Background: Interleukin (IL)-33 is a member of the IL-1 family of cytokines and is able to act cardioprotective. The aim of this study was to investigate the regulation of IL-33 by different statins, 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors, and bisphosphonates (BPs) in human cardiac cells. Methods: Human adult cardiac myocytes (HACM) and fibroblasts (HACF) were treated with different statins or BPs. IL-33 protein in cell lysates was measured by specific ELISA, and IL-33 mRNA was determined by RT-PCR. Results: The lipophilic statins fluvastatin, simvastatin, atorvastatin, and lovastatin as well as the nitrogenous BPs alendronate and ibandronate, but not hydrophilic pravastatin increased IL-33 mRNA and intracellular IL-33 protein levels in both types of cells. IL-33 was also upregulated by the general inhibitor of prenylation perillic acid, a RhoA kinase inhibitor Y-27632, and by latrunculin B. Statin-induced IL-33 expression was inhibited by mevalonate, geranylgeranyl pyrophosphate (GGPP), and RhoA activator U-46619, but not by squalene, coenzyme Q10, or farnesyl diphosphate. BPs-induced expression of IL-33 was reversed by GGPP, but not by mevalonate. Conclusion: As IL-33 was previously shown to exert cardioprotective effects, one could speculate that such upregulation of IL-33 expression could be a novel mechanism contributing to known cardioprotective effects of statins and BPs.