplemental data) that describe combinations of statins with absorption inhibitors and bile acids sequestrants.

3.5. Proprotein convertase subtilisin/kexin type 9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme than upon binding to the LDL receptor promotes its degradation. By inhibiting this process, clearance of LDL from circulation is augmented, and the levels of cholesterol in the blood decrease. The most common clinical strategy to inactivate PCSK9 is to use monoclonal antibodies specific to this protein [87].

These antibodies are a second-line treatment for hypercholesterolemia, especially useful when statins alone do not decrease LDL concentration satisfactorily [87]. We found nine patents (IDs 112–120 in Table 1 of the Supplemental data) published over the last 5 years that evaluated the concomitant treatment of statins with the administration of PCSK9 antibodies.

4. The role of statins in other diseases

Statins are competitive inhibitors of HMG-R that are largely used to treat dyslipidemias. These inhibitors are very effective, appropriately absorbed, and can be tolerated during long-term treatments. More recently, statins have been pointed out as powerful molecules with an impressive range of effects in the human body. In addition, they present a wide range of potential applications in many other disorders, such as neurodegeneration and neurodevelopmental diseases, different types of cancers and infections [79].

It was proposed that statins exhibit cholesterol-independent effects (pleiotropic effects), possibly through alterations in isoprenoid levels [89]. During cholesterol synthesis, and metabolic pathways, statins inhibit HMG-R leading to underproduction of mevalonate and nonsteroidal isoprenoids (farnesyl pyrophosphate and geranylgeranyl pyrophosphate). This inhibition appears to induce effective biochemical and behavioral improvements on several diseases, infections, and cancers [90]. On one hand, it was suggested that statins act by reducing the isoprenoid levels, inhibiting the isoprenylation of small GTP proteins (GTPases), such as Ras, Rho, and Rac [91]. More specifically, these GTPases are involved in numerous signaling pathways, including synaptic plasticity and cognition [92]. On the other hand, it was also proposed that statins may be involved in the peroxisome proliferator-activated receptor-α (PPARα)-cAMP-response element binding protein (CREB) pathway [93], as well as in the regulation of the oxidative stress and lipid peroxidation, by reducing reactive oxygen species [94].

Considering the large diversity of biomolecules produced by the mevalonate pathway, it is expected that statins may have many different pleiotropic effects on diverse diseases. Here, we will briefly describe the illnesses that were more frequently mentioned in the patents of statins’ composition published through 2011 till 2015. The complete list of patents (115 patents) is shown in Table 2 of the Supplemental data.
4.1. Inflammatory and autoimmune diseases

Further to its lipid-lowering properties, the benefits of statin-based therapy involve direct vascular effects, anti-inflammatory activity, and prevention of thrombosis (atherosclerotic vascular disease). It was proposed that statins might modify apoptosis in vascular endothelial cells, resulting in altered vascular function, and might also significantly reduce the risk of stroke and vasculopathy post-transplant. Statins have a wide range of anti-inflammatory effects in various tissues, as they suppress vascular and myocardial inflammation (reducing circulating C-reactive protein and proinflammatory cytokines levels); they favorably control the vascular and myocardial redox state (reducing vascular reactive oxygen species’ generation) and they increase the nitric oxide bioavailability [95].

The beneficial effects of statins on inflammatory diseases are evidenced in 22 patents listed in SI (IDs 64–85 in Table 2 of the Supplemental data, and 5 of each are also directed to immune diseases) that describe pharmaceutical compositions involving statins (e.g. a mixture of an inosine monophosphate dehydrogenase inhibitor with a statin) or isolated statin compounds. Compositions including atorvastatin may be used for treating vascular, autoimmune, and inflammatory diseases (IDs 65 and 71 in Table 2 of the Supplemental data), whilst a combination of pemrolast and a statin selected from pitavastatin, fluvastatin, simvastatin, lovastatin, rosuvastatin, pravastatin, and atorvastatin could also be used in inflammatory disorders (ID 74 of Table 2 of the Supplemental data). The rosuvastatin combined to a PDE4 inhibitor is used for the inflammatory pulmonary disease (IDs 67 and 77 in Table 2 of the Supplemental data), whereas its combination with metformin is used for autoimmune disease (ID 82 in Table 2 of the Supplemental data). These combinations significantly improve the treatment of vascular, autoimmune (such as multiple sclerosis), and inflammatory diseases, as well as immunological processes.

