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Pharmacological Actions of Statins: A Critical Appraisal in the Management of Cancer

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Abstract—Statins, among the most commonly prescribed drugs worldwide, are cholesterol-lowering agents used to manage and prevent cardiovascular and coronary heart diseases. Recently, a multifaceted action in different physiological and pathological conditions has been also proposed for statins, beyond anti-inflammation and neuroprotection. Statins have been shown to act through cholesterol-dependent and -independent mechanisms and are able to affect several tissue functions and modulate specific signal transduction pathways that could account for statin pleiotropic effects. Typically, statins are prescribed in middle-aged or elderly patients in a therapeutic regimen covering a long life span during which metabolic processes, aging, and concomitant novel diseases, including cancer, could occur. In this context, safety, toxicity, interaction with other drugs, and the state of

health have to be taken into account in subjects treated with statins. Some evidence has shown a dichotomous effect of statins with either cancer-inhibiting or -promoting effects. To date, clinical trials failed to demonstrate a reduced cancer occurrence in statin users and no sufficient data are available to define the long-term effects of statin use over a period of 10 years. Moreover, results from clinical trials performed to evaluate the therapeutic efficacy of statins in cancer did not suggest statin use as chemotherapeutic or adjuvant agents. Here, we reviewed the pharmacology of the statins, providing a comprehensive update of the current knowledge of their effects on tissues, biological processes, and pathological conditions, and we dissected the disappointing evidence on the possible future use of statin-based drugs in cancer therapy.

I. Introduction

Many studies have highlighted the fact that statins, besides their application in cardiovascular and coronary heart diseases as cholesterol-lowering agents, exhibit a wide range of pleiotropic effects that may significantly contribute to the treatment of conditions other than cardiac diseases, such as inflammatory and neurological pathologic conditions and even tumors. The commonly known pharmacological activity of statins relies on a potent inhibition of the endogenous mevalonate pathway, which leads directly to the biosynthesis of cholesterol and isoprenoids. Statins bind to mammalian HMG-CoA reductase at nanomolar concentrations, leading to an effective displacement of the natural substrate HMG-CoA, which binds instead at micromolar concentrations (Moghadasian, 1999). The interactions between statins and HMG-CoA reductase prevent the conversion of HMG-CoA to L-mevalonate resulting in the inhibition of the downstream cholesterol biosynthesis and numerous isoprenoid metabolites such as geranylgeranyl pyrophosphate (GGPP¹) and farnesyl pyrophosphate (FPP)

(Fig. 1). GGPP and FPP are lipid attachments that constitute key intermediates for post-translational events of several cell signaling proteins, including the small GTPase family members Ras, Rac, and Rho (Chow, 2009). The attachment of these lipids also known as isoprenylation is fundamental for the activation and intracellular transport of these proteins that act as molecular switches controlling multiple pathways and cell functions such as maintenance of cell shape, motility, factor secretion, differentiation, and proliferation. Considering that the key role of these prenylated proteins is an obvious expectation that statin effects may extend beyond their cholesterol-lowering actions. These cholesterol-

endothelial progenitor cells; ER, endoplasmic reticulum; ERK, extracellular signal-regulated protein kinase; FOLFIRI, folinic acid (leucovorin)/5-FU/irinotecan; FPG, fasting plasma glucose; FPP, farnesyl pyrophosphate; GGPP, geranyl-geranyl pyrophosphate; HCC, hepatocellular carcinoma; HDL-C, high-density lipoprotein cholesterol; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; JNK, c-Jun NH₂-terminal kinase; LDL-C, low-density lipoprotein-cholesterol; LFA-1, lymphocyte function-associated antigen-1; MAPK, mitogen-activated protein kinase; MHC, major histocompatibility complex; MS, multiple sclerosis; NF- κ B, nuclear factor- κ B; NSAID, nonsteroidal anti-inflammatory drug; OATP, organic anion transporting polypeptide; P450, cytochrome P450; P-gp, P-glycoprotein; PI3K, phosphatidylinositol 3-kinase; RAD-001, everolimus; RR, relative risk; SCC, squamous cell carcinoma; SMC, smooth muscle cell; STAT, signal transducer and activator of transcription; TACE, transarterial chemoembolization; TGF- β , transforming growth factor β ; UGT, UDP-glucuronosyl transferase; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

¹Abbreviations: 5-FU, 5-fluorouracil; A β , amyloid β ; AD, Alzheimer disease; Akt, protein kinase B; AML, acute myeloblastic leukemia; APP, amyloid precursor protein; ARF, ADP-ribosylation factor; ATRA, all *trans*-retinoic acid; AUC, area under the concentration versus time curve; BMD, bone mineral density; CAD, coronary artery disease; Cav1, caveolin-1; CI, confidence interval; CIITA, MHC-II transactivator; COX, cyclooxygenase; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; eGFR, estimated glomerular filtration rate; eNOS, endothelial nitric-oxide synthase; EPC,

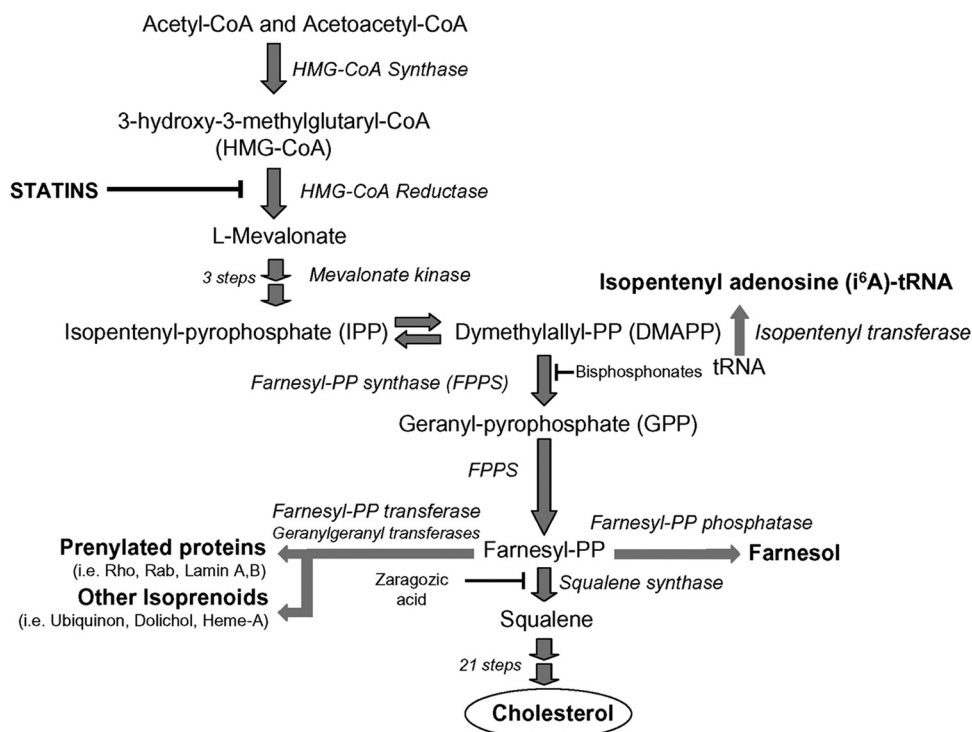


FIG. 1. The mevalonate pathway. Statins act by inhibiting HMG-CoA reductase, the key enzyme of the mevalonate pathway. Statins could have pleiotropic effects possibly through other products of the mevalonate pathway (e.g., i^6A tRNA, prenylated proteins, and other isoprenoids) that play central roles in cell signaling, protein synthesis, and cytoskeletal organization.

independent effects are known as pleiotropic effects and include, among others, improvement of endothelial function, inhibition of vascular inflammation and oxidation, and stabilizing of atherosclerotic plaques (Zhou and Liao, 2010).

In the present study, the pharmacology, mechanism of action, and metabolism of statins are reviewed, as well as their effects on tissues and numerous biological processes, such as those involved in the immune system, endothelia, smooth muscle, platelet function, in the metabolism, in the bone, and in the nervous system. Furthermore, a careful analysis is undertaken to provide a comprehensive view of pros and cons of the statin effects in cancer, including their cancer risk and prevention, their potential application as chemopreventive agents, and their use in combination with currently adopted chemotherapeutics.

II. The Isoprenylated Proteins

In the 1980s, studies on cholesterol biosynthesis led to the discovery that a compound derived from mevalonic acid, other than cholesterol, is incorporated into a specific set of protein-containing cysteine linked to a 15-carbon farnesyl or a 20-carbon geranylgeranyl group (Glomset et al., 1990). The synthesis of FPP and GGPP is catalyzed by FPP synthase and GGP synthase, respectively. FPP and GGPP are substrates of isopentenyl transferase involved in post-translational prenylation of a variety of proteins (Casey and Seabra, 1996). Three

distinct heterodimeric protein isoprenyl transferases have been described in metazoans, protozoans, fungi, and plants. Protein farnesyltransferase transfers a farnesyl group from farnesyl diphosphate to the cysteine residue of a carboxyl terminal CaaX motif (where "C" is cysteine, "a" is an aliphatic amino acid, and "X" is usually methionine, glutamine, serine, alanine, or cysteine) (Yokoyama et al., 1992). Protein geranylgeranyltransferase type I usually transfers a geranylgeranyl group from geranylgeranyl diphosphate (GGPP) to the cysteine residue of a similar CaaX motif (where "X" is leucine or isoleucine) (Taylor et al., 2003). Protein geranylgeranyltransferase type II (also called Rab geranylgeranyltransferase) transfers two geranylgeranyl groups from GGPP to the cysteine residues of XCCXX, XXCXC, XXCCX, XXXCC, XCXXX, or CCXXX motifs at the carboxyl terminus of Rab proteins bound to the Rab escort protein (Leung et al., 2006). After the attachment of the isoprenoids, proteins undergo two additional post-translational modifications, collectively referred to as CaaX processing. The diphosphate is cleaved off by the Ras-converting enzyme, and the Ste24p endogenous proteases remove the terminal three amino acids (-aaX). Upon cleavage of the terminal tripeptide, the remaining prenylated cysteine residue undergoes carboxymethylation by a methyl group, delivered from *S*-adenosylmethionine. This conversion is catalyzed by isoprenylcysteine carboxyl methyltransferase, which is located in the Golgi apparatus, ER, and nuclear membranes. Under

physiological conditions, the carboxymethylation is reversible. It is assumed that the intermediates during these subsequent enzymatic reactions exist only transiently and are rapidly converted into the mature prenylated proteins (Winter-Vann and Casey, 2005). Overall, prenylation enhances lipophilicity and favors lipid-lipid interactions of these proteins with cellular membranes, although, in many cases, the modified C terminus is important in protein-protein interactions as well (Zhang and Casey, 1996). Proteins containing a carboxyl-terminal CAAX motif are small GTPases proteins that play a fundamental role in a multitude of intracellular signal transduction pathways involving vesicle trafficking, cell growth, differentiation, and cytoskeletal function (Konstantinopoulos et al., 2007). RAS proteins containing the CAAX motif are members of this family and are particularly interesting because of their well established role in oncogenesis. H-Ras, K-Ras, and N-Ras are the most renowned members of this family and they are constantly activated because of the mutation in the proto-oncogen (Downward, 2003). Furthermore, the majority of the Ras subfamily members are known to be farnesylated and, interestingly, K-Ras and N-Ras but not H-Ras can be geranylgeranylated when physiological farnesylation is inhibited (Brunner et al., 2003; Downward, 2003). Several other CAAX proteins are involved in the initiation and progression of cancer, such as the RHO family of GTPases, which includes RAC and cell division cycle 42, which is implicated in both oncogenesis and metastasis (Ridley, 2001). Increased signaling by yet another GTPase, RAP1A, has been associated with myeloproliferation (Ishida et al., 2003). The 60 Ras-like proteins in the brain (Rab) represent the largest group within the superfamily of small GTPases (Pereira-Leal et al., 2001) and are mainly involved in intracellular vesicular transport (Zerial and McBride, 2001; Kimura et al., 2008; Bergbrede et al., 2009; Zhu et al., 2009).

Aberrant expression of RAB has also been documented in a variety of cancers. RNA microarray analyses demonstrated that approximately 50% of the RAB genes are overexpressed in ovarian cancer. RAB25 is also up-regulated in prostate cancer and transitional-cell bladder cancer (Cheng et al., 2004). Overexpression of RAB5A and RAB7 has been documented in thyroid adenomas, and RAB1B, RAB4B, RAB10, RAB22A, RAB24, and RAB25 are up-regulated in hepatocellular carcinomas and cholangiohepatomas (He et al., 2002; Croizet-Bergeret et al., 2002). The ADP-ribosylation factor (ARF) and secretion-associated and Ras-related proteins are mainly involved in vesicle formation and intracellular trafficking (Takai et al., 2001; Memon, 2004). From the ARF family, ARL5, SARA1 (also known as SAR1A), and SARA2 have been shown to be overexpressed in hepatocellular carcinoma, whereas the levels of ARF6 correlate with breast-cancer-cell invasiveness (He et al., 2002; Hashimoto et al., 2004). ARF-like tumor suppressor

protein 1, another member of the ARF family (also known as ARL11), functions as a tumor suppressor gene in humans, and a nonsense ARF-like tumor suppressor protein 1 polymorphism predisposes patients to familial cancer (Calin et al., 2005). Constitutive activation of G-protein-coupled receptor pathways can also contribute to transformation (Schwindinger and Robishaw, 2001; Daaka, 2004) and the γ -subunits of heterotrimeric G proteins are all CAAX proteins (Schwindinger and Robishaw, 2001). CAAX proteins also include many phosphatases and kinases and their mutations are associated with cancer (Cates et al., 1996; Collins et al., 2000). In both normal and transformed cells, CAAX proteins, including the nuclear lamins A and B, and the centromeric proteins CENP-E and CENP-F, are involved in processes that are important for cell division and nuclear-envelope assembly/disassembly (Ashar et al., 2000; Hutchison, 2002). In particular, three mammalian nuclear lamin proteins, lamin B1, lamin B2, and the lamin A precursor, prelamin A, undergo canonical farnesylation and processing at CAAX motifs. In the case of prelamin A, there is an additional farnesylation-dependent endoproteolysis, which is defective in two congenital diseases: Hutchinson-Gilford progeria and restrictive dermopathy (Young et al., 2006). Finally, one of the earliest myelin-related proteins expressed when OLGs differentiate, 2',3'-cyclic-nucleotide-3'phosphodiesterase is farnesylated and palmitoylated and is involved in the regulation of cytoarchitecture through its interaction with microtubules and microfilaments (Braun et al., 1991; Laezza et al., 1997; Bifulco et al., 2002).

III. The Pharmacology of Statins

A. Chemical Structure and Pharmacological Activity

The structural design of the statins has been modeled to achieve different functionalities tightly related to each particular component of the molecule. The chemical structure of the statins is constituted by two components, the pharmacophore, which is a dihydroxyheptanoic acid segment, and its moiety composed of a ring system with different substituents. The function of the pharmacophore relies on the inhibition of the HMG-CoA reductase enzyme in a competitive, dose-dependent, and reversible manner. The stereoselectivity of the HMG-CoA reductase enzyme dictates the stereochemistry of the statins, which present two chiral carbon atoms, C3 and C5, on their pharmacophore. The moiety of the pharmacophore, according to the chemical modified ring systems and the nature of the substituents, generates the different structures of the statins. The ring system is a complex hydrophobic structure, covalently linked to the pharmacophore, that is involved in the binding interactions to the HMG-CoA reductase. The binding interactions of the ring are able to reduce the competition for the binding site between the statin and the endoge-

nous HMG-CoA substrate because keeping the statin closed to the enzyme precludes the possibility of statin displacement by the endogenous substrate. The structure of the ring can be a partially reduced naphthalene (lovastatin, simvastatin, pravastatin), a pyrrole (atorvastatin), an indole (fluvastatin), a pyrimidine (rosuvastatin), a pyridine (cerivastatin), or a quinoline (pitavastatin). The substituents on the rings define the solubility of the statins along with many of their pharmacological properties. Different substituents on the ring generate different structures. For instance, on the partially reduced naphthalene ring, as substituent, can be located a CH_3 group and a 2-methylbutyrate ester (lovastatin), or a 2,2-methylbutyrate ester (simvastatin), which substantially increases the potency of the drug; on nitrogen-containing rings isopropyl and *p*-fluorophenyl substituents (atorvastatin and fluvastatin) can be attached. The statins are commonly grouped in two types; type 1, natural or fungal-derived statins (lovastatin, simvastatin, pravastatin), exhibit close structural homology and differ from the type 2 constituted by the synthetic statins (Schachter, 2005). Type 1 statins were originally identified as secondary metabolites of fungi (Alberts, 1988). Mevastatin, one of the first identified, was isolated from *Penicillium citrinum* by Endo et al. (1976) and, in its active form, resembles the cholesterol precursor HMG-CoA. Subsequently, a more active fungal metabolite, mevastatin or lovastatin, was isolated from *Aspergillus terreus* by Alberts et al. (1980). The functional difference between natural and synthetic statins relies on their ability to interact and inhibit the HMG-CoA reductase and on their lipophilicity. Type 2 statins are known to form more interactions with HMG-CoA reductase because of their structural characteristics; for instance, atorvastatin and rosuvastatin have additional hydrogen binding interactions. Indeed, rosuvastatin also exhibits a polar interaction between the methane sulfonamide group and the HMG-CoA reductase enzyme. These structural properties render this statin the most efficient in terms of dose able to reduce HMG-CoA reductase activity by 50% (Davidson, 2002). Among the statins mentioned, lovastatin, simvastatin, atorvastatin, and fluvastatin are lipophilic, whereas pravastatin and rosuvastatin are more hydrophilic. The lipophilic properties of the statins are accompanied, except for pitavastatin, by low systemic bioavailability because of an extensive first-pass effect at the hepatic level (García et al., 2003). Although this effect can be desirable, because, as site of cholesterol biosynthesis, the liver is the target organ, the statins' lipophilicity enables them to passively penetrate the cells of extrahepatic tissues, possibly leading to side effects that in some cases can be undesirable. On the other hand, hydrophilicity depends on an active transport process to enter the hepatocyte; thus, hydrophilic statins are more hepatoselective, because they are excluded by other tissues. However, the balance between desired and undesired effects of lipo-

philic and hydrophilic statins remains not clearly established. In summary, the different chemical structures, the lipophilicity/hydrophilicity rate, and as reviewed in section III.B, the kinetic profile, the rate of metabolism, and the formation of active and inactive metabolites govern the variability of the statin pharmacological activity, nonetheless contributing to their pleiotropic actions.

B. Pharmacokinetic Properties of Statins

The pharmacokinetic properties of the statins are orchestrated by several factors, including their active or lactone form, their lipophilic/hydrophilic rate, and their absorption and metabolism. Statins are administered orally as active hydroxy acids, except for lovastatin and simvastatin, which are administered as lactone prodrugs and then hydrolyzed to hydroxy acid form (Corsini et al., 1995). The statin pharmacological properties, referred to as doses administered as open acid and lactone forms, are shown in Table 1.

The percentage of absorption is between 30 and 98% and the time to reach peak plasma concentration (T_{max}) is within 4 h after administration (Pan et al., 1990; Tse et al., 1992; Cilla et al., 1996; Mück et al., 1997). The daily absorption may vary according to the time of administration (Cilla et al., 1996) and food intake (Garnett, 1995); for instance, changes in lipid and apolipoprotein values were similar after morning and evening administration of atorvastatin. Rate and extent of equivalent absorption of atorvastatin were lower during evening than morning administration (Cilla et al., 1996). When consumed with food, lovastatin is more efficiently absorbed (Garnett, 1995) with respect to fluvastatin (Smith et al., 1993), atorvastatin (Radulovic et al., 1995), and pravastatin (Pan et al., 1993a), which have a reduced absorption, whereas rosuvastatin (Davidson, 2002), simvastatin (Garnett, 1995), and cerivastatin (Mück et al., 1997) absorption is not affected by food consumption.

Because the liver is the target organ of statins, an efficient first-pass uptake may be more important than high bioavailability to achieve the statin effect. An extensive first-pass extraction implies a low systemic bioavailability; indeed, bioavailability of cerivastatin is approximately 60% (Mück et al., 1997) and that of pitavastatin is 80% (Kajinami et al., 2000), whereas fluvastatin bioavailability ranges from 19 to 29% (Tse et al., 1992). Furthermore, increased doses of fluvastatin enhance the drug circulating levels without time-related changes of its pharmacokinetic profile, thus suggesting a saturable first-pass effect of fluvastatin (Tse et al., 1992; Dain et al., 1993).

Pravastatin is the only statin not bound to plasma proteins; thus, as result of a systemic exposure to unbound drug, the pharmacologically active drug is relatively low (Corsini et al., 1999), and its circulating level is high compared with other statins (Hamelin and Turgeon, 1998).

