

EDITORIAL COMMENT

Pleiotropic Effects of Statins

Acutely Good, But Chronically Bad?*

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Inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) are powerful lipid-lowering drugs that have been proven effective in primary and secondary prevention of coronary artery disease (1). However, ongoing discussion persists on whether or not statins exert clinically relevant protection from cardiovascular disease independent of their lipid-lowering action (2,3), the so-called pleiotropic effects. The pleiotropic effects of statins are related to the reduced formation of isoprenoids, which are responsible for post-translational modification of proteins (for review, see Werner et al. [4]). Among those proteins, the reduced prenylation and thus activity of small G-proteins (Ras, Rho) appears to be of major importance.

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The small G-protein RhoA is involved in myocardial ischemia/reperfusion injury; its pharmacologic blockade reduces infarct size in mice after 30 min of coronary artery occlusion and 24 h of reperfusion (5). RhoA inhibits the activity of protein kinase B (PKB)/Akt, an enzyme that, together with the phosphatidylinositol-3 kinase (PI3K), is important for triggering the cardioprotection achieved by ischemic preconditioning (6,7) and for mediating the reduction of ischemia/reperfusion injury after treatment with bradykinin (8), insulin, insulin-like growth factor-1, or urocortin (for review, see Hausenloy and Yellon [9]) (Fig. 1). Downstream of PI3K and Akt, endothelial nitric oxide synthase 3 (NOS3) activation, mitochondrial adenosine triphosphate (ATP)-dependent potassium channel activation, and mitochondrial permeability transition pore inhibition all are involved in mediating the resulting cardioprotective effect (9).

Statins can activate the PI3K/Akt pathway directly by increased translocation of Akt to the sarcolemmal membrane (10) or indirectly by a reduced RhoA activity; Rho A inhibits PKB/Akt activity (11).

In agreement with its effect on PI3K/Akt, statins reduce infarct size after ischemia/reperfusion in mouse (12–15), rat (16–19), dog (20), and pig (21) hearts in vitro (14,16) or in vivo (12,13,15,17–19,21–23). Infarct size reduction by

statins is dose-dependent and effective when statin treatment is initiated within three days before ischemia or even when started just before reperfusion (14,19). Blockade of PI3K (14,19,20), NOS3 (13,14,18,19,22), or ATP-dependent potassium channels (23) abolishes the cardioprotective effect of statins. Increased survival after hypoxia/reoxygenation by statin treatment also has been observed in isolated human cardiomyocytes (24), indicating that interaction of different cell types is not required for the cardioprotection to be obtained.

So far, only a single study in rabbits failed to demonstrate an infarct size reduction by statin treatment; in this study, rabbits fed a cholesterol-rich diet for 16 weeks received pravastatin (5 mg/kg/day) for 8 weeks before the initiation of 30 min ischemia followed by reperfusion. Pravastatin had no significant effect on cholesterol levels, but it restored the cardioprotection achieved by ischemic preconditioning, which was otherwise lost in hearts from hypercholesterolemic rabbits (25). This finding suggests that the more acute/subacute direct cardioprotective effect of statins by modulating protein kinase activity is lost over longer treatment periods but that the potential to potentiate the cardioprotection achieved by other stimuli remains.

In line with this idea, the study by Mensah et al. (26) in this issue of the *Journal* also clearly demonstrates that atorvastatin (20 mg/kg/day), although reducing infarct size when given for less than three days before ischemia/reperfusion, lost its cardioprotective effect when administered for one or two weeks before ischemia/reperfusion. The authors are the first to associate this finding with an up-regulation of PTEN (phosphatase and tensin homolog deleted on chromosome 10), a protein phosphatase known to inhibit the function of PI3K (27). The expression of PTEN is controlled by peroxisome proliferator-activated receptor gamma and—at least in monocytes—peroxisome proliferator-activated receptor gamma activity is increased with chronic statin treatment (28). As a result, although acute/subacute statin treatment might increase PKB/Akt activity, chronic statin treatment might counteract PKB/Akt activation by increasing PTEN expression. Unfortunately, neither PI3K nor PKB/Akt nor NOS3 phosphorylation were assessed in the present study. Also of great importance, however, is that acute treatment with 40 mg/kg atorvastatin 3 to 4 h before ischemia on top of the chronic treatment restored the reduction in infarct size, suggesting that the inhibition of PI3K activity and subsequently PKB/Akt activity during chronic statin treatment can be overcome by acutely increasing PKB/Akt phosphorylation; such increased PKB/Akt phosphorylation occurs acutely after statin administration. However, to further prove this idea, studies with measurements of PI3K, PKB/Akt, and endothelial nitric oxide synthase phosphorylation during acute statin treatment on top of chronic therapy are required.