4.2. Cancer

In the past years, statins are suggested as potential agents to prevent cancer growth. They have potential therapeutic activity in a wide range of cancer types, such as breast, gastric, pancreatic, lung, colorectal, ovarian and prostate carcinoma, neuroblastoma, melanoma, mesothelioma, and acute myeloid leukemia cells. It was proposed that their modes of action involve exerting proapoptotic effects (inducing cell death with different sensitivities), anti-angiogenic effects (inhibiting angiogenesis by downregulation of pro-angiogenic factors, decreasing endothelial cell proliferation and reducing of adhesion to extracellular matrix by blocking ICAMs) and immunomodulatory effects (regulation of genes encoding key molecules that are involved in antigen presentation or involving the downregulation of the nuclear factor-kappa B, which is responsible for the transcription of several genes involved in immunologic pathways) [96].

There are 17 recent patents included in Table 2 of Supplemental data (IDs 28–44; 11 are general, whilst the other are specific for gastric (1), breast (2), prostate (1), lymphoma (1), and prostate/colon/pancreatic (1) cancers) supporting the ability of statins for treating, preventing, or ameliorating neoplasia. The patents propose several compositions containing statins for inhibition and reduction of metastasis in cancers, provide a cisplatin-resistant cancer cytotoxic agent, as well as present methods with novel combinations (e.g. lovastatin with an interferon and concurrent administration of selenium and calcium, ID 43 of Table 2 of the Supplemental data) that are more effective, tolerable, and less expensive than previous therapies. For example, lovastatin combined with a taxane may be used for the treatment of gastric cancer (ID 31); fluvastatin can be used for preparing antitumor drugs targeting the lymphoma (ID 34) and a low-dose combination of atorvastatin and hydrochlorothiazide can effectively inhibit growth of prostate cancer cells, pancreatic cancer cells, and colon cancer cells (ID 39). Atorvastatin, simvastatin, lovastatin, pitavastatin, fluvastatin, mevastatin, pravastatin, rosuvastatin, cerivastatin, compactin molecules (alone or in combination with conventional therapy) can be used for the treatment of breast cancer (IDs 30, 32, 36, 37, 43, and 44 of Table 2 of the Supplemental data).

4.3. Diabetes mellitus and metabolic diseases

Type 2 diabetes can be characterized by hyperglycemia, insulin resistance (that contributes to the abnormal lipid profile), or insulin deficiency. This metabolic disease is accompanied by hyperlipidemia that contributes to increased cardiovascular events. As statins mainly act by lowering LDL-C levels and have minor effects on other lipoproteins, their use is only recommended for diabetics with normal LDL levels. However, recently, it was observed that statins may have diabetogenic potential in patients with cardiovascular risk factors. In 2012, the US FDA changed the statin safety label, saying that statins may increase glycosylated hemoglobin and fasting serum glucose levels. This harmful effect of statins in diabetes may occur by different mechanisms such as downregulation of GLUT4 expression on adipocyte cells, which can lead to decrease in insulin-mediated cellular glucose uptake [97].

Fortunately, in the past years, 16 patents (IDs 45–60 in Table 2 of the Supplemental data) were published with novel pharmaceutical combinations including statins (e.g. acetyl L-carnitine mixed with an antihypertensive drug and a statin) that have the ability to prevent and reduce the risk of developing diabetes induced by the statin therapy. Some of these mixed formulations promote insulin secretion, reduce insulin resistance, and enhance insulin sensitivity. The statin compounds included in these compositions are simvastatin (the preferred one), lovastatin, pravastatin, compactin, fluvastatin, dalvastatin, atorvastatin, rosuvastatin, pitavastatin, itavastatin, bervastatin, cerivastatin, crilvastatin, dalvatatin, tenivastatin, and mixtures thereof.