TABLE 1
Pharmacokinetics of the statins

	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Dose, mg	40 ^e	0.3 ^a	20–40 ^e	40 ^e	2 ^e	40 ^e	20–40–80 ^e	40–60 ^e
Dose form	Open acid ^{a,b}	Open acid ^{a,b}	Open acid ^{a,b}	Lactone ^{a,b}	Open acid ^{a,c}	Open acid ^{a,b}	Open acid ^c	Lactone ^{a,b}
Optimal time of dosing	Any time of day ^d	Evening ^d	Bedtime ^d	With meals morning and evening ^d	Any time of day ^e	Bedtime ^d	Any time of day ^d	Evening ^d
Absorption, %	30 ^{b,c}	98 ^e	98 ^{b,c}	31 ^{b,c}	80 ^c	37 ^{b,c}	50 ^c	65–85 ^{b,c}
t _{max} , h	2–4 ^{a,b,c}	2.5–3 ^{a,b,c}	0.5–1.5 ^{a,b,c}	2–4 ^{a,b,c}	1–1.8 ^{a,c}	0.9–1.6 ^{a,b,c}	3–4 ^{a,c}	1.3–2.4 ^{a,b,c}
Bioavailability, %	12 ^{a,b,c,d}	60 ^{a,b,c,d}	10–35 ^{a,b,c,d}	<5 ^{a,b,c,d}	>60 ^{a,c,d}	18 ^{a,b,c,d}	20 ^{a,c,d}	<5 ^{a,b,c,d}
Solubility	Lipophilic ^d	Lipophilic ^d	Lipophilic ^d	Lipophilic ^d	Lipophilic ^d	Hydrophilic ^d	Hydrophilic ^d	Lipophilic ^d
Effect of food on bioavailability	↓13 ^{b,c,d,e}	No ^{b,d}	↓15–25 ^{b,c,d,e}	↑50 ^{b,c,d,e}	NO ^{d,e}	↓30 ^{b,c,d,e}	NO ^{b,c,d,e}	NO ^{b,c,d,e}
Protein binding	>98 ^{c,d,e}	↑23 ^c	>98 ^{b,c,d,e}	96–98.5 ^{b,c,d,e}	96 ^{c,d,e}	43–54 ^{c,d,e}	88 ^{c,d,e}	>95 ^{b,c,d,e}
logP (N-octanol/water partition coefficient)	1.11 ^{a,c}	>99.5 ^{b,c,d}	1.27 ^{a,c}	1.70 ^{a,c}	1.49 ^{a,c}	–0.84 ^{a,c}	–0.33 ^{a,c}	1.60 ^{a,c}
Primary metabolic pathway	CYP3A4 ^{a,b,c,d,e}	CYP3A4 CYP2C8 ^{a,b,c,d,e}	CYP2C9 ^{a,b,c,d,e}	CYP3A4 ^{a,b,c,d,e}	CYP2C9 Minimally ^{a,c,d,e} No ^{c,e}	CYP3A4 Minimally ^{a,b,c,d,e} Mainly inactive ^{c,e}	CYP2C9 Minimally ^{a,c,d,e} No ^{c,e}	CYP3A4 ^{a,b,c,d,e}
Lipid-lowering metabolites	Active ^{c,e}	Active ^{c,e}	Mainly inactive ^{c,e}	Active ^{c,e}	Minimally ^{a,c,d,e} No ^{c,e}	Mainly inactive ^{c,e}	Minimally ^{a,c,d,e} No ^{c,e}	Active ^{c,e}
IC ₅₀ , nM	15.2 ^e	13.1 ^e	17.9 ^e	2.7–11.1 ^{c,e}	6.8 ^{c,e}	55.1 ^{c,e}	12 ^{c,e}	18.1 ^e
Hepatic excretion, %	>70 ^{c,e}	>70 ^{c,e}	>68 ^{b,c,e}	>70 ^{b,c,e}	NA	46–66 ^{b,c,e}	90 ^{c,e}	78–97 ^{b,c,e}
Renal excretion, %	2 ^{c,d,e}	<30 ^{c,d,e}	6 ^{c,d,e}	30 ^{c,d,e}	<2 ^{c,d,e}	60 ^{c,d,e}	10 ^{c,d,e}	13 ^{c,d,e}
Clearance, l · h ⁻¹ · kg ⁻¹	0.25 ^b	0.20 ^b	0.97 ^b	0.26–1.1 ^b	0.81 ^b	0.81 ^b	0.45 ^b	0.45 ^b
t _{1/2} , h	11–30 ^{b,c,e}	2–3 ^{b,c,e}	0.5–2.3 ^{b,c,e}	2.5–3 ^{b,c,e}	11 ^{b,c,e}	0.8–3 ^{b,c,e}	20 ^{b,c,e}	1.9–3 ^{b,c,e}

^a Shitara and Sugiyama (2006).

^b Corsini et al. (1999).

^c Mukhtar et al. (2005).

^d Schachter (2005).

^e Saito (2009).

The solubility profile is a fundamental characteristic that governs the hepatoselectivity of the statins and their inhibitory effect on HMG-CoA reductase. Lipophilic statins enter the hepatocytes by passive diffusion, whereas hydrophilic statin uptake is carrier-mediated (Hamelin and Turgeon, 1998; Nezasa et al., 2003). Lipophilic statins show an efficient activity at both hepatic and extrahepatic sites, whereas hydrophilic statins are more hepatoselective (Hamelin and Turgeon, 1998). The human transporters involved in the hepatic uptake of statins are located either at the basolateral or apical membrane in polarized cells and may be classified as influx (uptake into cells) and efflux (out of cells) transporters. The sequential crossing of the basolateral and apical membranes may require interplay of influx and efflux transporters together with phase I and II metabolism. Indeed, in the liver, organic anion transporting polypeptides (OATP) may transport drug substrates from the portal blood into hepatocytes. In particular, pravastatin, cerivastatin, pitavastatin, rosuvastatin, and atorvastatin are substrates of human OATP1B1, a member of the OATP family (Sirtori, 1993; Hsiang et al., 1999; Shitara and Sugiyama, 2006). In the hepatocytes, other drug transporters, such as multidrug resistance protein, breast cancer resistance protein, and bile salt export pump, may be involved in the metabolite efflux (Ho and Kim, 2005). These mechanisms of transport may represent a crucial step for the statin metabolism and elimination (Niemi, 2007).

C. Metabolism of the Statins in Health and Disease

1. Cytochrome P450-Mediated Metabolism of Statins. In the liver, statin lactones are hydrolyzed to their open acid forms chemically or enzymatically by esterases or paraoxonases (PONs) (Duggan and Vickers, 1990). The open acid form is converted to its corresponding lactone via a CoA-dependent pathway and via glucuronidation by UDP-glucuronosyl transferase (UGT). Both acyl glucuronide and acyl CoA derivatives may return to statin acids by hydrolysis. In addition, whereas statin open acids are irreversibly cleared by β -oxidation and glucuronidation processes, statins as lactone forms rapidly undergo oxidation through the microsomal cytochrome P450 (P450) family of enzymes (Bottorff and Hansten 2000). The CYP3A4 isoenzyme is the major microsomal enzyme that metabolizes many statins, including lovastatin, simvastatin, atorvastatin, and cerivastatin, into active derivatives responsible for HMG-CoA reductase inhibition (Lennernäs, 2003). In particular, the major active metabolites of simvastatin are the β -hydroxy acid and its 6'-hydroxy, 6'-hydroxymethyl, and 6'-exomethylene derivatives (Prueksaritanont et al., 2003), whereas for atorvastatin, 2-hydroxy- and 4-hydroxy-atorvastatin acid are reported (Jacobsen et al., 2000). The formation of these active metabolites in *Bacillus megaterium* has been reported to occur through an enzymatic reaction catalyzed by another isoenzyme of cytochrome P450 BM3, CYP102A1 (Kim et al., 2011).

On the other hand, the metabolism of pravastatin in the liver cytosol and in the gastric tract (Quion and Jones, 1994) and of fluvastatin, predominantly occurring through the isoenzyme CYP2C9 (50–80%) and also through CYP3A4 and CYP2C8 (Fischer et al., 1999), produces several inactive metabolites. Likewise, cerivastatin can also be biotransformed by CYP2C8 (Mück, 1998).

Pitavastatin (NK-104), a non-P450-metabolizable statin, is rapidly glucuronized by UGT1A3 and UGT2B7 and then converted to pitavastatin lactone, its major inactive metabolite, by the glucuronic acid elimination reaction (Fujino et al., 2003). Unlike other statins, the cyclopropyl group diverts the drug away from metabolism by CYP3A4 and allows only a small amount of CYP2C9-mediated metabolism (Catapano, 2010).

2. Statin Excretion. Liver and kidney are involved in the elimination of statins from the systemic circulation via the bile into the feces. The hepatic elimination of the statins is limited by their uptake and controlled by the transporters on the basolateral membrane of the liver. Canalicular efflux transporters P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 are two of the major ATP-dependent efflux pumps for statin excretion into the bile. For example, the biliary efflux of rosuvastatin is mediated by multiple transporters multidrug resistance-associated protein 2, multidrug resistance protein 1, and breast cancer resistance protein (Kitamura et al., 2008).

On the other hand, the urinary excretion of statins, except for pravastatin, is quite low. Unlike other statins, up to 60% of intravenously administered pravastatin is excreted in the urine in humans (Hatanaka, 2000). Tubular secretion is the main mechanism involved in the renal excretion of pravastatin and is primarily mediated by the OAT3 transporter. However, when renal elimination is low, the exposure of statins in the liver depends only on the sequestration clearance and is independent of the uptake activity. Instead, when statins, such as pravastatin, undergo significant renal elimination, the increase in the AUC of the plasma concentration does not compensate the reduced hepatic uptake activity, resulting in a weaker pharmacological effect. The half-life elimination of all statins, except atorvastatin and pitavastatin, is very short (0.5–3 h), and drugs do not accumulate in plasma after repeated administrations (Table 1).

3. Factors That May Affect Statin Metabolism. Other factors or their concomitant occurrence may influence the statin metabolism. These factors including race or ethnicity, food intake, age and sex, and concomitant diseases may affect the pharmacokinetic and pharmacodynamic profile of the statins.

a. Race or ethnicity. There is no evidence of clinically relevant interethnic differences in cerivastatin pharmacokinetics in white, black, and Japanese patients after oral therapeutic doses (Mück et al., 1998).

b. Food intake. Concomitant administration of statins with food may alter their pharmacokinetic and pharmacodynamic profile. It has been reported that consumption of pectin or oat bran soluble fiber together with lovastatin reduces its absorption (Metzger et al., 2009), whereas alcohol intake does not affect the efficacy and safety of fluvastatin treatment (Smit et al., 1995). On the other hand, fluvastatin treatment in rats on high-fat and high-sucrose diet was lethal, suggesting that both altered statin metabolism and elimination increase plasma levels of aspartate aminotransferase and creatine kinase, resulting in skeletal muscle toxicity (Sugatani et al., 2010). Moreover, olive oil, consumed in a Mediterranean-style diet, can increase the cholesterol-lowering effect of simvastatin compared with sunflower oil. In contrast, the consumption of polyunsaturated rich oils, through the cytochrome P450 activation, could decrease the half-life of some statins and therefore their cholesterol-lowering effects (Vaquero et al., 2010).

c. Age and sex. The influence of differences in age and sex on pharmacokinetic properties of statins has also been reported. The administration of separate dosage regimens of lovastatin and simvastatin in patients with hypercholesterolemia increases the plasma concentrations of active and total statins only in elderly persons (aged 70–78 years) and in women. However, these age- and sex-related differences do not require modification of dosage regimens, because statin plasma concentrations are not necessarily related to their efficacy and the therapeutic window of lovastatin and simvastatin is quite wide (Cheng et al., 1992).

Likewise, age- and sex-related differences have been reported in the equivalent maximum concentration (C_{max}), in the AUC_∞, and in the half-life after the administration of a single dose of atorvastatin (Gibson et al., 1996). In contrast, the pharmacokinetic profiles of pravastatin are not affected by age and sex. Indeed, although the mean AUC of pravastatin is higher in the elderly women, C_{max} and $\beta t_{1/2}$ values are similar in young and elderly volunteers (Pan et al., 1993b).

Finally, several studies demonstrated that pharmacogenetic variants in HMG-CoA reductase influence the degree of lipid reduction during statin therapies. In particular, patients carrying HMG-CoA reductase single-nucleotide polymorphisms experienced reduced statin sensitivity and smaller reductions in cholesterol, apolipoprotein B, and triglyceride (Chasman et al., 2004; Medina et al., 2008).

d. Concomitant diseases. Statin treatment is required in patients affected by renal and hepatic diseases (Yoshida et al., 2009). However, in pathological conditions of severe renal dysfunction, the elimination kinetic of statins seems to be altered: indeed, plasma levels of total and active lovastatin are increased in affected compared with healthy subjects (Quérim et al., 1991). In contrast, in patients with hyperlipidemia and chronic renal failure subjected to hemodialysis, there was no

evidence of increased accumulation of atorvastatin or its major active metabolite upon multiple dosing, compared with healthy volunteers (Lins et al., 2003). Similar evidence has been also reported for fluvastatin administration (Ichimaru et al., 2004).

In patients receiving long-term dialysis, plasma concentrations of cerivastatin and its metabolites are higher (up to 50%) than in healthy subjects. The half-lives of both parent drug and metabolites remain unaffected without accumulation under repeated dosage. In addition, cerivastatin clearance is not increased by concurrent dialysis as would be predicted from the high plasma protein-binding without significant difference in cerivastatin exposure between the dialysis and the dialysis-free profile days (Mück et al., 2001). Moreover, in patients with end-stage kidney disease undergoing continuous ambulatory peritoneal dialysis, the pharmacokinetic profile of rosuvastatin is very similar to that observed in healthy volunteers; therefore, a lower dose of rosuvastatin may be administered (Bologa et al., 2009).

With regard to hepatic diseases, the steady-state pharmacokinetics of rosuvastatin and its lactone, after the administration of a single dose, are very similar in male patients with liver cirrhosis and male volunteers without liver disease. In contrast, these patients showed increased pitavastatin plasma concentration after administration (Hui et al., 2005).

It is noteworthy that, according to available data, genetic variations in the P450 family of enzymes alter the in vivo availability of many commonly used statins. For instance, gain or loss of catalytic function in the *CYP2C8* gene causes an alteration of cerivastatin metabolic clearance of up to six-fold compared with the wild-type enzyme, altering cerivastatin pharmacokinetics and influencing, at least in part, the susceptibility to the development of myotoxicity (Kaspera et al., 2010). Conversely, a recently discovered polymorphism of *CYP3A5* gene seems not to be an important factor in the modification of atorvastatin disposition and pharmacodynamics in humans (Park et al., 2008).

4. Clinically Relevant Drug-Drug Interactions with HMG-CoA Reductase Inhibitors. Statins are commonly well tolerated. The most frequent adverse effects are mild (such as gastrointestinal upset or discolored urine). The major clinical trouble associated with statin therapy is the hepatotoxicity characterized by an increase of hepatic aminotransferases, hepatocellular and cholestatic injury, autoimmune-type reactions, and fulminant liver failure (Liu et al., 2010). In addition, myotoxicity (myalgia, myopathy) occurs in approximately 10% of statin-treated patients, and it may progress to rhabdomyolysis, commonly characterized by massive muscle necrosis, myoglobinuria, and acute renal failure (Williams and Feely, 2002). The rank order of myotoxicity was cerivastatin > simvastatin acid > fluvastatin > atorvastatin > lovastatin acid > pitavastatin >> rosuv-

astatin = pravastatin, without a correlation with their cholesterol-lowering effects (Kobayashi et al., 2008). The adverse effects are generally due to excessive statin dosing or drug-drug interactions that inhibit statin metabolism.

Drug interactions involving statins have been studied since 2001, when the first case of fatal rhabdomyolysis after cerivastatin and gemfibrozil coadministration was reported (Pasternak et al., 2002). The inhibition or induction of P450 isoenzymes, involved in the metabolism of more than 50% of the drugs currently available in clinical practice, is the mechanism responsible for many drug-drug interactions (Bertz and Granneman, 1997).

a. Statins and CYP3A4 inhibitors. Most of the drug interactions with statins result from the inhibition of CYP3A4 enzyme. Indeed, statin binding and thereby its metabolism could be blocked by drugs with a higher affinity for CYP3A4 enzyme. Consequently, the coadministration of these drugs with a CYP3A4-dependent statin leads to an increase of its plasma levels and bioavailability of the statin and of the risk of statin-related side events. Among statins, simvastatin and lovastatin have the highest potential for clinically relevant interactions, followed by atorvastatin (Jacobson, 2004). The coadministration of the CYP3A4 inhibitor itraconazole with simvastatin and lovastatin increases their mean peak concentration and the AUC, causing rhabdomyolysis (Tiessen et al., 2010); this effect is lower on atorvastatin metabolism (Dong et al., 2008).

On the other hand, itraconazole does not interact with statins that are not substrates of CYP3A4 (Cooper et al., 2003) and with cerivastatin, although it is metabolized by CYP3A4 (Kantola et al., 1999) because of the greater contribution of CYP2C8 compared with CYP3A4 on its metabolism (Shitara et al., 2004). Several studies have reported that many substrates of CYP3A4 in the intestinal wall are also substrates of P-gps (Bertz and Granneman, 1997) and significantly contribute to drug interactions with statins (Benet et al., 2003).

b. Statins and calcium antagonists. The effect of calcium channel antagonists on the pharmacokinetics of statins, by inhibition of CYP3A4 and/or P-gp, has been widely reported (Wang et al., 2001). The coadministration of verapamil, a calcium blocker, substrate of both P-gp and CYP3A4 (Döppenschmitt et al., 1999), with lovastatin or simvastatin (Jacobson, 2004) as well as atorvastatin (Hong et al., 2009) increased their plasma concentrations. These interactions are probably caused by the inhibition of CYP3A-mediated metabolism in small intestine or in the liver and P-gp efflux pump in the small intestine (Choi et al., 2009).

Likewise, diltiazem, another calcium channel-antagonist, in combination with simvastatin, lovastatin and pravastatin (Azie et al., 1998), fluvastatin (Choi et al., 2006) and atorvastatin therapy (Hong et al., 2007), increases plasma levels of the statins and the risk of associated rhabdomyolysis and hepatitis (Kanathur et al.,

2001). A novel mechanism of simvastatin interaction with diltiazem, not based on CYP3A4 inhibition, has been proposed. In cardiac and skeletal muscle of rabbits, several biochemical changes, including an increase of serum creatine kinase MB and of troponin I levels (Jasińska et al., 2006) have been described. The massive creatine kinase MB production increases ATP release by depletion of ATP stores, resulting in a secondary insult to the initial muscle damage.

c. Statins and macrolides/ketolide antibiotics. Several macrolides/ketolide antibiotics, including erythromycin, clarithromycin, and azithromycin, are potent inhibitors of CYP3A4 isoenzymes and consequently can increase the plasma concentrations of coadministered CYP3A4-dependent statins (Niemi et al., 2001). Indeed, coadministration of erythromycin with simvastatin, lovastatin, and atorvastatin induces higher plasma concentrations resulting in rhabdomyolysis (Kahri et al., 2004). Unlike erythromycin and clarithromycin, azithromycin does not increase the plasma concentration of atorvastatin (Chiu et al., 2002); indeed, its inhibitory effect is lower (Ito et al., 2003). Moreover, Burtenshaw et al. (2008) outline a case of rhabdomyolysis, probably as a result of interaction of fusidic acid, a bacteriostatic antibiotic, with simvastatin.

d. Statins and protease inhibitors. Statins are used for the treatment of hypercholesterolemia in patients with HIV subjected to a long-term antiretroviral therapy with HIV protease inhibitors (such as indinavir, nelfinavir, ritonavir and saquinavir) (Calza et al., 2008). Several interactions of statins with the protease inhibitors have been described. As an example, coadministration of nelfinavir increases the concentration of simvastatin by more than 500% and consequently the associated risk of skeletal muscle damage. On the contrary, the effect of nelfinavir is moderate on atorvastatin concentrations that are instead increased by a combined therapy with ritonavir and saquinavir (Hsyu et al., 2001). On the other hand, the combination therapy with ritonavir or saquinavir and pravastatin, by inhibition of OATP1A2, reduced the plasma concentration of pravastatin (Cvetkovic et al., 1999) that is instead not affected by the coadministration of raltegravir (van Luin et al., 2010).

e. Statins and organic anion-transporting polypeptide 1B1 inhibitors. Uptake transporters of the OATP (SLCO) family are new additional regulators of drug disposition (König et al., 2000), including fexofenadine, digoxin, rifampicin, methotrexate, nonsteroidal anti-inflammatory drugs (NSAIDs), and HMG-CoA reductase inhibitors. In particular, pravastatin (Hsiang et al., 1999) and cerivastatin are substrates of OATP1B1 (SLCO21A6), a liver-specific uptake transporter.

HMG-CoA reductase inhibitors are used for the management of dyslipidemia in transplant recipient patients subjected to a post-transplantation immunosuppressive therapy with cyclosporine A. Shitara et al. (2003) exam-

ined the relative contributions of metabolism versus transport in the clinically observed interaction between cyclosporin A and cerivastatin. The increase of cerivastatin systemic concentrations with cyclosporin A occurs through the inhibition of the hepatic uptake transporter OATP1B1 rather than inhibition of CYP3A4- or CYP2C8-mediated metabolism. In contrast, cyclosporin A increases through OATP1B1 the plasma levels also of non-P450-mediated type of statins such as pravastatin, pitavastatin and rosuvastatin in the clinical situation (Launay-Vacher et al., 2005). Consequently, the statin therapy in cyclosporine A-treated transplant recipients should be initiated at the lower end of the dosage range. In contrast, fluvastatin has a low interaction with cyclosporine A because it is mainly metabolized by CYP2C9 (Holdaas et al., 2006).

A similar mechanism of statin interaction occurs with some oral antidiabetic drugs and has been reported to be responsible for diabetes-related cardiovascular disease. In particular, repaglinide, rosiglitazone, and metformin influence the transport of pravastatin by inhibition of OATP1B1 (Bachmakov et al., 2008). On the contrary, after coadministration of vildagliptin, another oral antidiabetic drug, with simvastatin, no interaction was observed in healthy subjects (Ayalasomayajula et al., 2007).