Do all statins act the same? Although an ongoing discussion persists on whether or not all statins behave

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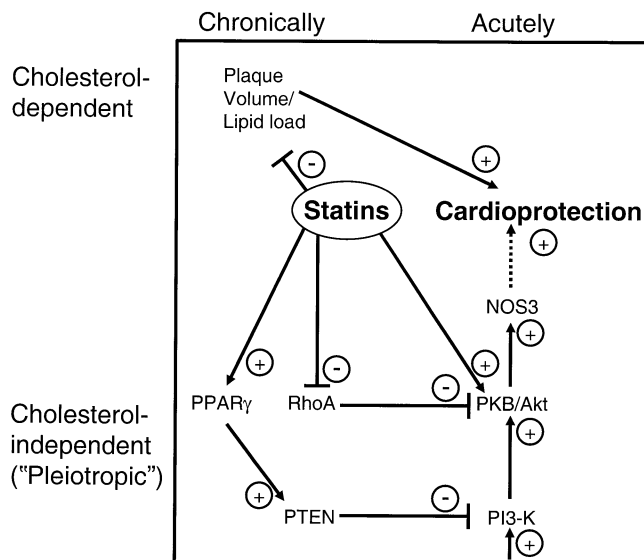


Figure 1. The acute cholesterol-independent cardioprotective effects of statins might be lost with chronic treatment by up-regulation of proteins (RhoA, phosphatase and tensin homolog [PTEN]), which inhibit kinases (phosphatidylinositol-3 kinase [PI3K], protein kinase B [PKB]/Akt) centrally involved in the signal transduction cascade, leading to cardiomyocyte survival (for more details, see text). PPAR = peroxisome proliferator-activated receptor; NOS3 = nitric oxide synthase 3 activation; + = activation; - = inhibition.

similar concerning cardiovascular risk reduction and pleiotropic effects (29), all available statins (atorvastatin, cerivastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), when given before ischemia/reperfusion, reduce infarct size in animal experiments. Differences might exist regarding the minimal duration between drug administration and initiation of ischemia as well as the required drug concentration, reflecting the different pharmacologic profiles of the drugs.

Is there any evidence that statins reduce the extent of infarction clinically? Plaque rupture occurring either spontaneously or during coronary interventions causes microinfarction secondary to coronary microembolization (for review, see Erbel and Heusch [30] and Heusch et al. [31]). The extent of microinfarction—as indicated by an increase in creatine kinase-myocardial band and troponin I—after coronary interventions is reduced in patients under statin treatment (32). Although during long-term statin treatment the plaque volume is reduced (33), thereby reducing the extent of coronary microembolization, reduced microinfarction is observed even when statin treatment is started just three (34) to seven days (35) before coronary interventions.

Thus, statins have clearly some acute cholesterol-independent beneficial cardioprotective effects that, however, might be lost during chronic use. Nevertheless, during chronic statin treatment, lowering of the lipid load is cardioprotective. Future clinical studies will have to elucidate whether or not the combination of an acute statin treatment on top of its chronic use exerts any benefit for the patient.

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REFERENCES

1. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *Br Med J* 2003;326:1423.
2. Bonetti PO, Lerman LO, Napoli C, Lerman A. Statin effects beyond lipid lowering—are they clinically relevant? *Eur Heart J* 2003;24:225–48.
3. Eto M, Lüscher TF. The cardioprotective effects of statins. *Coron Artery Dis* 2004;15:243–5.
4. Werner N, Nickenig G, Laufs U. Pleiotropic effects of HMG-CoA reductase inhibitors. *Basic Res Cardiol* 2002;97:105–16.
5. Bao W, Hu E, Tao L, et al. Inhibition of Rho-kinase protects the heart against ischemia/reperfusion injury. *Cardiovasc Res* 2004;61: 548–58.
6. Mocanu MM, Bell RM, Yellon DM. PI3 kinase and not p42/p44 appears to be implicated in the protection conferred by ischemic preconditioning. *J Mol Cell Cardiol* 2002;34:661–8.
7. Murphy E, Tong H, Steenbergen C. Preconditioning: is the Akt-ion in the PI3K pathway? *J Mol Cell Cardiol* 2003;35:1021–5.
8. Yang X-M, Krieg T, Cui L, Downey JM, Cohen MV. NECA and bradykinin at reperfusion reduce infarction in rabbit hearts by signaling through PI3, ERK, and NO. *J Mol Cell Cardiol* 2004;36:411–21.
9. Hausenloy DJ, Yellon DM. New directions for protecting the heart against ischaemia-reperfusion injury: targeting the reperfusion injury salvage kinase (RISK)-pathway. *Cardiovasc Res* 2004;61:448–60.
10. Skaletz-Rorowski A, Lutchman M, Kureishi Y, Lefer DJ, Faust JR, Walsh K. HMG-CoA reductase inhibitors promote cholesterol-dependent Akt/PKB translocation to membrane domains in endothelial cells. *Cardiovasc Res* 2003;57:253–64.
11. Ming X-F, Viswambharan H, Barandier C, et al. Rho GTPase/Rho kinase negatively regulates endothelial nitric oxide synthase phosphorylation through the inhibition of protein kinase B/Akt in human endothelial cells. *Mol Cell Biol* 2002;22:8467–77.
12. Lefer DJ, Scalla R, Jones SP, et al. HMG-CoA reductase inhibition protects the diabetic myocardium from ischemia-reperfusion injury. *FASEB J* 2001;15:1454–6.
13. Jones SP, Gibson MF, Rimmer DM, Gibson TM, Sharp BR, Lefer DJ. Direct vascular and cardioprotective effects of rosuvastatin, a new HMG-CoA reductase inhibitor. *J Am Coll Cardiol* 2002;40:1172–8.
14. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. *J Am Coll Cardiol* 2003;41:508–15.
15. Jones SP, Trocha SD, Lefer DJ. Pretreatment with simvastatin attenuates myocardial dysfunction after ischemia and chronic reperfusion. *Arterioscler Thromb Vasc Biol* 2001;21:2059–64.
16. Di Napoli P, Taccardi AA, Grilli A, et al. Simvastatin reduces reperfusion injury by modulating nitric oxide synthase expression: an ex vivo study in isolated working rat hearts. *Cardiovasc Res* 2001;51: 283–93.
17. Wayman NS, Ellis BL, Thiemermann C. Simvastatin reduces infarct size in a model of acute myocardial ischemia and reperfusion in the rat. *Med Sci Monit* 2003;9:BR155–9.
18. Tiefenbacher CP, Kapitzka J, Dietz V, Lee C-H, Niroomand F. Reduction of myocardial infarct size by fluvastatin. *Am J Physiol Heart Circ Physiol* 2003;285:H59–64.
19. Wolfrum S, Dendorfer A, Schutt M, et al. Simvastatin acutely reduces myocardial reperfusion injury in vivo by activating the phosphatidylinositol 3-kinase/Akt pathway. *J Cardiovasc Pharmacol* 2004;44:348–55.
20. Sanada S, Asanuma H, Minamino T, et al. Optimal windows of statin use for immediate infarct limitation. 5'-nucleotidase as another downstream molecule of phosphatidylinositol 3-kinase. *Circulation* 2004; 110:2143–9.