Furthermore, three other patents (IDs 61–63 in Table 2 of the Supplemental data) were recently published describing compositions comprising a statin (e.g. a biguanide compound combined with a statin, such as lovastatin, atorvastatin, fluvastatin, rosuvastatin, simvastatin, pravastatin, pitavastatin, or mevastatin) and methods to reduce cardiometabolic risk and improve the treatments of lipid metabolic diseases and metabolic syndrome.
4.4. Asthma, respiratory diseases, and inflammation

Statins also exhibit pleiotropic effects in decreasing oxidative stress and inflammation. They also interfere with the pathophysiology of asthma due to their role in enhancing airway smooth muscle contraction and airway hyperresponsiveness [98].

There are several studies suggesting that statins may reduce airway inflammation in asthmatics, mainly smokers and obese patients who respond poorly to the main anti-inflammatory medications (glucocorticoids, leukotriene modifiers, and anti-IgE antibody). However, statins do not allow for a significant improvement on lung function [99]. Recently, 10 patents (IDs 8–17 in Table 2 of the Supplemental data) pointed out medicinal compositions containing statins as medications to treat asthma and respiratory diseases. Although the statins lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, or pitavastatin may be used for this kind of diseases, the preferred one is rosuvastatin.

4.5. Bone regeneration

Another important pleiotropic effect of the statins is its ability to act as therapeutic agents in the area of bone regeneration, periodontal diseases, and bone tissue engineering. Statins may also have the potential to inhibit inflammatory arthritis, acting as protective agents against chondrocyte aging and degeneration of articular cartilage during the progression of osteoarthritis (OA). It was proposed that statins inhibit the IL-1β-induced production of cartilage matrix degrading the metalloprotease-1 and -13 enzymes and cellular senescence of chondrocytes [100]. Although the effect of statin on matrix metalloproteinases is mainly dependent of the inhibition of the mevalonate isoprenoid derivatives production, it was suggested a possible additional mechanism for statin in counteracting OA involving cartilage degeneration. The fact that statins can greatly improve the process of bone turnover and regeneration, making them as a possible solution to the destruction of cartilage by inflammation (as occurs in OA) in the field of orthopedics [101]. These effects, compositions containing statins and methods to treat osteoporosis, as well as the description of osteoconductive matrices and medical devices to sustain the release of statins on the fracture sites were clearly evidenced in 10 recent patents (IDs 18–27 in Table 2 of the Supplemental data). For example, the combination of vitamin D and simvastatin may be used for treating osteoporosis, whilst an implantable osteoconductive matrix can comprise cerivastatin, atorvastatin, simvastatin, pravastatin, fluvastatin, lovastatin, rosuvastatin, eptastatin, pitavastatin, velostatin, fluviodostatin, mevastatin, dalvastain, or a combination thereof.

4.6. Neurodegenerative disorders

Statins seem to have a therapeutic role in neurodegenerative disorders, such as dementia (including Alzheimer’s disease and Parkinson’s disease) [102], and neurodevelopmental disorders/autistic syndromes (such as Rett syndrome, fragile X syndrome, neurofibromatosis, and tuberous sclerosis). In addition, statin therapies also appear to have an antidepressant effect [103]. Interestingly, the cholesterol levels in brain are minimally affected by statin-based therapy, which do not compromise other cholesterol functions [90].

