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

Running title: Clarke et al.; Statins, cancer reduction after heart transplantation

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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 which 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 recognising the flaws inherent in interpreting the data from their single centre case series but non-the-less, 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?

The predominant aim of statin therapy is the reduction of cholesterol to less harmful levels but this may not be the means by which anti-cancer properties are affected. This notion is supported by the study’s data, which shows 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 emphasise, statins have pleiotropic anti-cancer effects, one of the most important being 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 behaviour which is responsible for the cancer progression and metastasis\textsuperscript{4}. There is controversy amongst 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 micro-domains which harbour many receptors for cellular signalling 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 signalling\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 centre series and to bear in mind that statins do have side effects. It is also important to recognise that not all statins are equal: lipophilic statins, by contrast with hydrophilic ones, have been shown to have differential modes of action\textsuperscript{4,6} and this affects their anti-cancer properties in testing \textit{in vitro}\textsuperscript{4}. Given that there is a good evidence base for the non-cancer benefits of these drugs in cardiac transplantation it seems unlikely that a randomised 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”, whilst recognising the fact that in this study, as in many others, the statistical arrows relating to statins and their anti-cancer effect are pointing in a similar direction.

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\textbf{References:}


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