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Statins, Bcl-2, and Apoptosis: Cell Death or Cell Protection?

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Abstract Statins have proven their effectiveness in the treatment of cardiovascular disease. This class of drugs has also attracted attention as a potential treatment for dissimilar diseases such as certain types of cancers and neurodegenerative diseases. What appears to be a contradiction is that, in the case of cancer, it has been suggested that statins increase apoptosis and alter levels of Bcl-2 family members (e.g., reduce Bcl-2 and increase Bax), whereas studies mainly using noncancerous cells report opposite effects. This review examined studies reporting on the effects of statins on Bcl-2 family members, apoptosis, cell death, and cell protection. Much, but not all, of the evidence supporting the pro-apoptotic effects of statins is based on data in cancer cell lines and the use of relatively high drug concentrations. Studies indicating an anti-apoptotic effect of statins are fewer in number and generally used much lower drug concentrations and normal cells. Those conclusions are not definitive, and certainly, there is a need for additional research to determine if statin repositioning is justified for noncardiovascular diseases.

Keywords Alzheimer's disease · Apoptosis · Bcl-2 · Cancer · Cholesterol · Isoprenoids · Neuroprotection · Neurodegeneration · Statins

Statins are well-recognized for their efficacy in the prevention/treatment of cardiovascular disease, a topic which has been extensively reviewed [1]. Statins reduce cholesterol synthesis and increase the uptake of low-density lipoproteins (LDL). Within the mevalonate pathway, these drugs also have cholesterol-independent effects, namely, the reduction of the two isoprenoids farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). Reducing FPP and GGPP decreases the prenylation of small GTPases, and it is thought that such a mechanism may contribute to the reduction in morbidity and mortality occurring in cardiovascular disease [2, 3]. In addition to the use of statins in the prevention/treatment of cardiovascular disease, it has been suggested, albeit with some controversy, that these drugs may have efficacy in treating diseases such as various cancers, ischemic stroke, inflammatory diseases, and certain neurodegenerative diseases [4–8]. One of the proposed mechanisms for the effects of statins in noncardiovascular diseases involves changes in expression levels of the pro-apoptotic and anti-apoptotic Bcl-2 family of proteins. Several reports found that statins reduced the levels of the anti-apoptotic protein Bcl-2 and increased apoptosis and cell death. Some of those studies are summarized in Table 1. In contrast, there is evidence that statins increase Bcl-2 abundance which would favor and, in some instances, reduce apoptosis and cell death, and these are listed in Table 2. The purpose of this mini-review will be to focus on studies within the context of what appears to be contradictory findings regarding the effects of statins on Bcl-2 expression levels, apoptosis, cell death, and cell protection.

Statins, Bcl-2 Family Members, and Cell Death

One of the earliest studies associating statins with apoptosis and cell death reported on the effects of lovastatin (0.1 μM) on growth in two cell lines, dexamethasone-resistant and dexamethasone-sensitive lines derived from human acute T cell leukemia patients [9]. Cell death was induced by both lovastatin and dexamethasone, and the observation was made that the cells had "characteristics of apoptosis" but markers of apoptosis were not reported. Since that study, there have been additional [10–14] reports on statin-induced apoptosis and cell death (Table 1). Statin-induced apoptosis and/or cell death occurs in cancer cell lines (e.g., human acute leukemia lines,

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Table 1 In vitro and in vivo studies on statins, cell death, apoptosis, and Bcl-2 family members