21. Lazar HL, Bao Y, Zhang Y, Bernard SA. Pretreatment with statins enhances myocardial protection during coronary revascularization. *J Thorac Cardiovasc Surg* 2003;125:1037-42.
22. Birnbaum Y, Ashitkov T, Uretsky BF, Ballinger S, Motamedi M. Reduction of infarct size by short-term pretreatment with atorvastatin. *Cardiovasc Drug Ther* 2003;17:25-30.
23. Tavackoli S, Ashitkov T, Hu Z-Y, Motamedi M, Uretsky BF, Birnbaum Y. Simvastatin-induced myocardial protection against ischemia-reperfusion injury is mediated by activation of ATP-sensitive K⁺ channels. *Coron Artery Dis* 2004;15:53-8.
24. Verma S, Rao V, Weisel RD, et al. Novel cardioprotective effects of pravastatin in human ventricular cardiomyocytes subjected to hypoxia and reoxygenation: beneficial effects of statins independent of endothelial cells. *J Surg Res* 2004;119:66-71.
25. Ueda Y, Kitakaze M, Komamura K, et al. Pravastatin restored the infarct size-limiting effect of ischemic preconditioning blunted by hypercholesterolemia in the rabbit model of myocardial infarction. *J Am Coll Cardiol* 1999;34:2120-5.
26. Mensah K, Mocanu MM, Yellon DM. Failure to protect the myocardium against ischemia/reperfusion injury after chronic atorvastatin treatment is recaptured by acute atorvastatin treatment: a potential role for phosphatase and tensin homolog deleted on chromosome ten? *J Am Coll Cardiol* 2005;45:1287-91.
27. Downes CP, Bennett D, McConnachie G, et al. Antagonism of PI 3-kinase-dependent signalling pathways by the tumour suppressor protein, PTEN. *Biochem Soc Trans* 2001;29:846-51.
28. Zelvyte I, Dominaitiene R, Crisby M, Janciauskiene S. Modulation of inflammatory mediators and PPAR-gamma and NFkB expression by pravastatin in response to lipoproteins in human monocytes in vitro. *Pharmacol Res* 2002;45:147-54.
29. Ready T. Despite hype, not all statins are the same, experts say. *Nat Med* 2004;10:442.
30. Erbel R, Heusch G. Brief review: coronary microembolization. *J Am Coll Cardiol* 2000;36:22-4.
31. Heusch G, Schulz R, Erbel R. Inflammatory markers in coronary heart disease: coronary vascular versus myocardial origin? *Circulation* 2003;108:e4.
32. Herrmann J, Lerman A, Baumgart D, et al. Preprocedural statin medication reduces the extent of periprocedural non-Q-wave myocardial infarction. *Circulation* 2002;106:2180-3.
33. Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome. Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. *Circulation* 2004;110:1061-8.
34. Briguori C, Colombo A, Airolidi F, et al. Statin administration before percutaneous coronary intervention: impact on periprocedural myocardial infarction. *Eur Heart J* 2004;25:1822-8.
35. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, Di Sciascio G. Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention. Results from the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) study. *Circulation* 2004;110:674-8.