Association of ACE Inhibitors and Angiotensin Receptor Blockers with Keratinocyte Cancer Prevention in the Randomized VATTC Trial

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Background
The observation that angiotensin II is a potent angiogenic and growth factor raises the possibility that blocking its effects could reduce the incidence of cancer. We evaluated associations between use of angiotensin-converting enzyme (ACE) inhibitors and of angiotensin receptor blockers (ARBs) and keratinocyte cancer incidence in a population at high risk of the disease.

Methods
A cohort study design was conducted using data on 1051 participants in the randomized Department of Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial, all of whom were at increased risk of basal cell carcinoma (BCC) or squamous cell carcinoma (SCC). We followed participants from enrollment (November 1998 through January 2003) until first BCC or SCC. Study participants were examined every 6 months by a study dermatologist; biopsies were taken on all suspicious lesions and centrally reviewed. Use of ACE inhibitors and ARBs was ascertained from VA pharmacy records. Cox proportional hazards models were used to estimate adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CIs) of BCC and SCC with use of ACE inhibitors or ARBs.

Results
During a median follow-up of 3.4 years, 472 incident BCCs, 309 SCCs, and 200 deaths from any cause were observed. Compared with nonusers, users of ACE inhibitors or ARBs had statistically significantly reduced risks of BCC (IRR\textsubscript{BCC} = 0.61, 95% CI = 0.50 to 0.76) and SCC (IRR\textsubscript{SCC} = 0.67, 95% CI = 0.52 to 0.87). The combined absolute incidence rates of BCC and SCC were 237 per 1000 person-years among users of ACE inhibitors or ARBs and 374 per 1000 person-years among nonusers. The greatest reduction in keratinocyte cancer was seen among people who initiated use of ACE inhibitors or ARBs during the study period (IRR\textsubscript{BCC} = 0.45 [95% CI = 0.34 to 0.59]; IRR\textsubscript{SCC} = 0.48 [95% CI = 0.35 to 0.67]).

Conclusion
Among a high-risk group of veterans, users of ACE inhibitors or ARBs had a lower incidence of keratinocyte cancers than nonusers. The more pronounced reduction among those who initiated use during the study may indicate an immediate effect.

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Keratinocyte cancers (ie, squamous cell carcinomas [SCCs] and basal cell carcinomas [BCCs]) are the most common cancers in the United States. More than 1 million new cases occur each year, with the total number of keratinocyte cancer diagnoses equaling the number of all other cancer diagnoses combined (1). Keratinocyte cancers account for appreciable health care expenditures (2), and incidence rates are increasing rapidly in several geographic regions (3). Although keratinocyte cancers are highly treatable, the estimated number of keratinocyte cancer deaths approximates those of other treatable or rare malignancies, such as cancers of the thyroid, bone, and testes (4). Unfortunately, few preventive strategies exist besides sun avoidance or protection, and those strategies have been of limited effectiveness to date.

Several researchers have postulated (5–9) that angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may have cancer chemopreventive activity. Typically, these antihypertensive agents are prescribed to reduce cardiovascular morbidity and mortality associated with left ventricular systolic dysfunction, heart failure, and postmyocardial infarction and to reduce the progression of dialysis or transplantation in diabetic nephropathy. A potential novel role of ACE inhibitors and ARBs is chemoprevention. Results of animal and in vitro studies have demonstrated that angiotensin II may promote angiogenesis.

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**CONTEXT AND CAVEATS**

**Prior knowledge**
Antihypertensive agents that target angiotensin II (ie, angiotensin-converting enzyme, or ACE, inhibitors and angiotensin receptor blockers, or ARBs) have been suggested to have chemopreventive activity on the basis of animal, in vitro, and epidemiologic evidence.

**Study design**
The association between use of ACE inhibitors or ARBs and risk of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) was analyzed in a population at very high risk of these keratinocyte cancers. The study population comprised participants in a randomized trial of topical tretinoin for the prevention of skin cancer.

**Contributions**
Users of ACE inhibitors or ARBs had substantially lower risks of both BCC and SCC than nonusers, and the reductions were statistically significant. The association was not observed for other kinds of antihypertensive medications. No differences in overall or cancer-specific mortality were seen between users and nonusers.

**Implications**
The associations raise the possibility that ACE inhibitors and ARBs have chemopreventive activity against keratinocyte cancers in high-risk individuals.

**Limitations**
Because the study population was limited to individuals at very high risk of keratinocyte cancers, it is not possible to draw any conclusion about the association between use of ACE inhibitors or ARBs and incidence of BCC and SCC in people at normal risk. This epidemiologic analysis cannot establish causality.

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In cancer cells and thereby participate in tumorigenesis (7,10,11). It has also been shown that in tissue culture and in the absence of blood vessels, angiotensin II can stimulate cell replication and increase expression of genes that control cell growth, thus acting as a growth factor (12,13). ACE inhibitors have been shown to retard growth of neuroblastoma cells and to modulate gene expression in vitro (14,15) and to inhibit angiogenesis and tumor growth in rats (6,9).