Treatment	Tissue	Effects	Ref.
In vitro, L, 0.1 μM,	Dexamethasone resistant and sensitive human acute T cell leukemia	↑AP	9
In vitro, L, 0.1 μM, 72 h	Human glioma cell lines	↑AP	11
In vitro, L, 10 μM, 12+h	Human promyelocytic HL-60 leukemia cells	↑AP, but 2 μM no effect	10
In vitro, L, 50 μM, 48 h	NIH/3T3 fibroblasts overexpressing oncogene HA-ras	↑AP in HA-ras cells but not low expressing cells; Bcl-2 rescued effects	12
In vivo, F, 92 μM, 6 days	Serum form human subjects incubated with human smooth muscle cells	↑AP, ↓Bcl-2	21
In vitro, L, 50–200 mM, 24 h	Myeloid leukemia cell lines	↑AP, ↓Bcl-2	60
In vitro, L, 1–10 μM, 24 h	Immortalized rat brain neuroblasts	↑AP, ↓Bcl-2, Bcl-xL	24
In vitro, A, S, 10–100 μM, 48 h	Rat thoracic vascular smooth muscle cells	↑AP, ↓Bcl-2, Bax (ne)	30
In vitro, L, 10 and 30 μM, 4 days	Myeloma cell lines, not all lines responsive to L	↑AP, ↓Bcl-2, Bax (ne)	31
In vitro, C, 1 and 3 μM, 20 h	Rat aortic vascular smooth muscle cells	↑AP, ↓Bcl-2	61
In vitro, S, 0.1–1 μM, 18–24 h	Mouse tubular cells w/wo expressing Bcl-xL	↑AP, ↓Bcl-xL, Bax (ne), Bid (ne), overexpression reduced effects of S	25
In vitro, L, 5 μM, 24–48 h	Human glioblastoma cells lines	↑AP, ↓Bim, no effects Bcl-2, Bcl-xL, Bak, Bid, Bax	32
In vitro, A, F, L, S, 10 and 20 μM	Human vascular endothelial cells	↑AP, ↓Bcl-2	62
In vitro, M, 0.003–0.006 μM/ml, 24 and 48 h	U266 human myeloma cells	↑AP, ↓Bcl-2 mRNA, protein	23
In vitro, A, C, F, L, S, 30 μM, 24 h	Human adult hepatocytes	↑AP, ↓Bcl-2 mRNA, protein, Bax (ne)	63
In vitro, A, F, 50 μM, 4 days	Human breast cancer cells	↑AP, ↓Bcl-2	64
In vitro, F, 10 μM, 24 h	Human $CD4^+$ T cells	↑AP, ↓Bcl-2, Bax (ne)	33
In vitro, A, 10 μM, 24 h	Human osteosarcoma cells	↑AP, ↓Bcl-2 protein, mRNA, Bax (ne)	34
In vitro, P, S, 0.1, 1.25, 5 μM, 48 h	Human cardiac myocytes	↑AP, ↓Mcl-1, Bax (ne), ↑Mcl-1 by P; ↓Mcl-1 mRNA by S, 5 μM	35
In vitro, S, 1 and 10 μM, 24 h	Barret's adenocarcinoma cells	↑AP, ↓Bcl-2 mRNA and protein, Bax (ne) protein, ↑mRNA at 10 μM	65
In vitro, L, 1, 10, 20 μM, 3–24 h	Rat brain neuroblasts	↑AP, ↑BimEL	13
In vitro, L, 20 μM, 24 or 48 h	Human colon cancer cells	↑AP, no effects on Bcl-2, Bcl-xL	66
In vitro, S, 5 μM, 48 h	Human breast cancer cells	↑AP↓Bcl-2 mRNA, no effects on Bcl-xL and Bax	36
In vitro, L, P, S, 20 μM, 24 h	Barret's adenocarcinoma cell lines	↑AP, ↑Bad, Bax mRNA and protein levels, no effects on Bcl-2, Bcl-xL	14
In vitro, S, 10 μM, 48 h	Human colon cancer cells	↑AP, ↓Bcl-2 and Bcl-xL mRNA and protein levels	27
In vitro, L, M, P, S, 1–20 μM, 72 h	Normal and abnormal human embryonic stem cells; breast adenocarcinoma cells	Inconsistent results on mRNA levels of Bcl-2 and Bax when incubated with S	67
In vitro, S, 1–20 μM, 12–24 h	MethA fibrosarcoma cells	↑AP, ↑Bax translocation to mitochondria	68
In vitro, F, 5–20 μM, 24 h	Human hepatocellular carcinoma cell lines	↑AP, ↓Bcl-2	69
In vivo, R, 20 μM, orally once daily for 6 weeks	CD4(+)C28(null) T of patients with acute coronary syndromes	↑AP, ↓Bcl-2	22
In vitro, S, 0.6–10 μM 72 h	ARH77multiple myeloma cell line	↑AP, ↓Bcl-2, Bax (ne)	37
In vitro, S, 25 μM, 16 h	Human prostate cancer cell lines	↑AP, BimL/BimS, ↓Bcl-2, Bcl-xL, pBad	28
In vitro, S, 20 μM, 24–72 h	MCF7 human breast cancer cells, SAEC human normal small airway epithelial cells, HepG2 human hepatocellular carcinoma cells, NCI-N87 human gastric cancer (NCI gastric cells), and NCiH12299 human non-small cell lung carcinoma (NCH lung) cells	Effects seen in cancer cells but not normal cells: ↑AP, ↑Bax mRNA, ↓Bcl-2 mRNA	52