It is noteworthy that, the pharmacokinetic of nateglinide was investigated in rabbits in the presence of HMG-CoA reductase inhibitors (fluvastatin, lovastatin) and calcium channel blockers (verapamil, nifedipine). Fluvastatin and nifedipine increase the systemic exposure of nateglinide, probably through the inhibition of the metabolism of nateglinide by CYP2C5 (human CYP2C9) (Kim et al., 2010).

f. Other interactions. Interactions between statins and coumarin anticoagulants such as warfarin, fludione, phenprocoumon, and acenocoumarol have been reported. The enantiomers of warfarin are metabolized by different P450 isoenzymes in the liver: metabolism of (*R*)-warfarin is primarily catalyzed by CYP3A4 and CYP1A2, whereas (*S*)-warfarin is primarily metabolized by CYP2C9. Reduced clearance of both warfarin enantiomers (10–20%) and reduced levels of the 10-hydroxy metabolite (60%) after coadministration of simvastatin or lovastatin have been reported (Hickmott et al., 2003), through CYP3A4 oxidation. Likewise, potential interaction between fluvastatin and warfarin has also been reported in some patients, unlike pravastatin, cerivastatin, and atorvastatin.

In vitro studies have demonstrated that fibric acid compounds (fibrates) such as gemfibrozil interact with the same family of glucuronidation enzymes involved in statin metabolism (Prueksaritanont et al., 2005). As a result of statin glucuronidation inhibition, the coadministration of gemfibrozil with statins generally increases the statin AUC, with the exception of simvastatin, pravastatin, atorvastatin, and rosuvastatin.

The administration of ezetimibe in combination with simvastatin improves the pro-atherogenic lipoprotein profile in subjects with type 2 diabetes (Ruggenenti et al., 2010), in patients receiving continuous ambulatory peritoneal dialysis (Suzuki et al., 2010), and in patients with coronary heart disease who fail to reach recommended lipid targets with statin therapy alone (Rotella et al., 2010). Likewise, coadministration of ezetimibe with rosuvastatin is well tolerated in patients with hypercholesterolemia (Kosoglou et al., 2004). In contrast, no interactions of dalcetrapib, an inhibitor of cholesteryl ester transfer protein, with pravastatin, rosuvastatin, or simvastatin were found in healthy men (Derks et al., 2010).

It is noteworthy that grapefruit juice intake has been described to inhibit simvastatin metabolism. Indeed, its active ingredient, bergamottin, has been shown to increase serum concentrations of lovastatin and its active metabolite (Kantola et al., 1998), as well as that of simvastatin and its active metabolite simvastatin acid (Le Goff-Klein et al., 2003), by inhibition of CYP3A4 in the small intestine. Consequently, bergamottin could be used as a marker to adjust posology in food-drug interaction studies. Moreover, the effect on simvastatin concentration is lower when simvastatin is taken 24 h after ingestion of high amounts of grapefruit juice, compared with concomitant intake of grapefruit juice and simvastatin. This effect dissipates within 3 to 7 days after ingestion of the last dose of grapefruit juice (Lilja et al., 2000). Although grapefruit juice also increases the AUC of atorvastatin, the actual increase in activity is low, probably because of a simultaneous effect of decreasing the AUC of active metabolites of atorvastatin (Saito et al., 2005). On the other hand, no interactions of pravastatin, fluvastatin, and rosuvastatin with grapefruit juice have been reported.

In addition, histopathological studies revealed that ginger reduces liver lesions induced by atorvastatin. Therefore, a combination of ginger with low dose of statins could be useful for the treatment of patients with hypercholesterolemia who are susceptible to liver function abnormalities (Heeba and Abd-Elghany, 2010).

g. Statin interactions with cytochrome P450 inducers. Statin-drug interactions associated with enzyme induction have also been described. Coadministration of drugs that are enzyme inducers with statins reduced statin plasma concentrations and therefore decreased their cholesterol-lowering effects.

As an example, when coadministered with rifampicin or with carbamazepine, the plasma AUC of simvastatin and its metabolite are reduced, through the induction of CYP3A4 (Niemi et al., 2003; Ucar et al., 2004). In addition, rifampicin reduces the AUC of fluvastatin and pravastatin although they are not metabolized by P450, probably by a mechanism that involves the induction of drug transporters.

IV. Effects of the Statins on Tissues and Biological Processes

A. Statins and Immune System

Numerous findings suggest that statins display immunomodulatory effects mainly triggering the major histocompatibility complex (MHC), the costimulatory molecules, the leukocyte migration, and the cytokine network.

1. Statin Effects on the Major Histocompatibility Complex. Statins interfere with the interaction between MHC (class I/class II) and CD8/CD4 required to achieve efficient T-cell activation. Initially, their immunomodulatory action was ascribable to the inhibition of MHC-II molecule; however, a recent clinical trial showed block of T-cell activation markers by atorvastatin (Ganesan et al., 2011). All the statins are able to block interferon- γ (IFN- γ)-induced MHC-II expression on endothelial cells, macrophages, and microglia by a mechanism involving block of the IFN- γ inducible expression of MHC-II transactivator (CIITA) promoter pIV that regulates the MHC-II expression. Another IFN- γ inducible CIITA promoter, promoter I, has also been found to be inhibited by statins (Kwak et al., 2000; Sadeghi et al., 2001; Youssef et al., 2002; Lee et al., 2008); however, simvastatin does not down-regulate CIITA mRNA or activity of the CIITA-PIII or CIITA-PIV promoters in several cells (Kuipers and van den Elsen, 2005a), suggesting that these drugs could regulate multiple promoters. Conflicting data have been reported on the regulation of MHC-I, possibly ascribed to different types of statins, natural or synthetic, and/or the different rate of lipophilicity. For instance, atorvastatin does not affect MHC-I expression on endothelial cells, whereas simvastatin inhibits both IFN- γ -induced MHC-I and also constitutively MHC-I expressed in several cells (Kuipers et al., 2005b). Thus, besides the direct immunosuppressive action, the reduced MHC-II availability might be related to potential therapeutic strategies to promote immune tolerance and decrease the rejection of transplanted organs. Nonetheless statins might find applications in disorders related to aberrant expression of MHC-II (type I diabetes, multiple sclerosis, rheumatoid arthritis) and chronic inflammatory pathologic conditions.

2. Statin Effects on Costimulation. An effective T-cell response requires the assistance of costimulatory molecules interacting with their ligands, such as CD80/CD86, CD28/CTLA4 and CD40/CD154. Statins inhibit constitutive as well as IFN- γ induced up-regulation of costimulatory molecules, CD80, CD86, CD40 on lymphocytes, macrophages, microglia and endothelial cells (Kuipers et al., 2005b, 2006). Indeed, statins suppress the cytokine-induced maturation of dendritic cells, which consequently fail to express these costimulatory molecules and to induce T-cell response (Yilmaz et al., 2004). Statins can elicit their immunosuppressive effects at various stages; however, it remains unknown

whether these effects actually take to immunosuppression in humans.

3. *Statin Effects on Adhesion Molecules.* Another component of the immunological synapse selectively blocked by the statins is the lymphocyte function-associated antigen-1 (LFA-1) (Weitz-Schmidt, 2003), an α/β heterodimeric receptor belonging to the $\beta 2$ integrin subfamily that plays a central role in lymphocyte homing and leukocyte trafficking. Initially, lovastatin was shown to block LFA-1 by binding to the allosteric site of the extracellular I domain on the α_L chain (therefore known as the lovastatin site). However, subsequent studies showed that lovastatin derivatives inhibited LFA-1 more potently without effect on the HMG-CoA reductase (Welzenbach et al., 2002). The interaction between activated LFA-1 and the intracellular adhesion molecule-1 (ICAM-1) providing signals for both leukocyte migration and costimulation is also blocked by statins. Other adhesion molecules in monocytes and T cells have been shown to be inhibited by statins, ICAM-1, CD11b, CD18, and CD49 (Weitz-Schmidt, 2003). A recent study in patients with acute coronary syndrome confirmed the reduced levels of adhesion molecules ICAM-1 and vascular cell adhesion molecule-1 after short-term atorvastatin preload (Patti et al., 2010). These effects might result in reduced migration and infiltration of the leukocytes along with strongly reduced T-cell activation.

4. *Statin Effects on Inflammatory Mediators.* Numerous studies suggest inhibitory effects of statins on proinflammatory cytokine production, such as IFN- γ , tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6 in several cells, including microglia, astrocytes, and mononuclear cells. These studies also propose a switch from Th1 to Th2 response by statins. However, whether this switch really occurs remains controversial, because several in vitro and in vivo models suggest a statin induction of Th2 cytokines, IL-4, IL-5, IL-10, and transforming growth factor (TGF- β) (Youssef et al., 2002; Zeiser et al., 2007), whereas, in a murine model of inflammatory arthritis, simvastatin suppresses the Th1 response without enhancement of the Th2 response (Leung et al., 2003). Moreover, in experimental autoimmune uveitis, lovastatin suppressed the disease without induction of Th2 (Gegg et al., 2005), whereas in a model of allergic asthma, simvastatin reduced Th2 production in the lung (McKay et al., 2004). Statin also affects the expression of chemokines and their receptors; macrophage inflammatory protein-1 α and IL-8 are reduced in peripheral blood mononuclear cells by atorvastatin in patients with coronary artery disease as well as the mRNA expression of the macrophage inflammatory protein-1 α receptors CCR1 and CCR2 (Waehre et al., 2003). In normal subjects, a recent study by DNA microarray analysis on human peripheral blood lymphocytes showed that atorvastatin significantly decreased the expression of six cytokines [IL-6, IL-8, IL-1, plasminogen activator inhib-

itor type, PAI-1, TGF- $\beta 1$, TGF- β] and five chemokines (CCL2, CCL7, CCL13, CCL18, CXCL1) and affected the expression of many inflammatory genes (Wang et al., 2011). Indeed, other inflammatory mediators are reduced by statins, such as matrix metalloproteinases (Hillyard et al., 2004) and nitric oxide in microglia and monocytes (Cordle and Landreth, 2005). The suppression of the immune response by statins is mainly ascribed to impaired cell activation, adhesion, cross-talk, and trafficking.

5. *Molecular Mechanisms of Statin Immunoregulation.* The molecular mechanisms of statin immunomodulation often involve multiple pathways along with the regulation of genes encoding key molecules of the antigen presentation and immune regulation. STAT family members represent a statin target. Lovastatin suppression of IFN- γ -induced CD40 expression in microglia is mediated by inhibition of STAT activation (Townsend et al., 2004); atorvastatin decreased the phosphorylation of STAT-4 and induced STAT-6, required for Th1 and Th2 commitment, respectively (Youssef et al., 2002). Another mechanism involves the down-regulation of the nuclear factor- κB (NF- κB) encoding the transcription of many immune genes such as MHC-1, chemokines, interferon-inducible protein-10, monocyte chemoattractant protein 1 (MCP-1), and COX-2. It was suggested that atorvastatin reduces these chemokines by inhibition of NF- κB activation (Martín-Ventura et al., 2005; Li et al., 2010). Statins are also able to disrupt lipid raft structures whose main component is cholesterol. This finding showed the relevance of rafts in the immune cell signaling, because several surface molecules are found in lipid rafts, and their association increases their local concentration at the level of the immunological synapse (He et al., 2005). Another mechanism of immunomodulation is the regulation of isoprenylated proteins such as Rho and Rac and their function (Greenwood et al., 2006). Simvastatin suppresses T-cell activation and proliferation by selectively impairing the Ras/MAPK pathway (Ghittoni et al., 2005). Several mechanisms can contribute to the immunomodulatory effects of statins; however, the precise mode of action is still an open issue.

B. Statins and Endothelial Function

1. *Statins and Angiogenesis.* Improvement of endothelial function and vasculoprotective action are well recognized statin pleiotropic effects. Statins have been reported to protect the brain from ischemic strokes and ischemia-reperfusion injury of the heart in animal models (Endres et al., 1998) and to increase blood flow, ameliorating vasomotor response in patients (Dupuis et al., 1999). Simvastatin administration induced neovascularization both in vitro and in the ischemic limbs of normocholesterolemic rabbits, through increased endothelial nitric-oxide synthase (eNOS) activity mediated by Akt pathway (Kureishi et al., 2000). The induction of

the angiogenic response is a protective physiological mechanism against ischemia and hence is considered a therapeutic strategy for coronary artery and peripheral vascular diseases. On the other hand, pathological angiogenesis is involved in the pathogenesis of cancer, atherosclerosis, diabetic retinopathy, rheumatoid arthritis, and other diseases. Statins were able to inhibit tumor-induced angiogenesis in mice and neovascular growth both in vitro and in vivo, through RhoA-dependent inhibition of vascular endothelial growth factor receptor (VEGFR), Akt, and focal adhesion kinases (Felleszko et al., 1999; Park et al., 2002). Actually, a dual effect of statins on angiogenesis is reported and explained by a dose-dependent biphasic effect: low doses (between 0.005 and 0.05 μM) are proangiogenic and induce the PI3K/Akt pathway, leading to eNOS activation, and high doses ($>0.05 \mu\text{M}$) are antiangiogenic and induce apoptosis and VEGF down-regulation. In murine models, low-dose statin therapy (0.5 mg/kg/dose) induced angiogenesis, whereas high concentrations of cerivastatin or atorvastatin (2.5 mg/kg/dose) were inhibitory (Weis et al., 2002). Because the serum levels reached by statins in patients range from 0.002 to 0.1 μM (Desager and Horsmans, 1996), a standard statin therapy might induce rather than inhibit neovascularization. Some exceptions to the biphasic theory have been reported; for instance, in swine, the same dose of simvastatin was proangiogenic in the ischemic kidney and antiangiogenic in early coronary atherosclerosis (Wilson et al., 2002; Chade et al., 2006). In the same animal and at the same dose, statins inhibited atherosclerosis progression by block of atheroma neovascularization and stimulated angiogenesis in the ischemic hind limb, meanwhile being effective to inhibit xenograft tumor growth (Sata et al., 2004). Moreover, cerivastatin was able to stimulate collateral vessel development after ischemia, even at a dose 1000-fold higher than those reported for serum statin levels in patients. On the other hand, the pro- and antiangiogenic effects might be related to the specific angiogenic stimulus, the mechanism of angiogenesis (physiological, pathological, inflammatory), and the local microenvironment (Sata et al., 2004). Low doses of simvastatin stimulated angiogenesis triggered by hypoxia, whereas inhibited tumor necrosis factor α -induced inflammatory angiogenesis. It is noteworthy that high doses of simvastatin (10 μM) inhibited angiogenesis under both conditions, probably as a result of cytotoxic effects. Inflammatory angiogenesis was inhibited by atorvastatin at both low and high doses (Araújo et al., 2010). The inhibitory effect of statins has been reported only when angiogenesis is stimulated by specific proangiogenic or inflammatory mediators (Vincent et al., 2002). On the contrary, statins may act in synergism with proangiogenic stimuli, such as hepatocyte growth factor and endothelial progenitor cells, stimulating angiogenesis (Urano et al., 2008). Statin ability to inhibit angiogenesis in pathological setting could be a

useful tool to contrast atherosclerosis as a result of plaque stabilization, cancer progression, and retinal angiogenesis. In this frame, statins could be able to promote collateral vessel growth in ischemic tissues, without proangiogenic effects or even being antiangiogenic in the atherosclerotic plaque (Sata et al., 2004). Fluvastatin has been reported to prevent retinal neovascularization through down-regulation of STAT3 and hypoxia-inducible factor-1 α and VEGF signaling (Bartoli et al., 2009). Statins may also exert beneficial effects on endometriosis, because inhibiting the proliferation of endometrial stroma affects both the angiogenic and inflammatory processes (Bruner-Tran et al., 2009).

2. Statins and Endothelial Dysfunction. Endothelial dysfunction has been recognized as an independent predictor of cardiovascular disease risk. All statins significantly ameliorate endothelial dysfunction in patients with coronary artery disease (CAD) (Järvisalo et al., 1999) through low-density lipoprotein cholesterol (LDL-C)-lowering effect and pleiotropic actions such as eNOS up-regulation and nitric oxide (NO) production; through Akt activation; and through inhibition of Rho prenylation, antioxidant, and anti-inflammatory effects. Atorvastatin increased NO availability, prevented the production of oxygen free radicals, and down-regulated the expression of COX-2 and the production of the contracting prostanoid 8-isoprostane (Viridis et al., 2009). Long-term pravastatin treatment in spontaneously hypertensive rats improved blood pressure, restored endothelial function, and decreased oxidative stress (Kassan et al., 2009). Pitavastatin treatment in long-term smokers was associated to reduced LDL-C oxidation and protection of endothelium from oxidative stress (Yoshida et al., 2010). In patients with stable CAD, pitavastatin ameliorated postprandial endothelium-dependent vasodilation, inhibiting oxidative stress (Arao et al., 2009). Moreover, pravastatin and fluvastatin had a direct scavenging radical activity (Yamamoto et al., 1998; Kassan et al., 2010). Pravastatin was also reported to inhibit the stimulatory activity of angiotensin II on NADPH oxidase, thereby contrasting the production of superoxide radicals (Alvarez et al., 2010).

Endothelial apoptosis is associated with endothelial dysfunction and is involved in the pathophysiology of atherosclerosis, leading to plaque erosion and thrombosis (Bombeli et al., 1997). Short-term atorvastatin treatment in patients with CAD was reported to be regenerative on the endothelium, through the inhibition of endothelial apoptosis (Schmidt-Lucke et al., 2010), even induced by hyperhomocysteinemia (Bao et al., 2009). On the other hand, high micromolar concentrations of statins, 100- to 200-fold higher than serum statin levels in patients, have been reported to induce apoptosis (Katsiki et al., 2010). Moreover, the inhibition of ubiquinone synthesis by statins, which is essential for a proper mitochondrial function, might be responsible for mitochondrial dysfunction, which has been proposed as a

possible cause of statin-induced myopathy, suggesting the possibility of contrasting such detrimental effect with supplements of ubiquinone (Dai et al., 2010).

Several pharmacological agents, called preconditioning agents, are able to protect the endothelium from the damage triggered by ischemia-reperfusion. The preconditioning potential of statins is multifactorial, because they up-regulate several enzymes, including ecto-5'-nucleotidase, eNOS and COX-2 (Liuni et al., 2010). Statins are also able to induce a postconditioning effect; that is, the protection of a tissue that suffered an intense ischemic episode. Post-treatment with simvastatin or atorvastatin protected from oxygen and glucose deprivation, stimulating reperfusion in endothelial cells (Wu et al., 2010). Endothelial cells under a disturbed proatherogenic blood flow show increased apoptosis and oxidative stress, eNOS inhibition, altered leukocyte adhesion, and LDL-C permeability (Berk, 2008). Atorvastatin induced the vasculoprotective heme oxygenase-1 expression through the Akt pathway, mainly at sites of laminar stress (Ali et al., 2009a). Endothelial response to statins could be therefore affected by wall shear stress, because it has been recently observed that the protective action of simvastatin depends on the hemodynamic forces, being compromised by low shear stress with reversing flow (Rossi et al., 2011).

3. Statins and Endothelial Progenitor Cell Biology. Bone marrow-derived endothelial progenitor cells (EPC) in peripheral blood express CD34, CD133, and VEGFR2 markers, possess a regenerative potential, and are able to differentiate into mature endothelial cells (Asahara et al., 1997). Neither ischemia- nor cytokine-induced mobilization of EPC, as well as ex vivo expansion and reinfusion in animal models, has been shown to promote new blood vessel formation in the injured areas, enhancing perfusion, and leading to recovery of ischemic tissue (Takahashi et al., 1999). Statins promote the mobilization of hematopoietic progenitor cells from the bone marrow and increase EPC proliferation, survival, and functional activity (Dimmeler et al., 2001; Llevadot et al., 2001). Statins increased EPC levels with a peak at 3 to 4 weeks of treatment (Vasa et al., 2001), whereas a treatment >4 weeks augmented the late EPC population, which displays higher proliferative potential than early EPC subset (Deschaseaux et al., 2007). Intensive statin treatments (80 versus 20 mg of atorvastatin) have been associated with higher EPC numbers (Leone et al., 2008), whereas longer standard therapeutic regimens (>8 weeks) have been associated with a reduction in EPC count in the peripheral blood (Hristov et al., 2007), probably because of the increased incorporation of the mobilized EPC into injury sites. The effects of statins on EPC could be due to their pleiotropic activity, because, at least in animal models, no significant changes of serum cholesterol levels were reported. However, a modified diet and lifestyle leading to cholesterol reduction also enhance EPC number (Umemura and Higashi,

2008). Potential molecular mechanism of statin action on EPC might involve the PI3K/Akt pathway (Dimmeler et al., 2001) and the inhibition of apoptosis (Urbich et al., 2005). The essential role of eNOS for mobilization of bone marrow-derived stem and progenitor cells has been ascertained; indeed the beneficial effects of atorvastatin on EPC were abolished in eNOS(-/-) mice (Landmesser et al., 2004). Moreover, the adverse effects of oxidized LDL-C, a known risk factor for CAD, on the functionality of EPC is reverted by statin treatment through the Akt/eNOS pathway (Ma et al., 2009). A limit in EPC cell therapy in humans is their rapid senescence during ex vivo expansion procedures as a result of low telomerase activity. An advantage of statins is their ability to prevent senescence, through a mechanism dependent on protein prenylation (Assmus et al., 2003) and the induction of telomere repeat-binding factor 2 (Spyridopoulos et al., 2004). Compared with cytokines or chemokines able to regulate EPC number, such as granulocyte-colony stimulating factor, statins improve re-endothelialization after balloon injury or carotid artery injury, also inhibiting neointimal thickening (Walter et al., 2002; Werner et al., 2002) and avoiding restenosis (Kang et al., 2004). The positive effect on re-endothelialization induced by fluvastatin treatment after implantation of sirolimus-eluting stents, is due in part to the increased mobilization of EPC (Fukuda et al., 2009). An innovative stent technology designed to trap CD34+ cells has been recently introduced into the clinic (Klomp et al., 2011), and the therapy with high doses of atorvastatin (80 mg) before stent implantation was reported to enhance the number of trapped EPC (Hibbert et al., 2011).

