Are statins 'smart bombs'?

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TO THE EDITOR: In their recent article (*Cleve Clin J Med* 2006; 73:760–766), Dr. Shishehbor and colleagues assert that statins lower the risk of cardiovascular events beyond the expected reduction attributable to cholesterol-lowering alone, and that this extra benefit might be explained by their potent anti-inflammatory action. Therefore, in addition to weight loss, exercise, and smoking cessation, statin therapy would represent the best therapeutic option to modulate inflammation. For these pleiotropic effects, statins are called "smart bombs" in an accompanying editorial.[1]

However, angiotensin II plays a significant role in the initiation and perpetuation of inflammatory processes.[2] Consequently, angiotensin-receptor blockade has also been shown to be related to a decrease in markers of systemic inflammation,[3] which may result in a reduction, or potentially a reversal, of atherosclerosis, as well as other inflammation-associated cardiovascular diseases.[4] In fact, angiotensin-converting enzyme inhibitors have been shown to have the broadest effect of any drug in cardiovascular medicine, reducing the risk of myocardial infarction, stroke, diabetes, renal impairment, and, above all, total mortality.[5]

On the other hand, total mortality is still a hard nut for statin trials to crack. Furthermore, the negative pleiotropic effects of statins should also be taken into account, as they may lead to the documented poor compliance with this therapy.[6] In fact, the relevance of subjective adverse effects for discontinuation of drug use is likely more pronounced in clinical practice than in clinical trials.[7]

Therefore, we don't know whether statins are really smart. We know, however, they are bombs to handle with care.

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REFERENCES

1. **Mandell BF.** Treating cardiovascular disease by treating inflammation: from magic bullets to smart bombs. Cleve Clin J Med 2006; 73:696.
2. **Suzuki Y, Ruiz-Ortega M, Lorenzo O, Ruperez M, Esteban V, Egido J.** Inflammation and angiotensin II. Int J Biochem Cell Biol 2003; 35:881–900.
3. **Mascitelli L, Pezzetta F.** Anti-inflammatory action of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. J Am Coll Cardiol 2006; 47:889.
4. **Ferrario CM, Strawn WB.** Role of the renin-angiotensin-aldosterone system and proinflammatory mediators in cardiovascular disease. Am J Cardiol 2006; 98:121–128.
5. **Remuzzi G, Ruggenenti P.** Overview of randomised trials of ACE inhibitors. Lancet 2006; 368:555–556.
6. **Jackevicius CA, Mamdani M, Tu JV.** Adherence with statin therapy in elderly patients with and without acute coronary syndromes, JAMA 2002; 288:462–467.
7. **Rief W, Avorn J, Barsky AJ.** Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. Arch Intern Med 2006; 166:155–160.

IN REPLY: Drs. Mascitelli and Pezzetta raise valid points regarding angiotensin-receptor blockers and their impact on clinical outcomes. A number of drugs currently used to treat various aspects of cardiovascular disease and diabetes exert part of their benefit through modulation of inflammation and oxidative stress.[1–3]

Statins have also been shown in numerous animal and human studies to exert potent systemic anti-inflammatory and antioxidant properties.[4,5] Therefore, it is believed that some of the benefit associated with the reduction in cardiovascular outcomes with statin therapy is related to these pleiotropic effects.[6]

We agree that statins, like many other drugs, are associated with side effects; however, this class of drugs remains among the most widely studied.[7] Therefore, with proper attention to symptoms and signs, side effects associated with this class of drugs are manageable.

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REFERENCES

1. **Bhatt DL, Topol EJ.** Need to test the arterial inflammation hypothesis. Circulation 2002; 106:136–140.
2. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002; 106:679–684.
3. **Marenzi G, Assanelli E, Marana I, et al.** N-acetylcysteine and contrast-induced nephropathy in primary angioplasty. N Engl J Med 2006; 354:2773–2782.
4. **Liao JK.** Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005; 96:24F–33F.
5. **Shishehbor MH, Brennan ML, Aviles RJ, et al.** Statins promote potent systemic antioxidant effects through specific inflammatory pathways. Circulation 2003; 108:426–431.
6. **Ridker PM.** Are statins anti-inflammatory? Issues in the design and conduct of the pravastatin inflammation C-reactive protein evaluation. Curr Cardiol Rep 2000; 2:269–273.
7. **Baigent C, Keech A, Kearney PM, et al.** Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366:1267–1278.