AP apoptosis, *A* atorvastatin, *C* cerivastatin, *F* fluvastatin, *L* lovastatin, *M* mevastatin, *ne* no effects, *P* pravastatin, *S* simvastatin

human promyelocytic HL-60 cells, malignant glioma cells, Barrett's esophageal adenocarcinoma cells) and noncancer cells (e.g., mouse fibroblasts, rat brain neuroblasts). There is some evidence suggesting that different types of cancer are more susceptible to statins as compared with others [4]. A common feature of many of those studies is that high statin

Table 2 In vivo and in vitro studies on statins, cell protection, apoptosis, and Bcl-2 family members

Treatment	Tissue	Effects	Ref.
In vivo, S, 120 μM/kg, orally, 21 days	Mouse, brain, microarray analysis, statin levels determined	↑Bcl-2 mRNA, protein levels	40
In vivo, S, 120 μM/kg, orally, 21 days	Guinea pig, brain and dissociated brain cells	↓AP,↑Bcl-2, ↓Bax↑P	41
In vivo, S, 2.4 μM/kg, i.p., 2 weeks	Rat quinolinic acid model of Huntington's disease, brain striatum	↑Bcl-2, ↓Bax, ↑P	42
In vivo, A, 41 μM/kg, orally, 3 weeks	Spontaneously hypertensive rats	No effects on AP, Bcl-2, or Bax	46
In vivo, Pita, 0.363 and 0.726 μM/kg, orally, 14 days	Rat ischemia model, heart tissue	↑Bcl-2, ↓Bax, CP	43
In vivo, S, 24 μM/kg, orally, 5 days	Rat ischemia model, ventricle tissue	↑Bcl-2, ↓Bax only in tissue from ischemic rats, CP	44
In vivo, S, 60 μM/kg, orally, 8 weeks	apoE null mice fed high-fat diet, aortic tissue	↑Bcl-2, ↑Bcl-xlL, Bax (ne), CP	45
In vitro, S, 0.1 μM, 6 days	Mouse primary neurons, SH-SY5Y cells	↓AP, ↑Bcl-2 mRNA, protein, CP	47
In vitro, F, 0.1 μM, 24 h	Human umbilical vein endothelial cells incubated with H_2O_2	↑Bcl-2 mRNA, protein, CP	48
In vitro, A, 1.0 μM, 6 h	Pig mesenchymal stem cells, hypoxic and serum-free conditions	↑Bcl-2, ↓Bax, CP	49
In vitro, S, 0.001–0.1 μM,	Human osteosarcoma cells treated with H_2O_2	↑Bcl-2, ↓AP, CP	50
In vitro, P, 50 μM, 5 min before and during 15 and 60 min reoxygenation	Human atrial trabeculae incubated under hypoxic and reoxygenation	↑Bcl-2 only during reoxygenation	51
In vitro, S, 5 μM, 48 h	Primary human skeletal muscle cells	↑Bcl-2, Bax, AP	29

AP apoptosis, *A* atorvastatin, *CP* cell protection, *F* fluvastatin, *ne* no effects, *Pita* pitavastatin, *P* pravastatin, *S* simvastatin

concentrations (from micromolar to millimolar amounts) were required to cause apoptosis and cell death, although there are exceptions [9], including a study showing that lovastatin beginning at 0.1 μM induced DNA degradation in human glioma cells [11]. Although in that study, the effects of lovastatin on DNA degradation in another cell line, anaplastic astrocytoma, was not apparent until a drug concentration of 1 μM.