The therapeutic potential of a pharmacological strategy aimed to enhance EPC number and functions may extend also to other pathological conditions, such as systemic sclerosis, characterized by low EPC levels and inadequate recruitment to sites of vascular injury (Mok et al., 2010). It is noteworthy that statin treatment was reported to transiently increase the EPC pool in patients affected by systemic sclerosis (Kuwana et al., 2009).

C. Statins and Vascular Smooth Muscle Cell Function

The phenotypic switching of vascular smooth muscle cells (SMCs) from contractile to synthetic state is critical for vascular repair but is also involved in vascular proliferative diseases (Owens et al., 2004). Statins have been reported to inhibit SMC proliferation, migration, and invasion in a way prevented by the recovery of the isoprenoid pathway intermediates and not by cholesterol (Corsini et al., 1993; Erl, 2005). In particular, the inhibition of Rho prenylation seems a predominant mechanism by which statins affect SMC functions (Laufs et al., 1999). Lipophilic statins have been shown to induce apoptosis directly or to sensitize SMC to apoptotic inducers. Hydrophilic statins seem to protect from apoptosis. However, the apoptotic effect is present at

doses higher than those administered in the clinical practice (Katsiki et al., 2010) and has been observed exclusively in cell culture studies, because in the spontaneously hypertensive rat, atorvastatin was unable to induce aortic SMC apoptosis (Doyon et al., 2011). Low doses of fluvastatin exerted a cytoprotective effect against oxidative stress, whereas higher doses were pro-apoptotic, suggesting a potential biphasic effect (Makabe et al., 2010).

Injury-induced SMC proliferation and migration in the arterial wall is a principal feature of restenosis after angioplasty and stent coronary implantation. The drug-eluting stents, coated with the antimetabolic paclitaxel or the immunosuppressive agent sirolimus, reduced the rate of restenosis and improved patient outcome (Inoue and Node, 2009). However, a major issue about the efficacy and safety of this approach is the negative impact of these compounds on endothelial proliferation, which could result in late thrombotic events. Because statins improve endothelial function and re-endothelialization through EPC mobilization and display direct inhibitory effects on SMC, they could be the “gold standard” for the new generation of drug-eluting stents. Indeed, beyond the efficacy of statins to inhibit neointimal thickening in experimental models of angioplasty (Preusch et al., 2010), observational studies in large cohorts of patients have shown that both pre- and postoperative statin treatment decreases neointimal thickening and restenosis after successful stent implantation (Corriere et al., 2009; Takamiya et al., 2009). It is noteworthy that a synergistic antiproliferative effect of fluvastatin and everolimus on SMC has been demonstrated in vitro (Ferri et al., 2008). Moreover, atorvastatin inhibited the PDGF-induced expression of Nur-77, a nuclear orphan receptor overexpressed by neointimal SMC after angioplasty (Wang et al., 2010b), which indeed could be a new putative target of statins. However, an oral statin therapy has been reported to not so efficiently inhibit in-stent restenosis (Verzini et al., 2011), probably as a result of insufficient local concentrations at the injury site. Cerivastatin-eluting stents display a safe profile and better efficacy in animal models (Jaschke et al., 2005; Miyauchi et al., 2008). A polymer-free cerivastatin drug-eluting stent based on the new technique of bioabsorbable “sol-gel” has been shown to inhibit neointimal thickening more efficaciously than the routinely used a polymer-based paclitaxel-eluting stent (Pendyala et al., 2010).

Hypertension alters the vascular structure through imbalance of SMC proliferation and apoptosis that is normalized by antihypertensive drugs (Deblois et al., 2005). In animal models of hypertension, long-term statin administration improved blood pressure and contributed to the normalization of vessel wall (Doyon et al., 2011). It is noteworthy that a synergism between statins and antihypertensive drugs has been observed in several clinical trials. Atorvastatin reduced primary events

of CAD by 35% versus placebo group; this effect was augmented up to 53% in combination with the calcium channel blocker amlodipine (Clunn et al., 2010). In spontaneously hypertensive rats, quinapril administered in combination with atorvastatin lowered blood pressure, ameliorating cardiac and vessel function and hypertrophy, through increased rates of SMC apoptosis (Yang et al., 2005). Moreover, statins, promoting the dedifferentiation of SMC, could up-regulate the expression of calcium channels, thereby reverting the loss of efficacy of calcium channel blockers that occurs with disease progression (Clunn et al., 2010). Simvastatin per se has been reported to block calcium entry through the inhibition of Rho/Rho kinase (Pérez-Guerrero et al., 2005). Statins have been also reported to protect from pulmonary arterial hypertension, reducing neointimal thickening and improving endothelial dysfunction and inflammation, in hypoxic, high pulmonary blood flow and embolism conditions (Nishimura et al., 2003; Girgis et al., 2007). Simvastatin inhibited platelet-derived growth factor-induced proliferation and migration of SMCs isolated from the lungs of patients undergoing lung transplant as a result of idiopathic pulmonary arterial hypertension (Ikeda et al., 2010).

An intensive field of research is represented by the possibility to target airway SMCs for asthma treatment. Indeed, asthma is characterized by hyperplasia and hypertrophy of airway SMCs, which may exacerbate airway narrowing and contribute to airway remodeling and inflammation (Camoretti-Mercado, 2009). With the exception of bronchial thermoplasty, which partially removes airway muscle mass, there are no therapeutic approaches targeting airway SMCs in asthma. Statins inhibited the proliferation of airway SMCs through RhoA (Takeda et al., 2006). In murine models of allergic airway inflammation and asthma, lovastatin administration decreased the magnitude of inflammatory cell infiltrate (McKay et al., 2004) and improved airway SMC hyper-reactivity through RhoA inhibition (Chiba et al., 2008).

D. Statins and Platelet Function

Some of the statin effects in reducing cardiovascular events can be ascribed to their ability to prevent thrombus formation by exerting modulatory effects on blood coagulation cascades, profibrinolytic mechanisms and platelet functions. One of the first effects reported is the reduction of the cholesterol content of the platelet membrane, which results in low cytosolic Ca^{2+} levels (Le Quan Sang et al., 1995) and intraplatelet pH modifications (Puccetti et al., 2002), as well as in decreased biosynthesis of thromboxane A_2 (Kaczmarek et al., 1993; Notarbartolo et al., 1995). The reduced platelet activity under statin treatment might also be due to its inhibitory effect on Rho-GTPase family such as Rap-1b members (Kaneider et al., 2002; Rikitake and Liao, 2005) and on the activity of other important signaling mole-

cules, such as Erk2, NF- κ B, and Akt, which have the capacity to affect platelet function (Mitsios et al., 2010).

Statins can also decrease platelet activation by modulating the NO bioavailability in platelets (Laufs et al., 2000; Haramaki et al., 2007; Lee et al., 2010) and rapidly reducing the CD36 and lectin-like ox-LDL receptor-1 (Mehta et al., 2001; Puccetti et al., 2005), specific receptors for ox-LDL that are considered potent platelet agonists. Furthermore, statins inhibit the platelet-induced tissue factor expression by monocytes and macrophages (Puccetti et al., 2000), counteracting the prothrombotic complications of atherosclerosis (Aikawa et al., 2001). In this context, statins, such as agonists of PPAR- α and - γ are also highly effective in reducing the platelet-mediated foam-cell generation via inhibition of matrix metalloproteinase 9 secretion (Daub et al., 2007). Moreover, statins inhibit collagen-induced platelet CD40 ligand (CD154) expression and release (Sanguigni et al., 2005; Pignatelli et al., 2007), whose high levels have been found in atherothrombosis and in the major adverse cardiovascular events (Aukrust et al., 1999; Garlich et al., 2001; Cipollone et al., 2002; Heeschen et al., 2003; Semb et al., 2003; Varo et al., 2003). Just through this molecule, platelets can interact with endothelium and, at the same time, quickly activate CD40-bearing immune cells and platelets themselves (Henn et al., 1998; Prasad et al., 2003; Zhang et al., 2011). Statins and fibrates, by activating the PPAR system in platelets (Ali et al., 2009b), may dampen the release of proinflammatory/prothrombotic mediators and aggregation (i.e., CD40L, thromboxane A₂, IL-1 β) (Phipps and Blumberg 2009; Marx et al., 2003). The protease-activated receptor-1 inhibition by statins study (Serebruany et al., 2006) has suggested for the first time that statins can also specifically target platelet thrombin protease-activated receptor-1, thereby modulating antiplatelet and antithrombotic properties. Finally, several statins exhibited an *in vitro* and *in vivo* inhibitory effect of the platelet-activating factor (Tsantila et al., 2011) and, more importantly, can also exert their antiplatelet effects by reducing platelet adhesion to the vessel wall or the endocardium (Tailor et al., 2004; Schäfer et al., 2005; Chello et al., 2008; Molins et al., 2010). Beyond platelets, statins may inhibit plasmatic pathways of thrombus formation (Undas et al., 2005) and may affect fibrinolytic pathways (Bourcier and Libby, 2000).

The first strong evidence of potential association between statin administration and reduced risk of thromboembolism has come from a case control study in postmenopausal women (Doggen et al., 2004) in which statin administration was associated with a slightly lower risk of venous thrombosis. Other case control studies (Lacut et al., 2004; Ramcharan et al., 2009; Sørensen et al., 2009) have also shown reduction in the risk of venous thrombosis ranging from 26 to 58%. On the other hand, two additional observational studies showed no association between the use of statins and the risk of venous

thrombosis (Yang et al., 2002; Smeeth et al., 2009). However, the recent randomized double blind Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study showed that rosuvastatin significantly reduced the occurrence of symptomatic venous thromboembolism in apparently healthy subjects with no significant differences between treatment groups in the rates of bleeding episodes (Glynn et al., 2009). This finding is in contrast with the previously registered protective effect of long-term statin use against the risk of bleeding in warfarin users (Atar et al., 2006; Douketis et al., 2007). Given the success of statins in preventing cardiovascular events and their promising antiplatelet and antithrombotic action, especially in CAD progression and regression (Heart Protection Study Collaborative Group, 2002; Nissen et al., 2004; Walter et al., 2010), they have been tested or are still under evaluation for efficacy outside the cardiovascular system in some related conditions characterized by increased platelet activation and risk of thrombotic events, such as in diabetes (Watala et al., 2007) and in subjects with hypercholesterolemia (Davi et al., 1992; Opper et al., 1995). Diabetes has a major impact on morbidity and mortality because of cardiovascular atherothrombotic events (Tschoepe et al., 1997; Resnick et al., 2000). Rosuvastatin treatment has been demonstrated to normalize endothelial function and reduce platelet activation in diabetic rats, which may account for the reduction of cardiovascular events by statins in patients with diabetes (Schäfer et al., 2007). In fact, in the recently completed Collaborative Atorvastatin Diabetes Study (CARDS), atorvastatin treatment resulted in 48% reduced relative risk of stroke in patients with diabetes without history of coronary artery disease (Colhoun et al., 2004). It is noteworthy that the effect of atorvastatin in patients with type 1 diabetes characterized by high levels of procoagulant platelet-derived microparticles (Mobarrez et al., 2010) resulted in efficient reduction by statin therapy (Tehrani et al., 2010). Multiple effects of statin treatment have been also described in hypercholesterolemia, including reversal of hypercholesterolemia-associated platelet activation and reduction of platelet reactivity, thromboxane biosynthesis, thrombin generation and aggregation, and thrombogenic potential (Takemoto and Liao, 2001; Thompson et al., 2002). Statins might have beneficial effects also in reducing arterial thrombosis and cardiovascular risk in postmenopausal women subjected to hormone therapy (Peverill et al., 2006; Canonico et al., 2008).

In conclusion, these data on statins are quite promising; however, it remains to be determined to what extent these pleiotropic effects account for a potentially beneficial statin therapy in the clinical setting. It is noteworthy that a large population-based cohort study, examining a range of clinical outcomes found to be positively or negatively associated with statins, failed to confirm a

protective effect of statins on the risk of venous thromboembolism (Hippisley-Cox and Coupland, 2010). However, in our opinion, this prospective study was characterized by more potential confounders, and a different cut-off of statistical significance used for the analysis ($p < 0.01$) might have underestimated the potential positive secondary effects of statins.

E. Statins and Metabolism

Recent randomized controlled trials and meta-analyses focused on the effects of different regimens of statin therapy in patients with coronary artery disease or at risk for cardiovascular events (Josan et al., 2008). The Cholesterol Treatment Trialists collaboration (Baigent et al., 2005, 2010) reported data from two cycles of meta-analyses, the first on 14 randomized clinical trials and the second on a total of 26 clinical trials including 170,000 participants. They found that for every 1 mM reduction of serum LDL-C achieved during standard statin therapy (e.g., 20–40 mg/day simvastatin), there was a proportional reduction of approximately 20% in the 5-year incidence of major coronary events (Baigent et al., 2005). More intensive statin treatments or the use of more potent and newer statins (40–80 mg/day atorvastatin or 10–20 mg/day rosuvastatin) resulted in a further reduction of approximately 15 percentage points in cardiovascular events (Baigent et al., 2010). Authors did not report evidence of any significant increase of adverse effects in statin-intensive trials compared with standard therapy. These findings, together with the observations by Josan et al. (2008) that the effects of a more intensive statin therapy (80 mg/day atorvastatin alone or in combination with antioxidant vitamins) is more efficacious than standard therapies (e.g., 40, 20, or 10 mg/day atorvastatin) in decreasing LDL-C levels, strongly suggest that targeting LDL-C is essential to reduce cardiovascular morbidity and mortality. Low HDL-C and elevated triglyceride content are a common pattern in patients with type 2 diabetes, metabolic syndrome, or obesity and account for the prevalence of cardiovascular events in these pathologic conditions (Bell et al., 2011). Some trials, analyzing the effects of statins in patients with diabetes, showed a significant decrease in cardiovascular events (Cziraky et al., 2008). The Collaborative Atorvastatin in Diabetes Study (CARDS) reported that 10 mg/day atorvastatin reduced cardiovascular disease outcomes by 37% in patients with type 2 diabetes without previous history of cardiovascular disease, with a mean decrease in LDL-C levels of 46 mg/dl and a mean triglyceride level decrease of 35 mg/dl (Colhoun et al., 2004). In contrast, other reports suggested that some statins such as lovastatin are almost ineffective in reducing triglycerides, lipoprotein(a), or enhancing HDL-C plasma levels, although statin treatment was still efficacious in reducing cardiovascular events (Cziraky et al., 2008; Jialal and Bajaj, 2009). This provides a rationale to use combined therapy with fibrate or

niacin to achieve either LDL-C- and triglyceride-lowering or HDL-C-enhancing goals in the management of diabetic dyslipidemia and metabolic syndrome (Cziraky et al., 2008; Jacobson, 2011). Few but rising studies explored the effects of statins on diabetic kidney disease. Data from trials involving patients with severe kidney disease showed modest beneficial effect either of atorvastatin or rosuvastatin therapy on cardiovascular events (Wanner et al., 2005; Fellström et al., 2009). The Collaborative Atorvastatin in Diabetes Study (CARDS) study group (Colhoun et al., 2009) analyzed the effects of atorvastatin on estimated glomerular filtration rate (eGFR) and albumin excretion rate in patients with diabetes. A moderate beneficial effect of statin therapy on eGFR was observed with an improvement of 0.18 ml/min per 1.73 m² in the annual rate of change. The improvement in eGFR rate reached 0.38 ml/min per 1.73 m² in the subjects with albuminuria. Nevertheless, independent of kidney disease stage, atorvastatin reduced cardiovascular disease endpoints (coronary events, revascularizations, and stroke) in these patients (Colhoun et al., 2009). The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trials also reported a slight efficacy of pravastatin on eGFR (Tonelli et al., 2005). It has been hypothesized that the modest or absent effect of statins might be due to high rate of angiotensin-converting inhibitors used in patients with diabetes (Colhoun et al., 2009). It is noteworthy that data from the JUPITER trial (Ridker et al., 2008) indicated a significant decrease of eGFR after statin therapy at 1 year. However, it remained to be established whether changes in eGFR observed in the trials are the consequence of a permanent effect on kidney function or reflect transient effect on plasma creatinine levels (Colhoun et al., 2009). An analysis on 3 years of follow-up from large Veterans Integrated Service Network database (VISN 16) estimated that patients under statin therapy had 13% decrease in the odds of developing kidney disease (Sukhija et al., 2008). A recent study from the same group reported that statin use is associated with an increase of fasting plasma glucose (FPG) in patients with and without diabetes. In particular, among patients with diabetes, FPG increased with statin use from 102 to 141 mg/dl and among nonusers from 100 to 129 mg/dl. This relationship between statin use and FPG seems to be independent of age and use of aspirin, β -blockers, and angiotensin-converting enzyme inhibitors (Sukhija et al., 2009). More in vitro and in vivo studies and further meta-analyses are required to ascertain a possible positive/negative effect of statins on glucose metabolism. However, the results from the major clinical trials suggest that statin mono- or combined therapy might be useful not only to reduce LDL-C levels but also to improve several dyslipidemia and diabetic endpoints delaying renal dysfunction.

F. Statins and Bone

The ability of statins to influence bone metabolism was first reported by Mundy et al. (1999), who screened a library of more than 30,000 natural compounds for osteoinductive substances. Only lovastatin was found to have this effect, with the consequent ability to stimulate new bone formation both *in vitro*, as observed in cultures of neonatal murine calvaria, and *in vivo* in animal models of postmenopausal osteoporosis. Similar effects were found with the lipophilic statins (simvastatin, mevastatin, and atorvastatin) (Sugiyama et al., 2000) that also now seem to be more effective than the hydrophilic statins (rosuvastatin and pravastatin) in protecting bone (Uzzan et al., 2007). In a bisphosphonate-like manner, statins can also inhibit osteoclasts activation by preventing mevalonate production, which leads to the loss of prenylation of small GTPases and, consequently, disruption of downstream intracellular signaling pathways in osteoclasts (Dunford et al., 2006; Hughes et al., 2007). Moreover, statins can finely modulate the osteoprotegerin/receptor activator of NF- κ B/receptor activator of NF- κ B ligand system that is a critical determinant for maintenance of skeletal integrity (Kaji et al., 2005; Ahn et al., 2008a). The bone anabolic action of statins also involves an increased expression and synthesis of osteocalcin by reducing the inhibitory effect of Rho-associated kinase in human osteoblasts (Ohnaka et al., 2001). Statins are also able to partially suppress osteoblast apoptosis through a TGF- β -Smad3 pathway (Kaji et al., 2008) and regulation of estrogen receptor α expression (Park et al., 2011). Moreover, the proliferation and recruitment of osteoprogenitor cells, critical steps in the early stages of bone healing, were enhanced by simvastatin-stimulated TGF- β 1 and bone morphogenetic protein-2 (Nyan et al., 2010). In addition to direct effects on bone, statins may increase bone formation by other indirect actions. Vascular invasion is a prerequisite for calcification during endochondral bone formation (Gerber et al., 1999); thus, the well established proangiogenic effect of statins might increase bone formation. Statins may also affect bone formation indirectly by inhibiting inflammation that is responsible for an imbalance in bone metabolism by favoring bone resorption (Tikiz et al., 2004; Tanaka et al., 2005). It is noteworthy that Yavuz et al. (2009) have described an interesting relationship between statins and the vitamin D physiology that might represent a new pleiotropic effect of this class of drugs with great bone anabolic potential.

Of course, the next major question that arises is whether statins really would have beneficial effects on human bone by increasing bone mineral density (BMD) and consequently reducing fracture risk. Edwards et al. (2000) published the first study in postmenopausal women to indicate a significant increase in BMD associated with statin administration. Next, statins have also been shown to exhibit a protective effect against

nonpathological fractures among older women (Chan et al., 2000; Chung et al., 2000; Meier et al., 2000; Wang et al., 2000c). With regard to the effects of statins on BMD, more recent evidence came from results of the studies on this endpoint in patients in treatment with statins for hypercholesterolemia. Overall, patients taking statins have a higher femoral bone mass density (by a mean \pm 0.2 S.D.) (Safaei et al., 2007; Uysal et al., 2007; Uzzan et al., 2007; Pérez-Castrillón et al., 2008; Tang et al., 2008). However, these studies have been conducted on small case series, so differences identified are minimal and fail to reach statistical significance (Luisetto and Camozzi, 2009). A recent large, randomized, placebo-controlled trial of atorvastatin showed instead a negative effect on bone mineral density and bone markers in dyslipidemic postmenopausal women (Bone et al., 2007), confirming data obtained in other past studies (Bjarnason et al., 2001; Stein et al., 2001; Braatvedt et al., 2004). A systematic review by Yue et al. (2010) of all randomized controlled trials involving postmenopausal women (3022 subjects) found that statin use does not prevent fractures or increase bone density in these subjects. At the same time, a recent prospective randomized control trial study enrolling 212 patients with hyperlipidemia and osteopenia has received particular attention in view of the positive effect of simvastatin to significantly increase bone mineral density and bone markers (serum c-telopeptide of type 1 collagen and N-terminal propeptide of procollagen type 1) even though, like many others, this study also suffers from some limitations and confounders that do not clarify whether statins are beneficial in either preventing and/or slowing bone loss in the aging osteoporotic population (Chuengsamarn et al., 2010). No clinical trials focusing on the statin effects on the reduction of fracture risk have been reported. In 2000, a first observational study found an inverse association between hip fractures and statin use (Wang et al., 2000c). After that, small retrospective studies (Chung et al., 2000; Meier et al., 2001; Pasco et al., 2002; Scranon et al., 2005) and a meta-analysis (Bauer et al., 2004) showed a lower risk of fractures. At the same time, a randomized trial (Bone et al., 2007) and three large population-based studies (van Staa et al., 2001; LaCroix et al., 2003, 2008) together with two previous cardiovascular prevention trials (Pedersen and Kjekshus, 2000; Reid et al., 2001), analyzed a posteriori, showed no benefits. These negative findings were recently confirmed by a very large population-based cohort study conducted to assess the effect of statins on a range of health outcomes (Smeeth et al., 2009). Likewise, in the last few months, another large population-based cohort study failed to confirm a protective effect of statins on the risk of osteoporotic fractures (Hippisley-Cox and Coupland, 2010). These disparate results can be explained by different possible reasons: differences in trial design; insufficiently large control group; patient identification methods; statin use definitions; insufficient dose to affect

bone; insufficient treatment duration; inclusion and exclusion criteria; and confounding factors controlled for obesity, physical activity, use of other drugs and comorbidities, diagnostic methods used, lack of objective assessment of fracture, and so called “publication bias.”