Four recent patents (IDs 2–5 in Table 2 of the Supplemental data) propose pharmaceutical compositions containing statins (atorvastatin, lovastatin, simvastatin, pravastatin, fluvastatin, rosuvastatin, cerivastatin and mevastatin) as treatments for Alzheimer’s disease and cognitive disorders, and another two patents (IDs 6–7 in Table 2 of the Supplemental data) relate statin (e.g. pravastatin) compositions with the prevention and treatment of damage in auditory neurons and ocular neurodegeneration (glaucoma). Amyotrophic lateral sclerosis (ALS) is an adult-onset motor neuron disease that causes progressive paralysis of skeletal muscles. It can be induced by dominant mutations in the gene encoding the Cu/Zn superoxide dismutase-1 (SOD1) enzyme [104]. A patent published in 2011 (ID 1 in Table 2 of the Supplemental data) also reports a formulation containing the atorvastatin that can be used as prophylactic and therapeutic drug for ALS prevention by determining the amount of SOD1 expressed using an astrocyte differentiated from induced pluripotent stem (iPS) cells from fibroblasts.

4.7. Other diseases

Analyzing the patents published in the last 5 years, we observe a pleiotropic effect of statins, when used alone or combined with other molecules. One patent (listed in Table 2 of the Supplemental data) was published relating statins to the prevention and treatment of arrhythmia (ID 94), HIV infections (ID 107), bacterial infections (ID 95), dental caries (ID 96), migraine (ID 86), scar formation (e.g. hypertrophic scars) (ID 88), biological tissue repair (ID 89), vascular dysplasia (e.g. cerebral cavernous malformation) (ID 90), gout (ID 91), chronic subdural hematoma (ID 101), drug addictions or in stopping drug consumption (ID 102), nonalcoholic fatty liver disease (ID 104), progeria (Hutchinson–Gifford syndrome), physiological ageing (ID 87), obesity (ID 103), and macular degeneration (ID 108). Two additional patents (listed in Table 2 of the Supplemental data) were published concerning the beneficial effects of statins to prevent and treat hepatitis C (IDs 105–106) and kidney diseases (e.g. renal ischemic damage) (IDs 92–93), as well as, four patents (IDs 97–100 in Table 2 of the Supplemental data) describing novel cosmetic and dermatological composition comprising statins for the treatment of skin and hair disorders.

Similar to what happened with the negative pleiotropic effect of statins in diabetes, the use of these molecules alone may have side effects in other conditions, such as myalgia, muscle toxicity, erectile dysfunction, rhabdomyolysis, renal toxicity, and myopathy. In the last 5 years, seven patents (IDs 109–115 in Table 2 of the Supplemental data) present innovative pharmaceutical compositions containing statins with other molecules to overcome the damaging effects caused by administration of statin-based therapy. For example, atorvastatin combined with losartan treats hypertension and prevents muscle-related side effects, while a composition containing a statin and β-hydroxy β-methylbutyrate prevents
the occurrence of myalgias or myopathic side effects involved in long-term use of the statins.

5. Conclusion

HMG-R is currently the main target to control cholesterol levels in the bloodstream. This enzyme is part of a complex and multistep biosynthetic pathway composed of more than 30 enzymes that are essential to produce cholesterol in cells, as well as other precursors required in the biosynthesis of steroid hormones and bile acids.

It is often desired to target enzymes that are located at the latest stages of a biosynthetic pathway. However, HMG-R is not one of these cases. This happens because all the attempts to inhibit the enzymes at the latter stages of cholesterol biosynthesis lead to the accumulation of their substrates, which was found to be highly toxic [105]. The substrate of HMG-R is, on the other hand, water soluble and there are alternative metabolic pathways for its breakdown when HMG-R is inhibited. Its accumulation does not offer any significant risk of toxicity and this has turned HMG-R into an attractive target to inhibit cholesterol biosynthesis.

Statins have been specifically developed by the pharmaceutical industry to inhibit HMG-R. The current commercial available statins, such as atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin, have been prescribed to millions of patients for nearly 30 years and provided incalculable benefits for their health. No other drug that is available on the market has been more evaluated and its risk more assessed than statins. However, as any drug, some patients have also observed few adverse effects and others have failed to reach LDL-C targets. This has prompted the pharmaceutical industry to seek for new ways to control cholesterol levels in the bloodstream.