The pivotal roles that Bcl-2 family members play in apoptosis and cell death are well-recognized, and that large body of work has been extensively reviewed [15–20]. There have been several studies showing that statins alter the expression levels of Bcl-2 family members. This section will examine reports indicating that statins alter levels of proteins such as Bcl-2, Bcl-xL, and Bax. Reductions in Bcl-2 and Bcl-xL and an increase in Bax favor a pro-apoptotic cell environment. An early study reported that serum from normal human subjects receiving fluvastatin (92 μM/day for 6 days) added to human smooth muscle cells in vitro reduced Bcl-2 protein levels and increased apoptosis [21]. Similar findings were seen in T cells of patients with acute coronary syndromes who received rosuvastatin (20 μM/day for 6 weeks) [22]. There have been several in vitro studies using different statins (lovastatin, atorvastatin, simvastatin, pravastatin, and cerivastatin) and different noncancer and cancer cell lines demonstrating that, generally, statins at high concentrations reduced Bcl-2 protein levels (Table 1). A notable exception to the observation that high statin concentrations are needed to act on Bcl-2 was a study that found that Bcl-2 protein and mRNA levels were reduced by lovastatin at concentrations of 2.4 and 6.2 nM/ml [23], although in that study, a Western blot showed that the lower lovastatin concentration had a larger reducing effect on Bcl-2 as compared with the higher concentration. The data did not appear to be semi-quantified (scanned); only a single experiment was shown, and so, it is not clear if differences were significant. Protein levels of another anti-apoptotic member of the Bcl-2 family, Bcl-xL were also reduced by statins (lovastatin and simvastatin) in different cell types (rat brain neuroblasts, mouse tubular cells, human myeloid KBM-5 cells, human colon cancer cells, and human prostate cancer cells PC3) [24–28]. While most studies using relatively high concentrations of statins have found that Bcl-2 levels were reduced, a recent study found opposite results [29]. Simvastatin (5 μM) significantly increased Bcl-2 protein levels in primary human skeletal myotubes, which was associated with decreased cell viability and enhanced oxidative stress [29]. A conclusion reached in that study was that the simvastatin-induced increase in Bcl-2 protein expression might have been a protective response to drug-induced cell death. In the same study, levels of the pro-apoptotic protein Bax were also significantly increased. Several studies have reported that statins did not alter Bax levels [25, 30–37].

Generally, at high statin concentrations, apoptosis is increased and Bcl-2 expression levels and cell viability are reduced. The mechanisms for the statin-induced reduction of Bcl-2 protein levels have not been forthcoming. Statins reduce cholesterol, FPP, GGPP, and protein prenylation, but how

those reductions trigger an attenuation of the anti-apoptotic protein Bcl-2 and increase the abundance of pro-apoptotic proteins such as Bax and Bim is not understood. There is evidence that statins can act outside of the mevalonate pathway. Statins, for example, bind to the lymphocyte function-associated antigen-1, which is a heterodimeric glycoprotein and is a member of the β2 integrin family [38, 39]. Directly related to the issue of statins and Bcl-2 is work discussed later in this review on Bcl-2 and cell protection showing that statins stimulate Bcl-2 gene expression and protein levels, which do not involve the mevalonate pathway.

Statins, Bcl-2 Family Members, and Cell Protection

In the previous section, studies that found that statins reduced Bcl-2 protein levels were reviewed. This section will examine in vivo and in vitro studies which found that statins increase Bcl-2 levels, and some of those studies are listed in Table 2. In 2005, our laboratory was the first to report that a statin, simvastatin, significantly increased Bcl-2 gene expression in brain tissue of mice receiving the drug orally (120 μmol/kg for 21 days) [40]. Separate groups of mice treated with lovastatin and pravastatin also showed increased Bcl-2 gene expression, but those differences were not significant. Simvastatin induction of Bcl-2 gene expression was detected using the Affymetrix DNA array and confirmed using RT-PCR. Bcl-2 protein levels were also significantly increased in simvastatin-treated mice. There were several other genes whose expression levels were also altered by statins (e.g., *Igfbp3*, *Hk1*, *c-fos*, *c-myc*, *Npy1r*, *MCT2*, *Sdc4*). In a subsequent study in collaboration with Walter Muller and Gunter Eckert, we replicated our findings on simvastatin induction of brain Bcl-2 protein levels but this time in the guinea pig, demonstrating that the drug increased Bcl-2 protein levels in another species [41]. In the same study, Bax protein levels were significantly reduced. Dissociated brain cells from the guinea pigs administered simvastatin in vivo exhibited neuroprotection when challenged ex vitro with sodium nitroprusside and the Bcl-2 protein inhibitor HA14-1. In an in vivo rat quinolinic acid model of Huntington's disease, simvastatin (2.4 μmol/kg i.p./day, 2 or 8 weeks) was neuroprotective [42]. Bcl-2 protein levels were increased, whereas levels of the pro-apoptotic protein Bax were reduced, results which are similar to what we observed in the brain tissue of simvastatin-treated guinea pigs [41]. Other in vivo studies [43–45] reported that statins increased Bcl-2 abundance and reduced apoptosis, and they are summarized in Table 2. An exception to those findings is a study showing that the administration of atorvastatin (41 μmol/kg for 3 weeks) did not significantly alter levels of Bcl-2 and Bax in aortic smooth muscle cells from spontaneously hypertensive rats [46]. Markers of apoptosis were not affected by atorvastatin treatment in those animals.