Overall, the beneficial effects are largely reported from studies with weaker study design, such as case-control trials. These observations suggest that there is clearly a need for properly conducted, adequately powered, randomized controlled clinical trials to assess conclusively whether statins could potentially reduce fracture rates. Until that moment, patients at high risk of fractures should be treated with currently approved medications.

G. Statins and Nervous System

Hypercholesterolemia is associated with vascular diseases that may increase the risk of cognitive dysfunction from mild deficits to vascular dementia and Alzheimer disease (AD) (Sparks et al., 1994; Hofman et al., 1997; Notkola et al., 1998; Moroney et al., 1999; Nash and Fillit, 2006). Cholesterol and LDL levels are independent determinants for developing dementia (Kalmijn et al., 1996; Moroney et al., 1999) and correlate with total Alzheimer amyloid ($A\beta$) peptide, by shifting the cleavage of amyloid precursor protein (APP) from α to β product (Sparks et al., 1994; Racchi et al., 1997; Refolo et al., 2000). Observational studies showed that the prevalence of AD in statin users was 60% lower than in the total population and 73% lower than patients taking other cardiovascular medications (Wolozin et al., 2000). Yaffe et al. (2002) performed an observational study on 1037 postmenopausal women with coronary heart disease and showed that higher serum levels of total and LDL cholesterol were associated with worse cognitive scores and greater probability of cognitive impairment. They also observed a positive trend for better cognitive performance in statin users that seemed to be independent of total cholesterol levels. Cramer et al. (2008) analyzed the association between the use of statins and the incidence of combined dementia and cognitive impairment without dementia over 5 years of follow-up. Unadjusted analyses and two models of analyses adjusted for baseline covariates such as diabetes, stroke, smoking status, presence of any apolipoprotein E ϵ 4 allele and Modified Mini-Mental State Examination (3MSE) score, showed that statin use was associated with a ~40% lower rate of dementia/cognitive impairment without dementia. Observational reports corroborated this finding in elderly patients suggesting that statin use could be associated with a lower risk of dementia and AD (Jick et al., 2000; Rockwood et al., 2002). Two other major studies reported no positive effects of statins in reducing the risk of dementia or AD (Shepherd et al., 2002; Zandi et al., 2005) and indicated that the use of statins such as pravastatin (PROSPER study) (Shepherd et al., 2002) or both water-soluble or lipophilic statins in the Cache County Study (Zandi et al., 2005) had no effect on cognitive

outcomes. The discrepancy of the results could be due to the analytical method adopted (i.e., cross-sectional or prospective analysis) (Miida et al., 2007). Moreover, these studies were performed on elderly cohorts of men and women with different mean range of age and with already established cognitive impairment or AD. A recent observational study carried out on people who participated in the Ginkgo Evaluation of Memory Study (GEMS) showed that the use of statins was significantly associated with a reduced risk of dementia and AD among participants without mild cognitive impairment at baseline. On the contrary, statins did not seem to exert protective cognitive effect when treatment started in the presence of baseline mild cognitive impairment and after (cerebro)vascular disease has developed (Bettermann et al., 2011). Results obtained in clinical studies do not answer the question whether statins could be useful in the prevention of dementia and AD. First, most of the studies were not designed primarily to analyze the effects of statins on cognitive functions and enrolled patients with advanced vascular diseases. Second, only a few recent clinical trials analyzed the effect of a single statin, whereas a number of studies were carried out in patients who received different kinds of statins with different bioavailability profiles and solubility. Lipophilic statins, which are able to cross the blood-brain barrier, might be more efficacious than soluble statins in preventing cognitive impairment and AD (Haag et al., 2009; Bettermann et al., 2011). Finally, it remains unclear whether the protective effects of statins are related to lipoprotein levels, to their pleiotropic effects (Vaughan, 2003; Miida et al., 2007), or to a direct effect on protein prenylation within the central nervous system. Increasing evidence in animal models indicate that statins exhibit a neuroprotective effect on AD onset and progression. In cultured hippocampal neurons, the formation of $A\beta$ is abolished after reducing cholesterol levels with lovastatin (Simons et al., 1998), and simvastatin is able to reduce levels of $A\beta$ 42 and $A\beta$ 40 in vitro and in vivo (Fassbender et al., 2001). In a recent study on a mouse model of neuroinflammation induced by intracerebroventricular injection of $A\beta_{1-40}$ peptide that mimics the early phase of AD, atorvastatin reduced neuroinflammation and oxidative stress response improving spatial learning and memory deficits (Piermartiri et al., 2010). Atorvastatin seems to reduce inflammation and synaptic loss by inhibiting the expression of glutamatergic transporter and COX-2 in the brain. Moreover, in APP transgenic (Tg) mice showing typical pathological hallmarks of AD, a 3 months' treatment with simvastatin improved memory (Li et al., 2006), decreased glial activation, cortical soluble $A\beta$ levels, and the number of $A\beta$ plaque-associated dystrophic neurites (Tong et al., 2009). Kurata et al. (2011) analyzed the effects of pitavastatin and atorvastatin in Tg mice and correlated serum lipid profiles with cognitive dysfunction, senile plaque, and phosphorylated τ -positive dystrophic neu-

rites. They demonstrated that statins prevented cognitive decline, but neither atorvastatin nor pitavastatin influenced serum triglycerides or HDL-C levels compared with control group. Indeed, statins down-regulate the isoprenoid pathway and its intermediate products, which are responsible for normal function of cellular isoprenylated proteins. In vitro experiments have demonstrated that statins at physiological concentrations are able to inhibit Rab family protein prenylation whose function is associated with A β production and APP trafficking (Ostrowski et al., 2007). Statins also reduce Rho GTPase protein expression in mouse microglial and neuronal cells reducing A β -induced inflammation and inhibiting A β secretion (Cordle et al., 2005; Ostrowski et al., 2007). It is noteworthy that the beneficial effects of statins on neuroinflammation and neurodegeneration have been reported also in non-AD animal models. Simvastatin has been shown to attenuate learning and memory impairment in both Tg and normal non-Tg mice without affecting A β levels in the brain (Li et al., 2006). These findings address a protective role of statins in preventing cognitive decline in non-AD-related dementia and suggest potential therapeutic applications in other chronic inflammatory disorders of the central nervous system such as multiple sclerosis (MS). Some studies in experimental allergic encephalomyelitis, the animal model of MS, indicated that lovastatin-treatment attenuates MS progression and reduces immune cell infiltration in the central nervous system (Stanislaus et al., 2001; Ifergan et al., 2006). The immunomodulatory effects of statins may exert protective effects in MS by down-regulation of proinflammatory Th1 cytokines or by promoting Th2 bias (Youssef et al., 2002; Peng et al., 2006). These observations provide a rationale to evaluate the efficacy of statins administered alone or combined with approved treatments for MS. At present only a few studies, enrolling a limited number of participants, showed that lovastatin or simvastatin decreased the relapses and the number and volume of gadolinium-enhanced lesions in relapsing-remitting MS (Sena et al., 2003; Vollmer et al., 2004). More recent studies provide contrasting results about reduction or progression of relapses in patients with relapsing-remitting MS (Birnbau et al., 2008; Rudick et al., 2009). Aimed to investigate the effects of statin-treatment combined to IFN β -1a in MS, at least six clinical trials are still ongoing (Kamm et al., 2009; Wang et al., 2010a), but results are incomplete; therefore, no sufficient information support mono or combination therapy with statins in MS.

V. Statins and Cancer

A. Effects of Statins in Cancer

Statin pleiotropic effects have been associated with both increased and decreased cancer risk. Despite this, several studies, summarized in Table 2, showed a fair antitumor effect of statins in both cellular and animal models of

human cancer. Low levels of serum cholesterol may be associated with increased cancer risk and accelerated development of already initiated tumors (Kritchevsky and Kritchevsky, 1992). Indeed, statins, reducing cholesterol concentration, have been reported to stimulate TGF- β signaling and increase protumor factors (Chen et al., 2008). In various cell lines, lovastatin treatment, at concentrations higher than those used in humans, increased mitotic abnormalities interfering with development and function of centromeres, thus enhancing the risk of mutations and malignancies (Lamprecht et al., 1999).

Decreased cancer incidence may be attributed to statin-induced suppression of tumor growth, induction of apoptosis, and inhibition of angiogenesis. The intermediates of mevalonate pathway are essential for different cellular functions. Statins reduce not only cholesterol levels but also mevalonate synthesis and the production of dolichol, GPP, and FPP, as well as tumor cell growth in vitro and in vivo (Soma et al., 1992). Primary N-Ras-mutated acute myeloid leukemia (AML) cells were less sensitive to simvastatin than nonmutated AML cells, suggesting a Ras signaling-independent inhibition of cell proliferation (Clutterbuck et al., 1998). In primary cultured human glioblastoma cells, lovastatin inhibited Ras farnesylation and reduced proliferation and migration (Bouterfa et al., 2000). Moreover, lovastatin showed that inhibition of cyclin-dependent kinase 2 through a Ras-independent pathway accounted for growth inhibitory effects (DeClue et al., 1991). Inappropriate Ras signaling pathway activation has a critical function also in thyroid disorders. Indeed, it has been reported that geranylgeranylated Rho has important roles in cell proliferation and apoptosis beyond the control of cell migration. As statins inhibit both farnesylation and geranylgeranylation (and hence Ras and/or Rho activation), it seems plausible that they might potentially inhibit the malignant phenotype of tumor cells (Bifulco, 2008). Inhibition of Rho geranylgeranylation by lovastatin has been shown to exert growth-inhibitory and proapoptotic effects and to induce differentiation of human anaplastic thyroid carcinoma cells resistant to conventional therapies. Furthermore, inhibition of geranylgeranylation (but not farnesylation) has been suggested as the main mechanism regulating lovastatin-induced apoptosis (Wang et al., 2003; Zhong et al., 2005). By contrast, we found that the isoprenoid pathway was markedly altered in the FRTL-5 rat thyroid cell line upon transformation with *K-ras* (but not *H-ras*). This effect occurred via induction of farnesyltransferase activity, which resulted in the preferential farnesylation and functional activation of the oncogene product (Laezza et al., 1998). Treatment with lovastatin inhibited proliferation and induced apoptosis of *K-ras*-transformed thyroid cells through the modulation of the cellular redox state (Laezza et al., 2008). The preferential inhibition of a specific Ras isoform might therefore represent an alternative mechanism of lovastatin action and so provide a

TABLE 2
Targets of statins in cancer

Tumor (cell type)	Statin	Effect	Mechanism of action	Reference
Breast cancer (MCF-7, ZR75T, MDA-MB-157, Hs578T, T47D, MDA-MB-231)	Lovastatin	Inhibition of cell proliferation	Cell cycle arrest at G ₁ phase; decrease of CDK2 activity through redistribution of p21 ^{Waf1/Cip1} and p27 ^{Kip1} from CDK4 to CDK2	Rao et al. (1998)
Breast cancer (MDA-MB-231)	Cerivastatin	Reduction of cell proliferation and invasiveness	Inhibition of RhoA-dependent cell signaling; down-regulation of cyclin D1, PCNA, c-myc, u-PA, MMP-9, u-PAR, PAI-1; up-regulation of p21 ^{Waf1} , p19 ^{Ink4a} , integrin β8, Wnt-5a	Denoyelle et al. (2003)
Breast cancer (MCF-7, SKBr3, MDA-MB-231)	Fluvastatin, lovastatin, simvastatin	Inhibition of cell growth	Transient decrease in p-MEK1/2; increase of IκBα and p21; decrease of cyclin D1, Bcl-2, and Bcl-xL	Campbell et al. (2006)
Breast cancer (MCNeuA cell line injected in female neuTg mice)	Simvastatin, fluvastatin (orally administered)	Inhibition of tumor growth in vivo	Reduction of tumor volumes; induction of central necrosis; induction of caspase-3 cleavage	
Breast cancer (MCF-7, MDA-MB-231)	Simvastatin	Inhibition of cell proliferation	Induction of cell cycle arrest and apoptosis; activation of JNK and increased phosphorylation of c-Jun	Koyuturk et al. (2007)
Colon carcinoma (HCT116, SW480, LoVo, HT29)	Lovastatin	Inhibition of cell proliferation	Induction of apoptosis; decrease of bcl-2 and increase of bax protein expression	Agarwal et al. (1999)
Glioblastoma multiforme (primary cell cultures from biopsies)	Lovastatin	Inhibition of cell proliferation and migration	Reduction of MAPK activity; induction of apoptosis;	Bouterfa et al. (2000)
Glioblastoma multiforme (U87, U251)		Inhibition of cell proliferation	disruption of actin cytoskeleton	
Leukemia (Jurkat, CEM, IM9, U266)	Lovastatin, simvastatin, pravastatin, cerivastatin, atorvastatin	Inhibition of cell proliferation	Activation of ERK1/2, c-Jun, and p38; up-regulation of Bim and induction of apoptosis	Jiang et al. (2004)
AML (OCI-AML-1, OCI-AML-2, OCI-AML-3, OCI-AML-4, and OCI-AML-5) and primary cell cultures from patients with AML, AML cell lines	Lovastatin, simvastatin, pravastatin, cerivastatin, atorvastatin	Inhibition of cell proliferation	Induction of apoptosis through cytosolic release Smac/DIABLO and activation of caspases 9, 3, and 8	Cafforio et al. (2005)
Acute Promyelocytic Leukemia (NB4)	Lovastatin	Inhibition of cell proliferation	Induction of apoptosis	Dimitroulakos et al. (1999)
Leukemic progenitors (primary bone marrow-derived from patients with AML) Promyelocytic leukemia (HL60 intravenously inoculated in SCID mice)	Lovastatin (low doses)	Induction of differentiation	Down-regulation of bcl-2; increase of the leukocyte integrin CD11b and CD18 expression	Dimitroulakos et al. (2000)
Promyelocytic leukemia (HL60)	Atorvastatin, fluvastatin	Inhibition of cell proliferation	Induction of cell differentiation and apoptosis; activation of Rac1/Cdc42 and of JNK pathway	Sassano et al. (2007)
	Fluvastatin	Inhibition of cell proliferation in vivo	Inhibition of leukemic CFU-GM colony formation	
	Simvastatin (subcutaneous continuous infusion)	Inhibition of cell proliferation in vivo	Reduction of the clonogenic cells in bone marrow and spleen of mice (Ras-independent mechanism).	Clutterbuck et al. (1998)
	Lovastatin	Inhibition of cell growth	Induction of apoptosis through release of mitochondrial cytochrome c and caspase-3 activation.	Wang et al. (2000)

TABLE 2—Continued.

Tumor (cell type)	Statin	Effect	Mechanism of action	Reference
Melanoma (A375M, SK-Mel 128, CHL ₁ , WM-166-4)	Atorvastatin	Alteration of melanoma cells morphology and inhibition of cell proliferation; inhibition of melanoma cell invasion	F-actin depolymerization and disassembly of stress fibers; up-regulation of RhoA and Rho exclusion from the membrane; increase of p21 ^{Waf1/Cip1} and p27 ^{Kip1} .	Collisson et al. (2003)
Melanoma (A375M injected in tail vein of SCID mice)	Atorvastatin (orally administered)	Inhibition of colonization and formation of metastatic lesions in the lung in vivo	Inhibition of the effects induced by RhoC overexpression.	
Myeloma (MCC-2)	Cerivastatin	Inhibition of cell proliferation	Induction of apoptosis through caspases activation; delocalization from membrane to cytosol of Rho and Ras	Cafforio et al. (2005)
Pancreatic cancer (PANC-1)	Fluvastatin, lovastatin	Inhibition of EGF-induced migration and invasiveness	Inhibition of RhoA translocation from cytosol to membrane; inhibition of actin stress fiber assembly	Kusama et al. (2001)
Prostate cancer (LNCaP)	Lovastatin	Inhibition of cell proliferation	Induction of apoptosis through proteolytic activation of caspase 7	Marcelli et al. (1998)
Anaplastic thyroid cancer (ARO)	Lovastatin	Inhibition of cell proliferation	Induction of apoptosis (higher doses)	Wang et al. (2003)
		Reduction of EGF-induced invasiveness	Induction of differentiation (lower doses)	
			Reduction of phosphorylated p125 (FAK) and paxillin; inhibition of RhoA and Rac1 geranylgeranylation and membrane translocation	Zhong et al. (2005)
Thyroid cancer (KiMol)	Lovastatin	Inhibition of cell proliferation	Induction of apoptosis; modulation of the cellular redox state	Bifulco (2008); Laezza et al. (2008)
			Cytoskeletal disorganization	Bifulco (2005)

PCNA, proliferating cell nuclear antigen; u-PA, urokinase plasminogen activator; MMP-9, matrix metalloprotease-9; u-PAR, urokinase plasminogen activator receptor; PAI-1, plasminogen activator inhibitor-1; IκBα, inhibitor of nuclear factor-κBα; Smac/DIABLO, second mitochondria-derived activator of caspases/direct IAP binding protein with low PI; CFU-GM, colony-forming units-granulocyte macrophage; FAK, focal adhesion kinase; MCNeuA, mammary carcinoma from Neu transgenic mouse A.

useful selective chemotherapeutic tool for tumors harboring K-ras mutations (Bifulco, 2008). Furthermore, in Fisher rat thyroid cell line-5 cells, lovastatin induced cytoskeletal disorganization and disconnection of microtubules from the plasma membrane (Bifulco, 2005). Antiproliferative effects of statins involving G₁-S arrest are suggested to be attributable to the up-regulation of the cell-cycle inhibitors p21^{WAF1/CIP1} and/or p27^{KIP1} (DeClue et al., 1991; Hirai et al., 1997; Rao et al., 1998). In breast cancer cell lines, cerivastatin treatment modulated the expression of 13 genes that may contribute to the inhibition of both cell proliferation and invasion, either directly or indirectly, through the inhibition of RhoA-dependent cell signaling (Denoyelle et al., 2003). Statins also modify normal cell phenotype; however, these cells seem to be more resistant to statin antiproliferative effects than tumor cells (Hindler et al., 2006). Therefore, statins might inhibit the growth of a variety of tumor cell types, including gastric, pancreatic, and prostate carcinoma, as well as neuroblastoma, glioblastoma, adenocarcinoma, melanoma, mesothelioma, acute myeloid leukemia, and breast cancer. Statins exert proapoptotic effects in a wide range of tumor cell lines, but their sensitivity to statin-induced cell death significantly differs among different cell types. For instance, acute myeloid leukemia and neuroblastoma cells are very sensitive to statin-induced apoptosis (Dimitroulakos and Yeger, 1996; Dimitroulakos et al., 1999). These apoptotic mechanisms may involve inhibition of GPP, required for potential Rho-mediated cell proliferation. Lovastatin apoptotic effect was completely reverted by mevalonate and GGPP and only partially by FPP, whereas other products of the mevalonate pathway did not revert its effect in acute myeloid leukemia cells. In colon cancer cells, GGPP prevented lovastatin-induced apoptosis, whereas the cotreatment with FPP was ineffective. Moreover, lovastatin treatment up-regulated the proapoptotic proteins Bax and Bim (Agarwal et al., 1999a) and decreased the antiapoptotic Bcl2 protein (Dimitroulakos et al., 2000). These effects have been observed in both hematological and solid tumors. Lovastatin increased Bim protein levels and induced cell death through the phosphorylation of Erk1/2, c-Jun, and p38 in glioblastoma cells (Jiang et al., 2004). In addition, the antitumor effect of statins in breast cancer cells has been associated to the suppression of the MEK/ERK pathway with decreased NF- κ B and adapter protein 1 DNA binding activities (Campbell et al., 2006). Moreover, simvastatin induced apoptosis in breast cancer cells via JNK pathway independently of their estrogen receptor or p53 expression status (Koyuturk et al., 2007). Thus, the antitumor effect of statins has been associated with the dual regulation of MAPK pathways involving both suppression of MEK/ERK activity and induction of JNK activity in breast cancer cells (Koyuturk et al., 2007) and in a similar way in leukemia cells (Sassano et al., 2007). Statins can also activate caspase

proteases involved in programmed cell death. Lovastatin induced apoptosis in leukemia and prostatic cancer cells through activation of caspase-7 and caspase-3, respectively (Marcelli et al., 1998; Wang et al., 2000a) and cerivastatin caused cell death in human myeloma tumor cells by activating caspase-3, caspase-8, and caspase-9 (Cafforio et al., 2005).

