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Noel W. Clarke and Michael D. Brown

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Should All Patients Receive Statins to Reduce Cancer Risk After Heart Transplantation?

Noel W. Clarke, MBBS, ChM; Michael D. Brown, PhD

The study by Frolich et al\textsuperscript{1} in this issue of *Circulation* adds to the body of evidence that statins as a class of drugs have effects that reduce the chance of cancer initiation and progression, recapitulating findings showing reductions in cancer-related mortality in statin users in other major malignancies such as breast and prostate cancer.\textsuperscript{2,3} The authors are explicit in recognizing the flaws inherent in interpreting the data from their single-center case series, but nonetheless, the size of their series is substantial, patients have been followed carefully for long and clinically relevant time periods, and the reduction in cancer incidence, from 34% to 13%, is impressive. Furthermore, there is an overall reduction in the cancer-related death rate, and this seems to be even greater in its extent in those patients receiving prolonged therapy. In the absence of another explanation the evidence for these findings being attributable to statins is alluring, but is this truly a statin-related effect, and if it is, how is the therapy working?\textsuperscript{4,5}

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The predominant aim of statin therapy is the reduction of cholesterol to less harmful levels, but this may not be the means by which anticancer properties are effected. This notion is supported by the data from the study by Frolich et al,\textsuperscript{1} which show that the cancer-reducing effect was not related in any way to the absolute levels of serum cholesterol. This is not particularly surprising. As the authors emphasize, statins have pleiotropic anticancer effects, one of the most important being 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA)–related inhibition of the Mevalonate pathway, a fundamentally important cancer pathway whose blockade results in disruption of neoplastic processes such as initiation of cancer growth\textsuperscript{2} and, in particular, the cellular migrational behavior which is responsible for cancer progression and metastasis.\textsuperscript{4} There is controversy among cancer experts as to whether the cholesterol-lowering effect is important, but in fact the critical inhibitory action on cholesterol metabolism may be within lipid rafts, cellular membrane microdomains which harbor many receptors for cellular signaling and where statins such as Simvastatin are known to reduce cholesterol levels and impair lipid raft function. Their action here is known to inhibit cancer-related cellular signaling.\textsuperscript{5}

In light of the evidence presented, is there a case for widespread use of statins as a cancer preventive in this important area of transplantation? It is important to keep a balanced perspective, given that this is a relatively small, single-center series and to bear in mind that statins do have side effects. It is also important to recognize that not all statins are equal: Lipophilic statins, in contrast to hydrophilic ones, have been shown to have differential modes of action,\textsuperscript{4,6} and this affects their anticancer properties in testing in vitro.\textsuperscript{4,6} Given that there is a good evidence base for the noncancer benefits of these drugs in cardiac transplantation, it seems unlikely that a randomized trial testing the use of statins against no statins will be possible. Perhaps the way forward, therefore, will be to follow Bayesian approaches in this area, consolidating this and other datasets to facilitate larger-scale and more sophisticated analysis to address the proposition that statins (of whatever type) should be used universally in heart transplant patients. For the moment, however, it may be safer to adopt a verdict of unproven, while recognizing the fact that in this study, as in many others, the statistical arrows relating to statins and their anticancer effect are pointing in a similar direction.

**Disclosures**

None.

**References**


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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Christie Hospital, Manchester, United Kingdom.

Correspondence to Noel W. Clarke, MBBS, ChM, Consultant Urologist, Professor of Urological Oncology, The Christie Hospital, Wilmslow Road, Manchester M20 4BX, UK. E-mail noel.clarke@christie.nhs.uk

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