There is a body of data from in vitro studies showing that statins increase Bcl-2 and reduce apoptosis (Table 2), which is in agreement with the majority of in vivo studies discussed in this section. We reported that simvastatin (0.1 μM) significantly increased Bcl-2 mRNA and protein levels and provided neuroprotection in mouse primary neurons when challenged with oligomeric amyloid β-protein(42) [47]. When Bcl-2 expression was inhibited by the antisense oligonucleotide G3139, simvastatin neuroprotection was abolished in cells. The finding that inhibition of Bcl-2 eliminates the protective effects of simvastatin was replicated using another statin, fluvastatin (0.01–0.1 μM), and a different cell type, human vascular endothelial cells, which were challenged with H_2O_2 [48]. In that study, it was also observed that fluvastatin increased Bcl-2 mRNA expression and protein levels, which is consistent with the earlier study using simvastatin and mouse primary neurons [47]. Treatment of different cell types (mesenchymal stem cells, human osteosarcoma cells, and human atrial trabeculae) with statins (atorvastatin, simvastatin, and pravastatin) increased Bcl-2 protein levels and reduced markers of apoptosis [49–51], and those studies are summarized in Table 2.

Biphasic Effects of Statins on Bcl-2 Family Members

Statins reduce Bcl-2 mRNA and protein levels and increase apoptosis and cell death (Table 1). In stark contrast, Table 2 lists the studies reporting that statins increase Bcl-2 mRNA and protein levels, reduce apoptosis, and are protective. Many of the in vitro studies supporting a detrimental effect of statins used cancer cell lines, suggesting that cancer cells may respond differently to statins as compared to normal cells. It was recently reported that simvastatin (20 μM) reduced Bcl-2 mRNA and increased apoptosis in different cancer cell lines (MCF7 human breast cancer cells, HepG2 human hepatocellular carcinoma cells, NCI-N87 human gastric cancer NCI gastric cells, and NCiH12299 human non-small cell lung carcinoma NCH lung cells), but normal cells (SAEC human normal small airway epithelial cells) were unaffected [52]. However, in view of the fact that a high concentration of simvastatin was employed, the absence of an effect in the epithelial cells may be a unique property of those cells. The majority of studies showing that statins increase Bcl-2 mRNA and proteins levels and reduce apoptosis have used normal cells (Table 2). Exceptions have been studies using human neuroblastoma cells (SH-SY5Y cells) [47] and human osteosarcoma cells (MG63 cells) [50].

The two studies using cancer cell lines cited previously [47, 50] used low statin concentrations to stimulate Bcl-2 expression. The study with SH-SY5Y cells used a

simvastatin concentration of 0.1 μM and the study with osteosarcoma cells used simvastatin at concentrations ranging from 0.001 to 0.1 μM. The question is raised if statin concentration is a determining factor in whether Bcl-2 levels are increased or reduced. Figure 1 plots in vitro studies showing statins reducing or increasing Bcl-2 mRNA and protein levels as a function of statin concentration. There are more studies showing that Bcl-2 levels are reduced by statins as compared with those studies showing an increase. The majority of studies showing that statins reduce Bcl-2 levels used statin concentrations of 5 μM or greater. Studies showing that statins increase Bcl-2 levels used concentrations of 1 μM or less. Certainly, there were exceptions, but a guarded conclusion is that, whether statins increase or decrease Bcl-2, such effects are dependent on statin concentrations.