Frick et al. (2003) reported multiple statin effects on blood vessel formation by inhibition of angiogenesis through down-regulation of proangiogenic factors, such as VEGF, inhibition of endothelial cell proliferation, and block of adhesion to extracellular matrix. Caveolin protein is essential to inhibit angiogenesis because it decreases eNOS, which is activated during angiogenesis; thus, endothelial cells with low caveolin concentrations may be more sensitive to the statin antiangiogenic effect (Brouet et al., 2001). High concentrations of statins can inhibit angiogenesis in a lipid-independent manner, and this effect can be reverted by mevalonate or GPP administration. (Weis et al., 2002). Cerivastatin inhibited endothelial proliferation at concentrations of 0.1 μ M, whereas simvastatin induced the same effect at 2.5 μ M and fluvastatin at 1 μ M (Schaefer et al., 2004). On the other hand, statins can also stimulate angiogenesis through protein kinase B induction (Kureishi et al., 2000) and eNOS activation at low to mid-range concentrations (Brouet et al., 2001). In conclusion, as discussed above, according to the statin type and dose used, inhibition or stimulation of angiogenesis can occur. Along with the above-mentioned effects, statins may also impair tumor metastatic process by inhibiting cell migration, attachment to the extracellular matrix and invasion of the basal membrane. In this context, findings showed that statins are able to reduce endothelial leukocyte adhesion molecule, E-selectin (Nübel et al., 2004) and matrix metalloproteinase (MMP)-9 expression (Wang et al., 2000b), as well as the epithelial growth factor-induced tumor cell invasion (Kusama et al., 2001). In human pancreatic cells, fluvastatin attenuated EGF-induced translocation of RhoA from the cytosol to the membrane and actin stress fiber assembly without inhibiting the phosphorylation of EGF receptor or c-erbB-2. Fluvastatin and lovastatin inhibited invasion in a dose-dependent manner in EGF-stimulated cancer cells, and this inhibition was reverted by the addition of all-*trans*-geranylgeraniol (Kusama et al., 2001). Likewise, the anti-invasive effect of cerivastatin on highly invasive breast cancer cell lines has been associated with RhoA delocalization from the cell membrane, with a consequent disorganization of actin fibers and disappearance of focal adhesion sites. Moreover, cerivastatin was also shown to induce inactivation of NF- κ B in a RhoA inhibition-dependent manner, resulting in decreased urokinase and matrix metalloproteinase-9 expression (Denoyelle et al., 2001). Atorvastatin inhibited in vitro the invasiveness of melanoma cells, through

negative modulation of geranylgeranylation, also reducing metastases formation in vivo (Collisson et al., 2003).

B. Statins and Cancer Risk Prevention

The worldwide use of statins as lipid-lowering drugs exponentially increased, in a short time, the number of statin consumers and consequently triggered growing concern about potential adverse effects in long-term users. Human data regarding the cancer risk associated with statin administration have highlighted conflicting results, and a large number of studies have analyzed the relationship between statin therapeutic regimen and cancer incidence. In this field, numerous potential misjudgments should be taken into account.

First, the onset of malignancies was mainly reported as a secondary endpoint in studies performed to evaluate lipid concentration and cardiovascular outcome. Data extrapolated from such trials lack sufficient hard information concerning clinical outcome, medical histories, presence of familial predisposition to cancer, and observational analysis in long-term use. Second, to ascertain their lipid-lowering efficacy, several statins, both hydrophobic and partially hydrophobic, have been tested, and the heterogeneous cancer types occurring frequently make it difficult to identify a real association between statin use and cancer risk rather than the lack of enough cases to detect significant differences or associations among users and nonusers.

The former studies suggested a potential carcinogenicity of statins, administered at doses higher than those usually used to treat hypercholesterolemia in human both in vitro and in vivo, in cancer cells, and in animal models. High doses of lovastatin (500 mg/kg day), but not doses lower than 180 mg/kg day, induced an increased incidence of hepatocellular and pulmonary cancer in animal models (MacDonald et al., 1988); in rodents, fluvastatin was found to be associated with thyroid cancer and forestomach papillomas (Robison et al., 1994). On the other hand, in mice and rats, the chemically induced colon carcinogenicity was reduced by both simvastatin and pravastatin (Narisawa et al., 1994; Narisawa et al., 1996), and pravastatin also decreased the number and volume of *N*-nitrosomorpholine-induced hepatic neoplastic nodules (Tatsuta et al., 1998).

Human clinical trials evaluating the cancer risk/prevention in statin users produced mixed (heterogeneous) and frequently conflicting results (Tables 3 and 4). The Atorvastatin versus Revascularization Treatment (AVERT) trial reported seven cases of cancer, three in the atorvastatin (80 mg) group and four in the angioplasty group (Pitt et al., 1999). No significant differences in cancer frequency were found comparing the simvastatin (28.5 mg)-treated patients with the placebo group in the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT) over a period of 4 years (Teo et al., 2000). Neither the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT-LLT) trial (ALLHAT Officers, 2002) for the pri-

mary prevention of cardiovascular events nor the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (LIPID Study Group, 1998) found significant differences in cancer risk between the pravastatin and the usual care for hypertension or pravastatin- and placebo-treated groups. In the Treating to New Targets (TNT) trial, LaRosa et al. (2005) analyzed the efficacy and safety of atorvastatin in 10,001 patients with stable coronary heart disease. Patients, randomly assigned to double-blind therapy, received either 10 or 80 mg of atorvastatin per day and were followed for 4.9 years. In this study, cancer (mainly lung and gastrointestinal) accounted for more than half the deaths from noncardiovascular causes in both groups, showing that cancer occurrence may not be associated with atorvastatin dose. Moreover, similar follow-up (4.8 years) of the patients included in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial demonstrated no significant differences in the percentage of cancer cases occurring in patients treated with simvastatin or atorvastatin (20 and 80 mg/day, respectively) (Pedersen et al., 2005). Finally, treatment with 80 mg of atorvastatin compared with placebo was unable to increase the cancer incidence also in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial (Amarenco et al., 2007). In the randomized placebo-controlled Heart Protection Study (HPS) trial, no significant increase of cancer risk was found in simvastatin (40 mg/day)-treated patients compared with those in the placebo-treated group (Heart Protection Study Collaborative Group, 2002). Similar results were obtained after a 10-year follow-up period in the Scandinavian Simvastatin Survival Study (4S) for two simvastatin-treated groups (20 and 40 mg/day) compared with placebo (Strandberg et al., 2004). Despite this evidence that seems to suggest a neutral effect of statins in the cumulative incidence of cancer, several studies demonstrated an increase, or sometimes a decrease, in the occurrence of selective cancer types in statin users. In the Air Force Coronary Atherosclerosis Prevention Study (AFCAPS), the patients treated with lovastatin showed a significantly lower incidence of melanoma (approximately 50%) compared with the group treated with placebo (Downs et al., 1998). On the other hand, the Cholesterol and Recurrent Events (CARE) trial showed a significant increase (higher than 5%) in breast cancer that occurred in postmenopausal women treated with 40 mg of pravastatin compared with placebo (Sacks et al., 1996). In the same study, the statin-treated group showed a consistent but not significant reduction of colon cancer incidence, without affecting that of the new diagnosed melanoma (Sacks et al., 1996). Pravastatin 40 mg induced an increased cancer incidence in patients included in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, and, in the same trial, breast cancer occurred preferentially in the pravastatin-treated group (Shepherd et al., 2002); however, more recently a meta-analysis of pravastatin and all statin trials performed in younger statin users have been unable to

TABLE 3
Randomized clinical trials reporting the effect of statin use on cancer risk

Study	Reference	Population	Duration <i>months</i>	Statin		Dose <i>mg/day</i>	Results
				Name			
AVERT	Pitt et al. (1999)	341	18	Atorvastatin		80	Seven cases of cancer (three in atorvastatin-treated and four angiotensin-treated patients)
SCAT	Teo et al. (2000)	460	48	Simvastatin/enalapril		28.5	No significant differences in simvastatin/enalapril-treated-group and placebo group
ALLHAT-LLT	ALLHAT Officers (2002)	10,355	97	Pravastatin		40	No significant differences in pravastatin-treated and usual care for hypertension
TNT	LaRosa et al. (2005)	10,001	57	Atorvastatin		10 or 80	Cancer occurrence may not be associated with atorvastatin dose
IDEAL	Pedersen et al. (2005)	8888	56	Simvastatin		20	No significant differences in simvastatin- and atorvastatin-treated groups
SPARCL	Amarencio et al. (2007)	4731	57	Atorvastatin		80	No significant differences in atorvastatin-treated and placebo group
LIPID	LIPID Study Group (1998)	9014	73	Pravastatin		40	No significant differences in pravastatin-treated and placebo group
AFCAPS	Downs et al. (1998)	6605	62	Lovastatin		20-40	No significant differences in treated and placebo groups
HPS	Heart Protection Study Collaborative Group (2002)	20,536	60	Simvastatin		40	No significant differences in simvastatin-treated and placebo group
4S	Strandberg et al. (2004)	4444	120	Simvastatin		20 or 40	No significant differences in simvastatin-treated and placebo group
PROSPER	Shepherd et al. (2002)	5804	38	Pravastatin		40	Significant increase of cancer incidence in pravastatin-treated and placebo group especially breast cancer
CARE	Sacks et al. (1996)	4159	60	Pravastatin		40	Significant increase in breast cancer in postmenopausal women treated with pravastatin compared with placebo. No significant reduction of colon cancer incidence and no decrease in the new diagnosed melanoma
WOSCOPS	Shepherd et al. (1995)	6595	57	Pravastatin		40	Significant increase of overall cancers in treated and placebo group
WOSCOPS	Ford et al. (2007)	Survivors of previous trials [Shepherd et al. (1995)]	120	Pravastatin		40	No significant increased risk in pravastatin treated and placebo group

confirm these results. Finally, a symptomatic example of the need of cautious evaluation of these studies has been evidenced by the West of Scotland Coronary Prevention Study (WOSCOPS). In the first evaluation, the authors demonstrated that in men with hypercholesterolemia, 40 mg/day pravastatin increased the incidence of overall cancers (Shepherd et al., 1995); however, the prolonged 10-year follow-up period showed no increased risk in pravastatin consumers (Ford et al., 2007).

Observational studies taking as primary endpoint the diagnosis of malignancy and as second endpoint the evaluation of specific cancer types also investigated the potential correlation between the use of statins and cancer risk. A hospital-based case-control surveillance study was conducted in 1132 women with breast cancer, 1009 men with prostate cancer, and 2718 subjects admitted for condition unrelated to statin use. In this analysis, 1.5- and 1.2-fold increased risks for breast and prostate cancer, respectively, have been found (Coogan et al., 2002). Friis et al. (2005) performed a population-based case-control study using data from the Prescription Database of North Jutland County and the Danish Cancer Registry. In a population of 334,754 subjects, they compared overall and site-specific cancers occurring in 12,251 statin users with cancer occurring in nonuser subjects and in 1257 patients using other lipid-lowering drugs, during a total follow-up period of 3.3 years. Results showed that cancer incidence in statin-user group was lower than that observed in both the control group and in other lipid-lowering drug users. Moreover, no preferential site-specific cancers occurred in the examined groups. Similar results were obtained in a case-control study performed using the Quebec Administrative Health Database (Blais et al., 2000). In a median follow-up period of 2.7 years, by comparing users of HMG-CoA reductase inhibitors with users of bile acid-binding resins to treat hypercholesterolemia, authors found a significant decrease (approximately 28%) of the new diagnosed cancers in statin-users. No increase of specific cancer was found preferentially associated with statin or resins consumer groups.

The PHARMO database, containing drug-dispensing records from community pharmacies and linked hospital discharge records for residents of eight Dutch cities, was used to evaluate the incidence of overall cancer by comparing subjects (3129) treated with statins (mainly simvastatin in this population) with people (16,976 control subjects) treated with other cardiovascular medications. Statin use has been associated with a 20% reduction in overall cancer risk, with a significant decrease for specific cancer subtype exclusive of renal carcinoma (Graaf et al., 2004).

More recently, the association between statin use and the occurrence of the ten most common types of neoplasia has been analyzed in a hospital-based case-control surveillance study (Coogan et al., 2007a). Hospitalized cancer patients (4913) have been compared with pa-

tients admitted for diagnosis other than cancer (3900). For all cancer types considered (breast, prostate, colorectal, lung, bladder, leukemia, pancreas, kidney, endometrial, and non-Hodgkin lymphoma), no significant differences were found among regular statin users compared with never-users. Moreover, duration of statin use, and a more selective analysis separately considering hydrophobic statin users and hydrophilic statin users, did not affect obtained results (Coogan et al., 2007a; Duncan et al., 2007).

The association between statin use and prostate cancer risk was studied in patients from the Veterans Affairs Medical Center in Portland, OR. Results demonstrated that statin use significantly reduced prostate cancer occurrence. Moreover, analyzing the correlation between statin assumption and the histological grade of the neoplasia, statin users showed a decreased risk of aggressive prostate cancer with Gleason score ≥ 7 (Shannon et al., 2005). It is noteworthy that data concerning 361,859 patients from the Kaiser Permanente Medical Care Program in Northern California showed an increased rate of overall cancers in statin users and a decreased, but not significant, rate for colon cancer in men and for liver and intrahepatic bile duct cancer in women. Moreover, in this population, statin users experienced an increased risk in stage 1 prostate cancer but not in more advanced stages of prostatic neoplasia (Friedman et al., 2008). More recently, a population-based case-control study in patients from the Taiwan National Health Insurance Research Database evaluated 388 prostate cancer cases and 1552 control subjects. Multiple logistic regression analyses demonstrated that the use of statins was associated with a significant increase in prostate cancer risk, and that increasing cumulative doses of statins were correlated with increasing prostate cancer risk (Chang et al., 2011).

The protective effect of statins toward colon cancer was evaluated by Poynter et al. (2005) using data from the Molecular Epidemiology of Colorectal Cancer (MECC) study, a population-based case-control study of patients who received a diagnosis of colorectal cancer in northern Israel. In particular, in 1953 patients with colorectal cancer and 2015 control subjects, the use of statins for at least 5 years (versus no use of statins) was associated with a significant reduction (47%) of the relative risk of colorectal cancer, persistent after adjustment for other risk factors (e.g., use of NSAID, presence or absence of family history of colorectal cancer, ethnicity, hypercholesterolemia). Moreover, the observed protective effect was specific for statins, because patients taking fibric-acid derivatives as cholesterol-lowering drugs showed a colorectal cancer risk similar to that observed in the control group. On the other hand, Coogan et al. (2007b) fail to find similar association in a case-control analysis of the Massachusetts Cancer Registry. In brief, among 1809 patients and 1809 matched control subjects, the use of statins for at least 3 months did not reduce the risk of colorectal cancer; nevertheless, the

TABLE 4
Observational studies of statins and the risk of developing cancer

All studies are case-control studies unless otherwise noted.

References	Population	Duration of Statin Use <i>months</i>	Statins	Primary Endpoint	Results
Blais et al. (2000)	6721 Patients aged ≥ 65 years with prescription for lipid-lowering agents in the Régie de l'Assurance-Maladie du Québec database	32	Lovastatin, pravastatin sodium, simvastatin	Diagnosis of any cancer	Decrease of overall cancer: RR, 0.72; 95%CI, 0.57–0.92
Graaf et al. (2004)	20,105 Patients with ≥ 1 prescription for cardiovascular drugs	48 (mean)	Simvastatin	Diagnosis of any cancer	Decrease of overall cancers, mainly renal cancer. Statin group vs. control group: OR, 0.8; 95%CI, 0.66–0.96 (adjusted); statins vs. lipid-lowering drugs: OR, 0.89; 95%CI, 0.56–1.41; renal cancer: OR, 0.27; 95%CI, 0.08–0.95
Friis et al. (2005)	334,754 Patients aged 30–80 years in the Prescription Database of North Jutland County and Danish Cancer Registry	39 (mean)	All statins	Primary diagnosis of cancer (overall and cancer specific)	Decrease of overall cancers in statin users vs. nonusers: RR, 0.86; 95%CI, 0.78–0.95
Coogan et al. (2002)	4859 Patients, of which 1132 women with breast cancer, 1009 men with prostate cancer, and 1331 women and 1387 men as controls from hospital-based Case-Control Surveillance Study of Drugs and Serious Illnesses				Increased risk of breast and prostate cancer. For breast cancer: OR, 1.5; 95%CI, 1.0–2.3; for prostate cancer: OR, 1.2; 95%CI, 0.8–1.7.
Coogan et al. (2007b)	3618 Patients with adenocarcinoma of the colon or rectum, and healthy control subjects from hospitals in Massachusetts and the Massachusetts Cancer Registry	1–120	All statins	Occurrence of colorectal cancer	Not reduced risk of colorectal cancer in statin users vs. nonusers: OR, 0.92; 95%CI, 0.78–1.09
Coogan et al. (2007a)	8813 Patients aged 40–79 years admitted to hospitals in New York, Philadelphia, and Baltimore	1–60	All statins	Occurrence of any of 10 cancers	No significant differences for 10 cancer types in statin use vs. nonuse: Breast cancer: OR, 1.2; 95%CI, 0.8–1.8. Prostate cancer: OR, 1.2; 95%CI, 0.9–1.7. Colorectal cancer: OR, 0.8; 95%CI, 0.5–1.2. Lung cancer: OR, 0.7; 95%CI, 0.4–1.1. Bladder cancer: OR, 1.3; 95%CI, 0.8–2.3. Leukemia: OR, 1.1; 95%CI, 0.6–2.0. Pancreatic cancer: OR, 0.7; 95%CI, 0.3–1.4. Kidney cancer: OR, 1.1; 95%CI, 0.6–1.9. Endometrial cancer: OR, 1.3; 95%CI, 0.7–2.4. Non-Hodgkin's lymphoma: OR, 1.2; 95%CI, 0.6–2.4.

TABLE 4—Continued.

References	Population	Duration of Statin Use	Statin	Primary Endpoint	Results
Poynter et al. (2005)	3968 Patients with colorectal cancer and healthy control subjects from northern Israel	>60	All statins	Occurrence of colorectal cancer	Significant reduction of risk of colorectal cancer in statin users vs. nonusers: OR, 0.53; 95%CI, 0.38–0.74
Cauley et al. (2003)	7528 Women with mean age 77 years		All statins	Occurrence of breast cancer	Significant reduction of risk of breast cancer in combined statins group (RR, 0.28; 95%CI, 0.09–0.86) and among women who used other lipid-lowering drugs (RR, 0.37; 95%CI, 0.14–0.99) in comparison to nonusers.
Cauley et al. (2006)	156,351 Postmenopausal women aged 50–79 years	80	All statins	Occurrence of breast cancer	In breast cancer, no significant differences in statin use vs. nonuse: HR, 0.91; 95%CI, 0.80–1.05. Hydrophobic statin use was associated with a lower breast cancer incidence: HR, 0.82; 95%CI, 0.70–0.97.
Kumar et al. (2008) ^a	2141 Female patients listed in 2003 as incident cases of breast malignancy in the Kaiser Permanente Northern California Cancer Registry		Lovastatin, Simvastatin and Atorvastatin	Occurrence of hormone receptor phenotype of breast cancers	Fewer ER-PR-negative breast tumors of lower grade and stage in hydrophobic statin users. Moreover, statin use may influence the phenotype of tumors. OR, adjusted for age, of developing an ER/PR-negative tumor was 0.63; 95%CI, 0.43–0.92 for statin use \geq 1 year before breast cancer diagnosis compared with statin use <1 year (including nonuse). Breast cancers in patients with \geq 1 year of statin use were more likely to be low grade (OR, 1.44) and less invasive stage (OR, 1.42).
Shannon et al. (2005)	302 Patients in the Portland Veterans Affairs Medical Center	2–35	All statins	Occurrence of prostate cancer	Significant reduction of risk of prostate cancer in statin use vs. nonuse: OR, 0.35; 95%CI, 0.20–0.64.
Friedman et al. (2008)	361,859 Patients enrolled for >20 years in the KPMCP and in the KPMCP Cancer Registry	59 (median)	Lovastatin, simvastatin or both	Occurrence of any cancer	No strong evidence of either causation or prevention of cancer by statins.
Chang et al. (2011)	483,733 Patients from the Taiwan National health Insurance Research Database aged \geq 50 years and with a first-time diagnosis of prostate cancer		All statins	Occurrence of prostate cancer	After adjustment for smoking habit, data were consistent with a slight protective effect of statins for lung cancer
Khurana et al. (2007)	483,722 Patients in the VIGN-16 database from south-central United States	>6	All statins	Occurrence of lung cancer	Ever-use of any statin was associated with a significant increase in prostate cancer risk (OR, 1.55; 95%CI, 1.09–2.19)
Farwell et al. (2008) ^a	62,842 Patients aged \geq 65 years in the Veterans Affairs New England health care system who were taking antihypertensive drugs	60 (median)	All statins	Occurrence of cancer excluding nonmelanoma skin cancer	Reduced risk of lung cancer in statin users vs. nonusers: OR, 0.55; 95%CI, 0.52–0.59
					Reduced risk developing cancers in statin users vs. nonusers. 95%CI 0.033–0.043 ($P < 0.001$)

OR, odds ratio; HR, hazard ratio.

^a Retrospective.

occurrence of high-grade colorectal cancer was significantly lower among statin users than nonusers.