As the inhibition of other enzymes in the cholesterol biosynthesis continues to present several undesirable side-effects, HMG-R is still an attractive and effective target to inhibit cholesterol biosynthesis. Most of the new inhibitors targeting HMG-R are derivatives of the commercially available statins, but new types of inhibitors with different chemical entities and scaffolds are also being developed. In this regard, the steroid, terpenoid derivatives and small peptides are currently gaining some importance in many therapeutic areas. Particular importance is being given to the peptidic derivatives since they are highly selective, efficacious and, at the same time, relatively safe and well tolerated.

The inhibition of HMG-R also interferes with the synthesis of many other nonsteroidal isoprenoidic compounds that have mevalonate as precursor (the product of HMG-R). As all of these compounds are involved in many different cellular functions, statins can also produce an impressive range of effects in the human body. Recent studies have gathered a deeper understanding of these effects and have found that the commercial available statins can also be used in the treatment of other diseases, such as neurodegeneration and neurodevelopmental diseases, different types of cancers and infections, diabetes, asthma, bone regeneration, among others.

All these new findings indicate that in the near future statins will continue to be a valuable and effective treatment in many therapies. It will undoubtedly continue to be the top drug of choice to lower down the levels of cholesterol in the bloodstream and therefore in the treatment of CVDs. In addition, new therapeutic uses of statins will also be revealed. Particular importance is being given in neurodegenerative diseases and cancer.

6. Expert opinion

Statin therapy has been a case of success. The finding of two generations of very potent and efficient inhibitors of HMG-CoA reductase, and the demonstration in a number of clinical trials that they do lower the risk of acute cardiovascular events (one of the most relevant factors of mortality worldwide) made the statins the mainstay of cholesterol treatment. However, all statins have been reported to cause adverse side effects, especially when administered at high doses, and this is their most relevant weakness.

The ultimate goal in this field should be to avoid the deleterious side effects of the drugs, as the efficiency of the drugs is already very high. Statins do reduce circulating LDL levels to below the recommended thresholds in most patients if an adequate dose is used. However, dose is still limited by side effects.

The benefits of statins are unquestionable for people suffering from CVD, and in many cases they overcome the secondary effects the drugs might have. However, such trade-off is much less clear when statins are used in healthy individuals that have no additional risk factors beyond having high LDL cholesterol levels in the blood. Therefore, the main goal of research on HMG-R inhibition should be to find out new drugs that are equally potent and efficient but that have a better safety profile.

It is our opinion that the main challenge for this field is the understanding of the source of the side effects they provoke. The effort made for understanding the underlying physiological effects of statins is clearly insufficient. It is a shame that the side effects of one of the most widely sold drug classes in the world are still poorly understood. Nowadays, the effort is focused in trying to find new drugs, new scaffolds with the hope, or the faith, that they might show less toxicity. We do not believe that this method will lead to great advances in the future. The quest for affinity is already gained, and better affinity will not solve the problem. The quest for a better safety profile is the way forward, and it will probably not succeed by blind trial and error. Instead, the way forward should pass through serious physiology studies, to definitively clarify the mechanism causative of myopathies (and other malignancies) in people having statins and, only after, to derive new drugs that overcome these side effects, in a conscientious and rational manner. The pleiotropic effects of HMG-R inhibitors, many of them not related to the impairing of the mevalonate pathway, are a clear suggest that statins are acting on multiple targets, most of them unknown at present. The pharmaceutical industry has been successful in the past in avoiding specific side targets. The advent of massive bioinformatics and computational tools is gaining a growing importance in this regard. The pursuit of ‘intelligent specificity’ is the way to the future, if we want to keep
these formidable drugs in the market, increasing their health value. Again, such pathway must be based in serious physiology studies that tell us exactly from where the side effects of statins come from. Such approach might help also to tackle the cases of risk patients that do not achieve the desired LDL levels, by allowing an increase in the dose, together with the administration of coadjuvant therapies.

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Declaration of interest

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