Mechanisms of Statin-Induced Changes in Bcl-2

Statins reduce cholesterol by reducing the production of mevalonate and upregulate the LDL receptor, producing an increase in the removal of LDL from the blood. Mevalonate is not only the precursor of cholesterol but it is the precursor of the two isoprenoids, FPP and GGPP. FPP is a midpoint precursor of cholesterol and the direct precursor of GGPP. Both FPP and GGPP prenylate small GTPases such as the Rho, Ras, and Rab family of proteins whose coordinated activity is critical for cell structure/function. Simvastatin reduces FPP and GGPP levels [53] and it has been proposed that the beneficial effects of statins may be due to a reduction in prenylation of specific proteins [3, 8, 54–56]. How such changes in the mevalonate pathway would cause changes in Bcl-2 levels is unclear. Bcl-2 gene expression has been found to be activated by the transcription factor NF-κB [57]. Simvastatin at a high concentration (50 μM) inhibited TNF-α-induced NF-κB activation which was associated with a reduction in Bcl-2 protein levels in human myeloid KBM-5 cells [26]. In the same study, however, it was noted that simvastatin alone had no effect on NF-κB activation.

There is evidence that endothelin-1 (ET-1) can increase Bcl-2 abundance via the transcription factor nuclear factor of activated thymocytes (NFATc) [58]. We found that simvastatin increased ET-1 gene expression whose product is the precursor of the ET-1 protein [40]. The hypothesis that simvastatin stimulation of Bcl-2 involves the upregulation of ET-1 and binding of NFATc to Bcl-2 promoter sites in SH-SY5Y human neuroblastoma cells was tested [59]. Simvastatin increased both intracellular and secreted ET-1 protein levels. Exogenous ET-1 increased Bcl-2 protein abundance, which was inhibited by ET-1 receptor antagonists. Simvastatin increased the translocation of NFATc3 to the nucleus while reducing nuclear NFATc1 and having no effect on NFATc4. The Bcl-2 promoter has multiple NFAT binding sites [58], and we found that treatment of cells with simvastatin stimulated the binding of NFATc3 to the Bcl-2 promoter. This study was the first to directly identify a transcriptional mechanism for the regulation of statin-induced changes in Bcl-2 protein levels. These results do not preclude other mechanisms, and the role of protein prenylation in Bcl-2 regulation remains unknown. Also, further study is needed on how statins alter levels of other Bcl-2 family members.

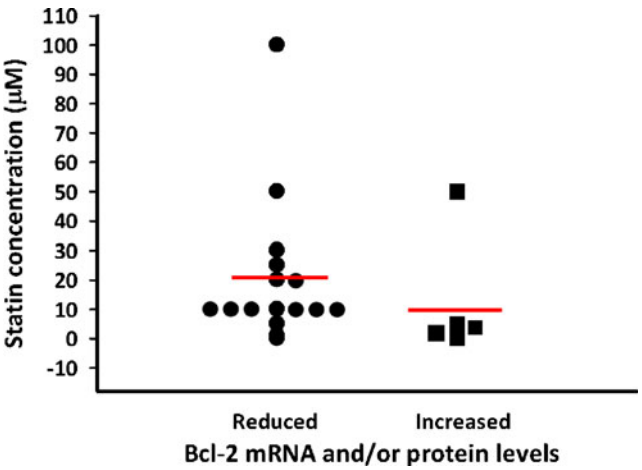

Fig. 1 Effects of statin concentration on Bcl-2 mRNA and protein levels in vitro. Studies reporting a reduction in Bcl-2 levels: 23–25, 28, 30, 31, 33, 34, 36, 37, 52, 60–66. Studies reporting an increase in Bcl-2 levels: 29, 40, 48–51. *Red lines* represent the means of each group

Summary

There is evidence that statins may be efficacious in treating certain types of cancers by acting on Bcl-2 family members and increasing apoptosis and cell death. Equally compelling are studies showing that statins reduce apoptosis and increase Bcl-2. Much, but not all, of the evidence supporting a pro-apoptotic effect of statins is based on data in cancer cell lines and the use of relatively high drug concentrations. Studies indicating an anti-apoptotic effect of statins are fewer in number and generally used low drug concentrations and normal cells. Several questions remain unanswered regarding statin effects on apoptosis, cell death/protection, and Bcl-2 family members. There has not been a comprehensive examination of differences in cell types, malignant versus nonmalignant in response to statins, or for that matter, comparisons across different normal cells types (e.g., neurons, astrocytes, endothelial cells, etc.). The clinical use of statins for the treatment of cardiovascular disease began in the 1970s. Much more work is needed to determine if statins have efficacy in noncardiovascular diseases such as different cancers and neurodegenerative diseases.

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