A multicenter prospective cohort study conducted at four community-based clinical centers in the United States evaluated the breast cancer incidence in a total of 7528 women (mean age, 77 years), divided into statin users, users of lipid-lowering agents other than statin, and nonusers. In this population, lipid-lowering drug users and statin users showed a reduction in the risk of breast cancer reaching 68 and 72%, respectively, compared with nonusers (Cauley et al., 2003). The same authors (Cauley et al., 2006) investigated associations among potency, duration of use, and type of statin used and risk of invasive breast cancer in a larger population of 156,351 postmenopausal women (50–79 years old) enrolled in the Women's Health Initiative. The average follow-up covered 6.7 years; unsurprisingly, no significant differences were found in breast cancer occurrence between user and nonuser patients. Nevertheless, the use of hydrophobic statins (i.e., simvastatin, lovastatin, and fluvastatin), but not of pravastatin and atorvastatin, was significantly associated with 18% reduction of breast cancer risk (Cauley et al., 2006).

Finally, a retrospective cohort analysis via the electronic pharmacy records from the Kaiser Permanente Northern California Cancer Registry explored the hormone receptor (both estrogen and progesterone receptors) phenotype in 2141 breast cancers. Among all patients, 387 used hydrophobic statins (mainly lovastatin) and showed proportionately fewer estrogen/progesterone receptor-negative tumors compared with nonusers (Kumar et al., 2008).

In patients enrolled in the Veterans Integrated Service Networks (VISN) 16 VA database, Khurana et al. (2007) studied the potential correlation between use of statins and lung cancer incidence, analyzing 483,733 patients. Among these patients, 163,662 were receiving statins and 7280 had a primary diagnosis of lung cancer. Results showed that statin use for at least 6 months, but not for shorter durations, was associated with a reduced risk of lung cancer. Moreover, in a retrospective cohort study of veterans performed by Farwell et al. (2008), the rate of lung, colon, and prostate cancer was found to be decreased in statin users. It is noteworthy that in these patients, simvastatin doses (10–40 mg) and risk of cancer occurrence showed a close dose-response relationship, because higher statin regimens correlated with the lowest occurrence of both lung and colorectal cancers (Farwell et al., 2008).

C. Statins in Cancer Treatment

To investigate the potential efficacy of statins in chemotherapy protocols, several studies evaluated, *in vitro* and *in vivo*, the combined effects of statins with drugs commonly used in cancer treatment. Statins were able to potentiate the antitumor effects of anthracyclines in both cellular and animal models. In mice, lovastatin

synergistically potentiated doxorubicin-induced cytotoxicity in colon and breast carcinoma (Feleszko et al., 2000; Rozados et al., 2008) and showed an additive effect in lung cancer cell lines (Feleszko et al., 2000). Similar synergistic effects with different anthracyclines were also found for simvastatin and fluvastatin in human rhabdomyosarcoma cells (Werner et al., 2004) and breast cancer cell lines (Budman et al., 2007), respectively. Moreover, atorvastatin and mevastatin increased the sensitivity to anthracyclines of both lung cancer (Roudier et al., 2006) and human primary acute myeloid leukemia cell lines (Stirewalt et al., 2003), respectively. Several mechanisms have been proposed to explain the observed combinatorial effects (Fig. 2). First, statins suppress insulin-like growth factor 1 receptor glycosylation and its correct localization into the cell membrane (Girnita et al., 2000; Siddals et al., 2004) and inhibit NF- κ B activation (Inoue et al., 2002; Wang et al., 2005). Both the reduced expression of insulin-like growth factor 1 receptor (Benini et al., 2001) and the inhibition of NF- κ B (Arlt et al., 2001) sensitize tumor cells to doxorubicin. Moreover, statins, inhibiting the prenylation of RAS protein (Khosravi-Far et al., 1992), interfere with RAS-mediated pathways responsible for the resistance to doxorubicin and to several chemotherapeutic compounds (Jin et al., 2003). Because doxorubicin and statins induced an arrest of the cell cycle in the G₂ and G₁ phases, respectively (Sivaprasad et al., 2006; Javanmoghadam-Kamrani and Keyomarsi, 2008), the combined use of these drugs could exert a cumulative inhibitory effect in the cell cycle progression.

The potential interactions of statins with platinum compounds have been also tested. Lovastatin potentiated the antitumor effects of cisplatin in cellular and murine models of melanoma (Feleszko et al., 1998), increasing, at least partially, the apoptotic effect of oxaliplatin in human head and neck squamous cell carcinoma (SCC) (Mantha et al., 2003). In human colon cancer cell lines, the pretreatment with lovastatin increased the apoptotic death induced by cisplatin (Agarwal et al., 1999a). In combined use, simvastatin has been found able to reduce the liver toxicity induced by cisplatin treatment (Işeri et al., 2007). The main mechanism able to explain these interactions is the statin-induced inhibition of the MAPK/ERK kinase pathways (Fig. 2) (Nishida et al., 2005; Cerezo-Guisado et al., 2007). Finally, increasing evidence suggests that cisplatin-induced toxicity, mediated by cell-cycle arrest in G₁ phase (Donaldson et al., 1994), was highest in cells previously treated with compounds such as statins that were able to potentiate the block in G₁ phase (Sivaprasad et al., 2006; Javanmoghadam-Kamrani and Keyomarsi, 2008).

In human colon cancer cell lines (Agarwal et al., 1999a), but not in breast cancer cell lines (Mantha et al., 2003), the cytotoxic effects of 5-fluorouracil (5-FU) were potentiated by the combined use of lovastatin. Similar increases in 5-FU antiproliferative effects were also ob-

tained with atorvastatin or simvastatin combined with 5-FU in human non-small-cell lung cancer cell lines (Roudier et al., 2006) or in human myeloid leukemia cell lines (Ahn et al., 2008b), respectively. The statin-induced inhibition of NF- κ B activation seems to be responsible for the increased sensitivity to 5-FU (Ahn et al., 2008b).

NSAIDs are associated with reduced colon cancer incidence, and in human colon cancer cell lines, celecoxib combined with lovastatin or atorvastatin induced a persistent cell cycle arrest in G₀/G₁ phase followed by an activation of the apoptotic process greater than that obtained with celecoxib alone (Feleszko et al., 2002; Swamy et al., 2002; Xiao et al., 2008). Atorvastatin-mediated inhibition of colon cancer cell growth also involved a decrease of the membrane-bound Rho-A in HT29 and HCT116 colon cancer cell lines (Yang et al., 2010).

It is noteworthy that the combinations of both sunitinib with lovastatin and celecoxib with atorvastatin showed a significant inhibition of the cancer incidence and progression in experimental models of chemically induced colorectal carcinogenesis (Agarwal et al., 1999b; Reddy et al., 2006). The high extent of COX inhibitors antiproliferative effects induced by statins, involved several mechanisms, such as inhibition of kinase pathways, modulation of cyclin-dependent kinase activities, and arrest of cell cycle progression (Agarwal et al., 1999b; Zheng et al., 2007; Xiao et al., 2008; Guruswamy and Rao, 2009). Moreover, in the human HCT-116 colon cancer cell line, lovastatin and celecoxib suppressed caveolin-1 (Cav1) expression, impaired its membrane localization and inhibited Cav1-dependent cell survival pathways (Guruswamy et al., 2009). The inhibition of NF- κ B and the synchronized arrest in different phases of the cell cycle have been also suggested as the main cellular mechanisms through which synergistic effects of statins (mainly lovastatin and simvastatin) and paclitaxel occurred (Holstein and Hohl, 2001a; Ahn et al., 2008b). These combinations efficaciously potentiated the paclitaxel-induced cytotoxic effects in human leukemic cells (Holstein and Hohl, 2001b; Ahn et al., 2008b) but not in human breast cancer cell lines and in head and neck SCC cell lines (Mantha et al., 2003).

The etoposide antiproliferative effects were increased by atorvastatin in both hepatoma and non-small-cell lung cancer cells (Roudier et al., 2006), potentially through the inhibition of PI3K/Akt pathways by mammalian target of rapamycin-mediated mechanisms triggered by statins (Krystal et al., 2002). Moreover, in leukemia cell lines, fluvastatin enhanced the apoptotic effects of both rapamycin and its analog RAD-001 (everolimus), two inhibitors of mammalian target of rapamycin (Calabro et al., 2008). In acute promyelocytic leukemia cell lines, the combination of low concentrations of ATRA with atorvastatin or fluvastatin resulted in a strong cell differentiation, and in retinoid-resistant cell lines, statins reverted the resistance to

ATRA-induced differentiation (Sassano et al., 2007). It is noteworthy that, in NB4 human acute promyelocytic leukemia cells, several genes associated with differentiation and apoptosis were selectively induced by treatment with the atorvastatin and ATRA combination through direct or indirect activation of the JNK-mediated pathways (Sassano et al., 2009). Evidence demonstrated an increased efficacy of cytosine arabinoside used in combination with fluvastatin or mevastatin in both leukemic cell lines and in primary culture of cells obtained from patients with AML (Holstein and Hohl, 2001a,b; Lishner et al., 2001; Stirewalt et al., 2003; Roudier et al., 2006). In particular, an additive effect was demonstrated for mevastatin combined with cytosine arabinoside, whereas fluvastatin associated with cytosine arabinoside seemed to possess synergistic activity. In pancreatic cancer cell lines treated with gemcitabine and fluvastatin, similar results were obtained (Bocci et al., 2005). The antileukemic additive effects of statins seem ascribable to the inhibition of ERK1/2 kinases (Holstein and Hohl, 2001a,b).

The combined effect of statins and multikinase inhibitors has been also tested in several different tumor cell lines. In particular, lovastatin and sorafenib produced a synergistic cytostatic effect through induction of cell cycle arrest in G₁ phase (Bil et al., 2010). On the other hand, this combination showed a strong synergistic cardiotoxic effects in rat H9c2 cardiomyoblast cell line (Bil et al., 2010).

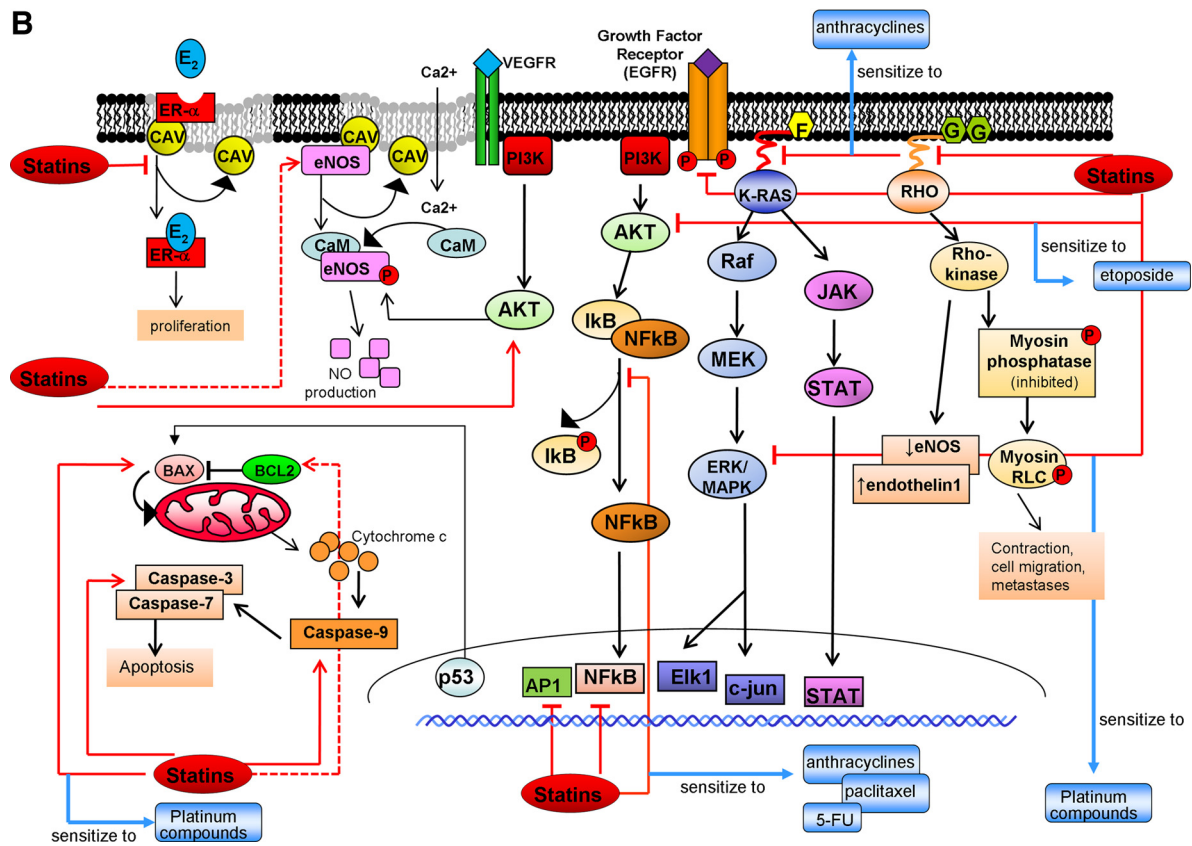
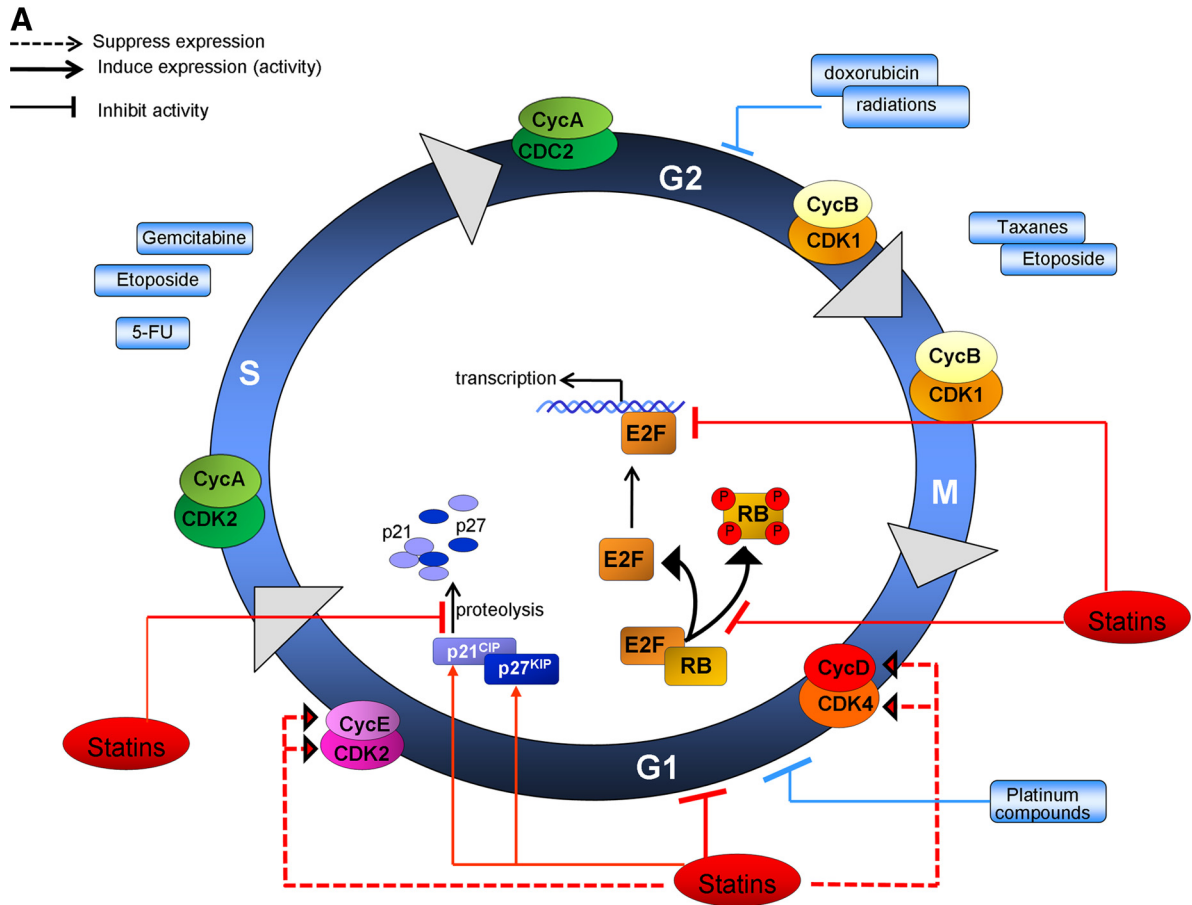
Finally, increasing evidence showed that statins enhanced the sensitivity of tumor cells to radiotherapy (Fritz et al., 2003). This effect was mediated by direct interference with RAS functions (Grana et al., 2002) and G₁ arrest of the cell cycle (Sivaprasad et al., 2006; Saito et al., 2008; Javanmoghadam-Kamrani and Keyomarsi., 2008), in addition to the arrest in G₂ phase induced by radiation.

D. Clinical Trials: Monotherapy and Combined Therapy Using Statins in Human Cancer

In patients with cancer, the efficacy of the statins as chemotherapeutic drugs has been evaluated both in monotherapy and in combined therapy with currently used chemotherapeutic drugs (Table 5).

Lovastatin administered by mouth (2–45 mg/kg per day) for 7 days at monthly intervals, has been tested in patients with cancer for whom standard therapy failed or who harbored a disease for which no therapy was helpful (Thibault et al., 1996). Results showed that one patient (among 88 treated) affected by recurrent high-grade glioma, achieved a minor response. Moreover, patients treated with doses higher than 25 mg/kg per day experienced myopathy, which was counteracted by the coadministration of ubiquinone.

Because statins have been showed to increase the radiosensitivity of tumor cells, a group of patients with relapse after radiotherapy was treated with 30 mg/kg lovastatin per day consecutively administered for 7 days



and than repeated after 4 weeks. In the same study, patients first receiving the diagnosis of glioma were treated with radiotherapy combined with various doses of lovastatin. One patient was stable for more than 402 days; a minor response and a partial response were observed in two different patients (Larner et al., 1998). A similar therapeutic protocol (one daily administration of lovastatin 30 mg/kg, combined with ubiquinone, for 7 days, repeated at 4-week intervals) was used in patients with advanced unresectable gastric adenocarcinoma (Kim et al., 2001). Results showed that no patients achieved a response or a persistently stable disease.

Increasing doses of lovastatin (starting at 5 mg/kg per day for 2 weeks, every 21 days) were tested in advanced cancer of the head and neck (SCC) and of the cervix in a phase I-II study (Knox et al., 2005). The aim of the phase I study has been to identify safety, maximum tolerated dose, and recommended phase II dose of lovastatin. The scheduled treatment with 7.5 mg/kg lovastatin per day administered for 21 days, every 28 days, did not find an objective response but induced stable disease for more than 3 months in 23% of patients.

The efficacy of pravastatin in chemotherapy was tested in patients with unresectable hepatocellular carcinoma in a controlled randomized trial performed by Kawata et al. (2001). At diagnosis, patients underwent transcatheter arterial embolization and then were treated with oral 5-FU for 2 months. Among 91 patients initially enrolled in the

study, 83 were then randomly assigned to control and pravastatin (20 mg daily for 2 weeks followed by 40 mg daily) groups. Both groups received concomitant 5-FU chemotherapy. Results showed that pravastatin slowly but significantly reduced the diameter of the main hepatic lesions 1 year after the start of the treatment. Moreover, the median survival was 18 months in the pravastatin group versus 9 months in the control group.

A significant prolonged survival has been also reported in a recent cohort study analyzing 183 patients with hepatocellular carcinoma (HCC) (Graf et al., 2008). All patients received palliative treatment with transarterial chemoembolization (TACE) and then were assigned to a treatment group (oral pravastatin at 20–40 mg/day; $n = 52$) or to a control group (treated with TACE alone; $n = 131$). Results showed that during the ≤ 5 -year observation period, median survival was significantly longer in patients with HCC treated by TACE and pravastatin (20.9 months; 95% CI, 15.5–26.3; $p = 0.003$) than in those treated by TACE alone (12.0 months; 95% CI, 10.3–13.7). On the other hand, pravastatin failed to improve the median survival of patients with HCC analyzed in the randomized controlled trial performed by Lersch et al. (2004).

