ACE Inhibitors and ARBs: Do They Reduce the Risk of Cancer?

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Do agents that antagonize the renin-angiotensin system affect cancer risk? Since angiotensin II stimulates neovascularization, and thus could be postulated to act as a growth factor for cancer, an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) could conceivably reduce cancer risk. Alternatively, stimulation of angiotensin II receptor type 2 (AT2) receptors, or blockade of angiotensin II receptor type 1 receptors with an ARB, which would result in unopposed AT2 receptor stimulation, could stimulate tumor angiogenesis and thus increase cancer risk.

Previous studies that have examined whether ACE inhibitors or ARBs affect cancer risk have offered conflicting results. Recent studies and meta-analyses have suggested no association or possibly an increased risk.[1–6] In this issue of the *Journal*, Chiang and colleagues[7] in a retrospective analysis, compared the incidence of cancer in hypertensive patients treated with an ACE inhibitor or ARB vs patients treated with other antihypertensive drugs. The investigators found that the incidence of cancer was 20% lower in ARB-treated patients and 50% lower in ACE inhibitor–treated patients than in patients treated with other antihypertensive agents. The findings are extremely provocative in suggesting the possibly considerable effect, particularly of ACE inhibitors, in the prevention of cancer.

In this study, the populations treated with an ACE inhibitor or ARB differed substantially from the population treated with other antihypertensive drugs; differences in patient characteristics were handled by propensity matching.

The findings would seem potentially groundbreaking but must be regarded cautiously. First, the paper must be viewed in the context of previous studies and meta-analyses, most of which do not support the finding of a substantially reduced incidence of cancer.[1,2,4,5] Second, the striking 50% decrease in cancer incidence within a mere 2.3-year follow-up period also raises concern about the reliability of the findings. Finally, this is a retrospective study, and it examined two populations that were very different from each other. The assumption that the striking differences between populations were eliminated by propensity matching needs to be questioned.

The differences between the ACE inhibitor and ARB groups and their respective control groups were not random or minor. Further, such differences were evident with regard to the majority of the clinical characteristics that were reported. For example, the incidence of diabetes was 29% in the ARB group vs 8% in the control group, similarly heart disease was 20% vs 8%, and the metabolic syndrome was 31% vs 16%. All of the differences indicated that the ACE inhibitor– and ARB-treated populations were sicker than the control populations. In matching the populations, the sickest of the patients from the control population were selected to match the sicker population that was treated with an ACE inhibitor or ARB. Although the paper matched for several clinical characteristics, innumerable other characteristics that likely differed substantially between groups were not examined or matched or reported, leaving the likelihood that the two populations remained very different from each other despite the propensity matching.

Another obvious concern not addressed in the paper is why ACE inhibitors and ARBs were prescribed in one population and not in the control population despite the presence of the same compelling indications for their use in perhaps half or more of the matched population. What was different about those patients, or their physicians, that led to avoidance of ACE inhibitors and ARBs despite clear and widely accepted indications for their use is not known.

Aside from these considerations, the important and overriding question in this and other studies remains: does propensity matching truly overcome substantial differences between populations? Does matching for 5 or 10 or even 20 reported clinical characteristics provide truly similar populations for comparison, or do the countless other major differences between two profoundly different populations that cannot be realistically matched, ie, unmeasured confounders, negate the validity of using propensity matching in such studies? Although the presence of unmeasured confounders can always be proposed, it is particularly germane when the populations being compared differ so greatly with regard to so many clinical characteristics, and particularly when unexpected results are observed.

In this study, where the findings run contrary to most previous studies, and in which ACE inhibitors were found to be spectacularly effective in preventing cancer, the assumption that propensity matching provides similar populations must be questioned. Before accepting the findings of this study, the validity of propensity matching in comparing two very different populations must be carefully questioned and judged.

Further, even if propensity matching could provide reliable estimates of treatment effects in general, one

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must also question the specific propensity matching methodology used in this study. No information was provided on the development of the propensity score. What model was used to estimate the propensity score? Was it multivariable logistic regression? What variables were included in the model to estimate the propensity of receiving ACE inhibitor vs control or ARB vs control? Were two separate models created to estimate (1) the propensity to receive ACE inhibitor or control and (2) the propensity to receive ARB or control? What type of matching on the propensity score was performed when matching ACE inhibitor (or ARB) patients to control patients? The precise matching algorithm was not adequately described. Was matching done within a range of the propensity score? Was the Greedy algorithm used, for example, which is a common method for propensity score matching?

After groups were matched on the propensity score (which is a way to make the groups comparable on confounding factors), why was multivariable cox regression performed to evaluate cancer occurrence? If the groups were well-matched, and if these factors were used in the original propensity score formulation, why then are they controlled for again in the Cox model to estimate cancer occurrence? Also unmentioned, was colinearity between comorbidities addressed before simply placing all of them into the propensity score multivariable model (assuming such a model was done)?

Another major limitation of the propensity score is that no variability in the propensity score is captured for an individual patient. When an individual's propensity score (to receive treatment vs control) is generated from a multivariable logistic regression model, it also comes with a 95% confidence interval (CI) around the probability estimate. However, when propensity matching is performed, only the propensity score estimate itself is used during the matching process. The 95% confidence limits around the propensity probability estimates are rarely taken into account during the matching process. Thus, no variability (ie, precision) is accounted for in the propensity score for individual patients. In fact, one could argue that standard multivariable logistic regression techniques that adjust for confounders at least provide 95% confidence limits around the odds ratio estimates that are generated from the model; specifically, the odds ratios and 95% CIs for the confounders in the model can greatly impact the odds ratio for the treatment (group) effect in the model.

Finally, as discussed above, the authors briefly state that some patients in the control group may have had indications for treatment but were not given treatment. But that is the whole idea of the propensity score. The propensity score is the probability that a patient will receive treatment (ie, ACE inhibitor/ARB) based on factors used in a multivariable logistic regression model for predicting this probability (propensity) estimate. Then the patients who truly had treatment are matched to controls who truly did not receive treatment, but perhaps should have been based on their propensity score to receive treatment. So if the propensity to receive treatment is 80% for a given patient, for example, then we would match a truly treated patient with an 80% propensity score to a true control patient who also had an 80% probability of receiving treatment (but in fact did not receive it).

A final concern is that propensity matching is best suited for comparing the outcome of two possibly equivalent treatments given to similar populations. It is reasonable to compare the outcome of an ACE inhibitor or ARB vs other antihypertensive drugs in two similar hypertensive populations for which drugs other than an ACE inhibitor or ARB are considered an acceptable alternative. The inherent limitation in this study is that as many as half, or possibly more, of the matched control population had specific indications other than hypertension for which nearly all guidelines recommend the use of an ACE inhibitor or ARB. Undescribed differences between populations have to exist to explain why so many in the control population were denied the recommended treatment. It did not happen by chance alone.

Given the retrospective nature of this study, the lack of details about the propensity score, and the likelihood that the two matched populations were not similar, it cannot be concluded that the cancer risk is lower with treatment vs control. The results of this study would clearly need to be reproduced in another setting or study.

The incidence of cancer after long-term treatment with various therapeutic agents is a real and important concern. However, the statistical methods used must be challenged when populations that differ greatly from each other are compared, particularly when a large effect, not previously evident, is reported. Although propensity matching is a valuable tool, this study illustrates the hazards of assuming that its use has provided truly matched populations, particularly when the results are unexpected, and the two populations are very different.

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