In a retrospective multivariate analysis, statin use significantly improved the response to neoadjuvant chemoradiation in patients with resectable nonmetastatic rectal cancer (Katz et al., 2005). Simvastatin has

Fig. 2. Cellular and molecular sites of action of statins. Potential positive and negative effects of combined use of statins and chemotherapeutic drugs. The figure shows the mechanisms involved in statin antitumor effects. Red arrows indicate the effect of statins on cell cycle phases and on specific components of the intracellular pathways; blue arrows indicate the site of action of chemotherapeutic drugs (A) and statin-mediated effects able to sensitize cancer cells to specific chemotherapies (B). A, statins inhibit the proliferation of cancer cell lines by G₁-phase cell-cycle arrest through increased expression of the cell-cycle kinase inhibitors p21^{Cip1/WAF1} and p27^{Kip1} and inhibition of their proteolysis. Another mechanism by which statins inhibit cancer cell growth involves the down-regulation of cell-cycle-promoting mediators cyclin D1 (CycD), cyclin E (CycE), and cyclin-dependent kinase (CDK) 4 expression as well as the reduction of both levels and activity of CDK2. Finally, statins inhibit retinoblastoma protein (Rb) phosphorylation and consequently stabilize the transcriptionally inactive complex E2F-Rb. A direct inhibition of the E2F transcription factor activity has been also reported. The proliferative response of cancer cells is blocked by platinum compounds or anthracyclins combined to radiotherapies by arrest of G₁- or G₂-phase of the cell cycle, respectively. Statins showed a synergistic or an additive inhibitory effect on human cancer cell proliferation, when used in combination with these chemotherapeutic drugs, acting by several mechanisms at different phases of the cell cycle. B, in human cancer cell lines, statins control cancer cell growth by interfering with several intracellular pathways that differ according to cancer histological type, dose, and statin type (see section V.C for details). At least four potential antitumor mechanisms have been described, some of which also seem to be responsible for statin-induced sensitization of cancer cell lines to the treatment with chemotherapeutic drugs: inhibition of the small G-protein activities, modulation of several transduction pathways, induction of apoptosis, and destabilization of lipid rafts and caveolae. Moreover, statins can modulate the angiogenesis and impair the metastatic potential of tumor cells. Statins reduce the amount of farnesylated (mainly K-Ras) and geranylgeranylated (Rho and Rac) proteins localized in the plasma membrane by inhibition of the HMG-CoA reductase activity. Delocalization of the small G-protein Rho into the cytoplasm impairs the activation of the Rho-kinase pathway, which induces contraction, cell migration, metastatic processes, and modulation of the endothelin1 and eNOS. The statin-induced inhibition of K-Ras farnesylation improves the sensitivity of tumor cells to the anthracyclines by impairing the activation of the serine-threonine kinase Raf-1 and of the downstream effectors of the MAPK pathways involved in cell cycle progression and proliferation. Moreover, statins directly inhibit the activation of both Akt and MAPK/ERK kinases, sensitizing several human cancer cell lines to the effects of etoposide and platinum-derived compounds, or to anthracyclines, taxanes, and 5-FU by stabilizing NF- κ B inactive cytoplasmic form associated with inhibitor of NF- κ B (I κ B). Finally, statins block the DNA-binding activity of the transcription factors adapter protein 1 (AP1) and NF- κ B. Specifically, lovastatin inhibits EGF-induced EGFR autophosphorylation, whereas combination of lovastatin and gefitinib (a reversible selective EGFR-tyrosine kinase inhibitor) or lovastatin and cetuximab (a monoclonal antibody targeting the EGFR) results in enhanced cytotoxicity. Statin treatment suppresses the expression of the antiapoptotic Bcl2 protein and up-regulates that of the proapoptotic Bax, responsible for cytochrome *c* release from the mitochondria, leading to the activation of caspase 9. Statins can also directly induce caspase 3, 7, and 9 activity. Lipid rafts and Cav1, a membrane protein localized in the cholesterol-rich domain named caveolae, regulate several signal transduction proteins, including steroid (both androgen and estrogen) receptors and the inactive form of eNOS. Signal transduction pathways involving Cav1 can be impaired by drugs that disperse plasma membrane cholesterol or disaggregate the lipid rafts. The palmitoylated cytosolic estrogen receptor α (ER- α) localizes to the plasma membrane associated with Cav1. The estradiol-induced activation of ER- α dissociates the receptor from Cav1 and triggers proliferation of breast cancer cells. Statins, impairing the ER- α -Cav1 association, inhibit ER- α localization to the plasma membrane and reduce the proliferation triggered by the estrogen-mediated nongenomic pathway in breast cancer cell lines. A similar mechanism of action has also been demonstrated for the membrane-associated androgen receptor in human prostate cancer cell lines. In endothelial cells, the activation of VEGFR, or the increase of cytosolic calcium through the activation of calmodulin (CaM), induces the release of eNOS from Cav1. eNOS binds to calmodulin, becomes phosphorylated by VEGFR-activated Akt, and produces NO, which triggers endothelial cell proliferation, migration, and vascular permeability, all processes involved in angiogenesis. Low doses of statins dissociate eNOS from Cav1, induce Akt activation, and stimulate angiogenesis. On the other hand, high doses of statins seem to inhibit the proangiogenic pathway.

TABLE 5
Human clinical trials reporting statin use in cancer therapy

Study	Statin	n	Tumor Type	Therapeutic Protocol	Results	Side Effects
Thibault et al. (1996)	Phase I: Lovastatin (2–45 mg/kg/day)	88	38 Prostate 7 Breast 4 Colorectal 4 Ovary 3 Sarcoma 2 Lung 6 Others	p.o. for 7 consecutive days in monthly cycles, increasing doses in the next cycle when well tolerated in the first	Minor response (45% reduction in tumor size maintained for 8 months) in one anaplastic astrocytoma	Incidence and severity of toxicity (mainly myopathy, nausea, diarrhea, fatigue, abdominal pain) increasing for dose level higher than 25 mg/kg Myalgias partially controlled by ubiquinone administration
Vitols et al. (1997)	Open nonrandomized pilot study: simvastatin (40 mg)	10	B-cell CLL, previously untreated	p.o. 40 mg daily by a single oral dose for 12 weeks	No significant change in the clinical disease status during treatment; 40% of patients developed progressive disease during the subsequent year and 60% within 2 years after stopping simvastatin	No adverse reactions experienced during the treatment
Larner et al. (1998)	Phase I: lovastatin	18	Anaplastic glioma or glioblastoma multiforme	Lovastatin 30 mg/kg/day for 7 days at 4-week interval; recurrent disease after radiotherapy (<i>n</i> = 9) received lovastatin alone; newly diagnosed patients (<i>n</i> = 9) received radiotherapy plus lovastatin	One partial response; one minor response; one stable disease for a period longer than 400 days	Mild toxicity; mild pain in 2 patients
Kawata et al. (2001)	Randomized controlled trial: pravastatin (40 mg)	83	HCC pretreated with TAE, infusion of 30 mg doxorubicin followed by oral 5-FU (200 mg daily) for 2 months	Pravastatin group (<i>n</i> = 41): p.o 20 mg/day for 2 weeks, followed by 40 mg/day (for 16.5 ± 9.8 months); control group (<i>n</i> = 42), not treated with any anticancer drugs.	No significant differences in Karnofsky performance status between treated and control group; slight improvement or stable status in the liver functions in treated group compared with control; in pravastatin-treated group, median survival higher than in control group (18 vs. 9 months)	No adverse reactions experienced during the treatment
Kim et al. (2001)	Phase II: lovastatin (35 mg/kg/day)	16	Locally advanced and metastatic adenocarcinoma of the stomach, previously treated with systemic chemotherapy	p.o. 35 mg/kg/day in four divided doses for 7 consecutive days in monthly cycles (median, two cycles) ubiquinone (p.o. 240 mg daily) coadministered with lovastatin	No significant responses	Anorexia in the 64% of patients; myalgia in two patients (12.5%)
Minden et al. (2001)	Case report lovastatin	1	Relapsed AML	40 mg/day	Partial control of the leukemic blast cells	Not reported

TABLE 5—Continued.

Study	Statin	n	Tumor Type	Therapeutic Protocol	Results	Side Effects
Lersch et al. (2004)	Randomized controlled trial: pravastatin (40–80 mg)	58	HCC previously treated with 3 × 200 µg/day octreotide for 2 months	Octreotide group (n = 30): 20 mg octreotide LAR every 4 weeks; pravastatin group (n = 20), 40–80 mg pravastatin; gemcitabine group (n = 8), 80–90 mg/m ² over 24 h weekly in cycles of 4 weeks	No significant differences in tumor responses; pravastatin failed to prolong median survival	Not reported
Katz et al. (2005)	Retrospective multivariate analysis: all statins	349	Clinically resectable nonmetastatic rectal cancers; among these 33 statin users	Prasugely neoadjuvant chemoradiation (median dose, 50.4 Gy) and concurrent chemotherapy with 5-FU	No differences in clinical stages at time of diagnosis; in statin users, improved pathologic complete response rate after neoadjuvant chemoradiation	
Knox et al. (2005)	Phase I: Lovastatin (5–10 mg/kg/day)	26	14 HNSCC and 16 CC, advanced or recurrent	Lovastatin (5–10 mg/kg/day) for 2 weeks every 21 days	No significant responses; slight effect in disease stabilization	Muscle toxicity at 10 mg/kg/day for 14 days
Graf et al. (2008)	Cohort study: pravastatin	183	HCC patients selected for palliative treatment by TACE; 52 received TACE combined with pravastatin; 131 received chemoembolization alone	Pravastatin (20–40 mg/day)	In HCC treated by TACE and pravastatin, median survival was significantly longer than that in HCC treated by TACE alone (20.9 vs. 12.0 months)	Not reported
Kornblau et al. (2007)	Phase I: Pravastatin (40–1680 mg/day)	37	15 Newly diagnosed patients with AML; 22 salvage patients with AML	Pravastatin (40–1680 mg/day) administered p.o. once daily for 8 days; idarubicin (12 mg/m ² /day), intravenously, days 4–6; and cytarabine (1.5 g/m ² /day) by continuous infusion, days 4–7, coadministered with pravastatin	Among 15 newly diagnosed patients 11 experienced complete remission; in 9 of 22 salvage patients, a complete remission was obtained	No toxicity occurred at a frequency higher than that expected with the standard idarubicin-cytarabine protocols; no significant increase in the frequency and severity of toxicity associated with pravastatin dose escalation.
Lee et al. (2009)	Phase II: Simvastatin	49	Metastatic adenocarcinoma of the colon or rectum	Simvastatin (40 mg, p.o. once daily during the period of chemotherapy) coadministered with FOLFIRI (irinotecan 180 mg/m ² /90-min infusion; leucovorin 200 mg/m ² , 2-h infusion; 5-FU 400 mg/m ² bolus injection followed by 2400 mg/m ² as a 46-h continuous infusion), repeated every 2 weeks	Response rate (46.9%) and median survival time (21.9 months) similar to that obtained with FOLFIRI alone; modestly prolonged TTP (9.9 months) compared with FOLFIRI alone	No toxicity higher than that induced by FOLFIRI alone; no patients experienced myotoxicity or increase in serum creatine phosphokinase

CLL, chronic lymphocytic leukemia; TAE, transcatheter arterial embolization; CC, cervix carcinoma; HNSCC, head and neck SCC.

been tested in combination with folinic acid (leucovorin)/5-FU/irinotecan (FOLFIRI), a conventional second-line therapy used in colorectal cancer (Lee et al., 2009). Forty-nine patients affected by metastatic adenocarcinoma received 40 mg of simvastatin once daily by mouth during the period of FOLFIRI chemotherapy. In these patients, the overall responsive rate and the median survival were similar to that obtained with FOLFIRI alone. Moreover, the simvastatin-FOLFIRI combination treatment induced a slight increase in the time to progression (9.9 months; 95% CI, 6.4–13.3), and simvastatin did not increase the toxicity achievable with FOLFIRI alone. Finally, lovastatin and simvastatin were tested in patients affected by different histological types of leukemia. In 10 patients with chronic lymphocytic leukemia, oral simvastatin (40 mg daily for 12 weeks) induced no significant change in the clinical disease status, and 40% of the patients experienced a progression of the neoplasia during the subsequent year (Vitols et al., 1997). In a case report (Minden et al., 2001), lovastatin, at a dose double than that usually recommended for hypercholesterolemia, induced apparent control of the leukemic blast cells in a 72-year-old woman with relapsed AML. Because the AML blasts exposed to cytostatic agents increased their cellular cholesterol levels, which represents a mechanism able to induce chemoresistance, it is possible that statins, acting as HMG-CoA reductase inhibitors, improved the sensitivity to antitumor treatments. Encouraging results reported by a phase I study (Kornblau et al., 2007) seem to corroborate the effectiveness of statin use as adjuvant compounds in AML. Thirty-seven subjects (15 newly diagnosed and 22 salvage patients) received the Ida-HDAC regimen [idarubicin, 12 mg/m² per day, days 4–6, and high-dose cytarabine (HDAC), 1.5 g/m² per day, by continuous infusion, days 4–7], coadministered with pravastatin (40–1680 mg/day, by mouth, days 1–8). Complete remission was obtained in 73% (11/15) of new patients and in 41% (9/22) of salvage patients. Moreover, this scheduled treatment induced a toxicity similar to that expected with the standard Ida-HDAC protocols (Kornblau et al., 2007).

VI. Conclusions and Future Directions

Increasing evidence demonstrates the pleiotropic effects of statins, suggesting a potential use of these compounds beyond their lipid-lowering properties in several acute and chronic diseases. To date, in our opinion, the more promising applications of statins in human seem to be related to their antiinflammatory effects, mediated by both direct (via modulation of the immune-response) and indirect (via inhibition of platelet functions) mechanisms, and their ability to modulate bone metabolism.

A number of studies analyzed the cancer risk in statin users. The main difficulties in ascertaining the real role of statins in cancer occurrence are the lack of clinical and historical data for the examined patients; the pres-

ence of a consistent number of confounding variables, which produced conflicting results and accounted for unconvincing evidence; the moderate number of studies considering the cancer incidence as primary endpoint; and the heterogeneity in patient samples and in cancer types considered. Large, rigorous meta-analyses (Dale et al., 2006; Kuoppala et al., 2008) showed that statins have a neutral effect on cancer risk, and no type of cancer was affected by statin use. A meta-analysis evaluating the risk of colorectal cancer was performed by Bonovas et al. (2007). They found no evidence of association between statin use and risk of colorectal cancer either among randomized controlled trials (RR, 0.95; 95% CI, 0.80–1.13) or among cohort studies (RR, 0.96; 95% CI, 0.84–1.11), even if case-control studies suggested a slight reduction in the risk of colorectal cancer occurrence (RR, 0.91; 95% CI, 0.87–0.96). On the other hand, to date, no sufficient data are available to define the long-term effects of prolonged statin use up to 10 years and beyond.

Some authors have suggested a partial protective effect of statins on the occurrence of high-grade cancers, which account also for the favorable prognosis of the tumors and good response to therapies. In our opinion, this hypothesis suffers from a common confusing variable: patients taking statins are subjects that frequently undergo clinical and serological evaluations aimed to control therapy and chronic disease. The medical surveillance and the early evidence of the neoplasia is the real cause of the lack of high-grade tumors and, then, of the reduced number of relapse and of nonresponder status.

The potential efficacy of statins as therapeutic drugs has been also evaluated. At least two problems have to be considered. First, statins differ in their solubility and their hydrophobic/hydrophilic rate, which governs their biochemical function at extrahepatic sites (Duncan et al., 2005). In particular, hydrophilic pravastatin does not enter normal extrahepatic cells or malignant cells of extrahepatic origin, and this property could account for a reduced effect in cancer types other than HCC. Moreover, tumor tissues are frequently sites of edema, necrosis, vascular remodeling, all processes that could significantly modify the doses of statins able to penetrate tumor tissues. Second, statin doses able to induce both antiproliferative and antiangiogenic effects were higher than those used in lipid-lowering protocols. Several studies showed that lovastatin used at doses higher than 25 mg/kg per day (Thibault et al., 1996) or at 10 mg/kg per day for 14 days (Knox et al., 2005) induced severe muscle toxicity and frequently anorexia, nausea, diarrhea, fatigue, and abdominal pain, often only partially counteracted by a very modest anticancer effect.

An encouraging result has been reported by Kawata et al. (2001) in a randomized controlled trial performed in patients with HCC. The authors found that 40 mg/day pravastatin significantly increased the median survival (doubled in pravastatin-treated group compared with

untreated group). Similar results have been reported from the analysis of a cohort of 183 patients with advanced HCC treated with palliative TACE and pravastatin (Graf et al., 2008). On the other hand, Lersch et al. (2004) failed to replicate these results in HCC previously treated with octreotide for 2 months. Knox et al. (2005) found a disease stabilization of 23% in patients with cervical carcinoma or head and neck SCC treated with prolonged administration of lovastatin. The authors considered the obtained results encouraging, but stable disease (more than 2 years) was obtained in only one patient treated with EGFR inhibitor, despite progression of the disease, before taking lovastatin.

In metastatic colorectal cancers, 40 mg of simvastatin administered without resting during FOLFIRI chemotherapy (Lee et al., 2009) showed a weak cytostatic effect proved by a prolonged time to progression but did not improve the median survival. Fair results have been obtained in a phase I study performed in patients with AML treated with the combination IdA-HDAC and high doses of pravastatin (Kornblau et al., 2007). Among 37 patients enrolled in the study, 54% experienced a complete remission, and subjects receiving repeated cycles relapsed at a median period longer than 20 months.

In summary, clinical trials performed with statins used as anticancer treatment in human are largely heterogeneous and produced slight evidence of a real efficacy as adjuvant therapy. The statins possess mainly cytostatic but not cytotoxic effects on tumors, patients experienced relapse at the end of the treatment with high doses of statins, and the prolonged median survival seems not to be achievable in different types of cancer. However, it is relevant to consider that combining a specific statin with different chemotherapies or administering statins after several first-line treatments does not necessarily produce similar results. In our opinion, data obtained from trials in HCC, in AML, and partially in colon cancer deserve the planning of larger and homogeneous trials able to elucidate the tumor types, the therapeutic regimen, and the subgroup of patients that could really benefit from statins used as adjuvant drugs. Moreover, a large clinically and socially relevant goal will be to evaluate the role of statins in the possibility of overcoming resistance to biological therapies (e.g., cetuximab and bevacizumab) or at least to improve the responsiveness in tumors carrying Ras or ErbB2 activation.

Despite the partial or minor response obtained in clinical trials, *in vitro* evidence showed great anticancer potential for statins used in combination with chemotherapeutic compounds usually used in the clinical practice. In the last decade, a significant improvement in polychemotherapies has been obtained with the introduction of monoclonal antibodies, also known as biological agents. In human breast cancer cell lines, fluvastatin combined with trastuzumab (a monoclonal antibody against ErbB2) demonstrated a synergic cytotoxic effect; thus, their combination seems to represent a good chance to increase the incom-

plete efficacy achievable with trastuzumab alone in Her2-positive breast tumors (Budman et al., 2007). Moreover, daily oral intake of simvastatin or fluvastatin produced significant *in vivo* antitumor effects in the ErbB2-transformed Neu transgenic mouse A mammary cancer model through reduction of both proliferation and survival of the tumor cells (Campbell et al., 2006).

In human HCC cell lines, fluvastatin showed a synergistic antiproliferative effect with cetuximab, a monoclonal antibody targeting the EGFR (Huether et al., 2005). HCC cell lines carrying mutations of p53 are less sensitive to cetuximab treatment, but in these cellular models, the combined use of cetuximab and erlotinib or fluvastatin induced a significant reduction of the cell growth (Huether et al., 2005).

Finally, statins (mainly lovastatin) potentiated the antiproliferative effects of gefitinib, a potent tyrosine kinase inhibitor of EGFR, in SCC, non-small-cell lung cancer, colorectal cancer cell lines (Mantha et al., 2005), and glioblastoma-derived cell lines (Cemeus et al., 2008), probably through enhanced inhibition of the PI3K/Akt pathway.

The management of cancer patients frequently needs to accommodate, besides the tumor control and the choice of the therapeutic options, several concomitant diseases and complications triggered by the neoplasia, which represent the main cause of therapy disruption and the reduced quality of life. In this matter, statins could provide some benefit.

A new field of research is highlighting that statin use might confer protection against the risk of developing venous thromboembolism in patients with solid organ tumors, who are considered to be another high-risk population for the thrombotic events attributed to the hypercoagulable state caused by the disease and its treatments (Caine et al., 2002). In this context, a retrospective, case-control study reviewing 740 consecutive patients with a diagnosis of solid organ tumor suggested for the first time that in cancer patients, the use of statins decreased the odds ratio (0.33) of developing venous thromboembolism (95% CI, 0.19–0.57; $p \leq 0.05$) compared with nonstatin users (Khemasuan et al., 2010). These preliminary data are encouraging but suffer from some limitations, so a prospective, randomized, placebo-controlled trial would provide further support and stronger evidence for this finding, making the statins a possible safe alternative anticoagulant medication to the commonly used warfarin for venous thromboembolism in cancer patients. In the same context, it has been proposed that statins, thanks to their potent antiplatelet and anti-inflammatory effects, together with the cytoreductive potential and restoration ability of endothelial dysfunction, may have potential clinical benefits in decreasing the thrombohemorrhagic complications in patients affected by classic Philadelphia chromosome-negative myeloproliferative disorders, polycythemia vera, essential thrombocythemia, and idiopathic myelofibro-

sis (Hasselbalch and Riley, 2006). Moreover, taking advantage of their antiplatelet functions, statins might also act as modulators of allograft outcome, potentially reducing the hypercoagulability seen in transplant recipients (Mehra et al., 2002).

Metastases to bone are a frequent progression of several tumors and pain associated with this localization of the neoplasia represent a heavy burden for patients. Bone can be affected by several neoplastic conditions, which can include both primary bone tumors and metastatic diseases. Bisphosphonates are a class of agents most frequently used to reduce these types of skeletal cancer-related events by inhibiting osteoclast activity. In the light of this evidence, statins, by inhibiting the same pathway, may be useful to decrease these skeletal cancer-related events. To date, statins have been demonstrated to exert antitumor effects on primary osteosarcoma cells, and very recently, *Cyr61* gene has been identified as a new target of this action (Fromiguet et al., 2011). As proposed, simvastatin acts as an inhibitor of osteolysis, preventing skeletal metastasis in a mouse model of breast cancer skeletal metastasis of human mammary cancer cell MDA-MB-231, which expresses the mutant p53R280K. This effect has been associated with the decreased expression of CD44, which highly correlates with the level of oncogenic p53 (Mandal et al., 2011) and the invasive potential of the tumor.

In conclusion, despite the inconclusive results obtained in human by the little phase I-II studies performed to date, the statins could represent a fair possibility to improve adjuvant therapies at least in some cancer types, such as HCC, colorectal cancer, and AML, but this hypothesis needs to be corroborated by large and well planned clinical trials.

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Authorship Contributions

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