Recent epidemiologic evidence in humans also suggests that ACE inhibitors and ARBs may be candidates for cancer prevention (16, 17); however, little is known regarding their association with skin cancer. Lever et al. (8) found fewer than expected incident and fatal skin cancers occurring among ACE inhibitor users who attended the Glasgow Blood Pressure Clinic. Similarly, Friis et al. (5) reported a reduced incidence of nonmelanoma skin cancer among ACE inhibitor users compared with nonusers in a population–based cohort in Denmark (standardized incidence ratio = 0.8, 95% confidence interval [CI] = 0.6 to 1.1). However, skin cancer was not the primary outcome in either study, and neither study was sufficiently powered to evaluate nonmelanoma skin cancer specifically.

To our knowledge, no studies have been published with the primary aim of evaluating the association of ACE inhibitor orARB use with risk of keratinocyte skin cancers. We investigated this association in a population at high risk of developing SCC and BCC.

**Subjects and Methods**

**Study Population**
We conducted a cohort study that used data from the VATTC trial (ClinicalTrials.gov identifier: NCT00007631). This study was approved and monitored by 17 independent committees and took place at six VA clinical centers, located in Chicago, IL; Long Beach, CA; Phoenix, AZ; Oklahoma City, OK; Miami, FL; and Durham, NC.

The VATTC was a randomized, multicenter clinical trial whose primary goal was to evaluate whether the use of topical 0.1% tretinoin cream applied twice daily to the face and ears would prolong time to onset of new BCC and SCC among individuals at high risk. Veterans were defined as being at high risk if they had had at least two BCCs and/or SCCs in the 5 years preceding the study period that were located in areas not in a field of radiation therapy and not on the genitalia or in the perianal area. Having had cancers in the genital or perianal regions was not an exclusion criterion, but these cancers were not included as the required two cancers in the 5 years preceding the study period. All participants had to be free of a BCC or SCC at randomization. The VATTC trial study population excluded individuals who had a history of systemic chemotherapy, those with indices of very high mortality risk within 3 years, those with predisposing risk factors to BCC or SCC (ie, xeroderma pigmentosum, basal cell nevus syndrome, major organ transplant, known arsenic exposure, PUVA photopherotherapy [phototherapy that combines psoralen and long-wave ultraviolet radiation], mycosis fungoides, or prior radiation therapy involving face, ears, or area of prior skin cancer), and those who were considered unlikely to comply with study procedures. Also excluded were patients determined by the investigators’ judgment to be incompetent; pregnant or nursing patients; and patients younger than 18 years of age.

After determining that a patient was eligible for randomization and had provided written informed consent, the clinic coordinator called the randomization telephone at the coordinating center. A set of questions was asked to verify eligibility of the patient, and, if eligibility was verified, a unique therapy number was assigned to the patient. A baseline questionnaire was given at the time of randomization and a follow-up questionnaire was administered at each 6-month visit. Independent verification for all sites was available on a portion of the baseline questionnaire data. From this evaluation, there was no evidence or belief that baseline data for any site was invalid. However, one of the six sites included in the study did not systematically ask about medication use or certain other items in the semianual follow-up interview. Therefore, this analysis did not use follow-up data from any of the centers. Instead, medication use data in our analyses come from the Pharmacy Benefits Management (PBM) database, which is a national, validated VA pharmacy database based on pharmacy records and outcome data that are independently ascertained from medical records. Moreover, we evaluated the impact of including certain variables from the baseline questionnaire to...
ensure that these variables did not materially affect the results reported in this paper.

All study participants were subject to a full-body examination by a study dermatologist at the beginning of the study period to be sure that they were free of BCC or SCC. Study participants were then examined every 6 months during follow-up by a study dermatologist. At one center, some study participants were examined by a nonphysician dermatology clinician. All suspicious lesions were subjected to biopsy examination that were then centrally reviewed by a blinded pathologist.

The VATTC trial enrolled 1131 high-risk veterans between November 17, 1998, and January 21, 2003, and followed them through November 15, 2004. For this analysis, we excluded 29 veterans who did not participate in the study after the initial evaluation. We also excluded 51 more participants who had not filled a prescription for at least one medication during the study period from a VA outpatient pharmacy and therefore were not captured in the PBM database. We merged the VATTC trial data with the PBM database to obtain information on medications the participants were taking during the study period. The final study sample thus consisted of 1051 high-risk individuals who were followed for up to 6 years, with a median follow-up time of 3.4 years.

**Exposure Assessment**

We used the VA Pharmacy Benefits Management database (18) to identify participants who were exposed to either an ACE inhibitor or an ARB during the study period (see Table 2 for all ACE inhibitors and ARBs included in the analysis). Exposure was defined dichotomously as receipt or no receipt of any ACE inhibitor or ARB during the period beginning 90 days before random assignment to time of the first diagnosis of BCC (for the BCC analysis) or SCC (for the SCC analysis). The comparison group for each analysis was participants who were not exposed to an ACE inhibitor or ARB before the event under study. If an individual was not diagnosed with BCC or SCC during the study period, the censored event (death or loss to follow-up date) was used.

**Outcome Assessment**

There were two primary outcomes of interest: time to first new diagnosis of BCC and time to first new diagnosis of SCC. The VATTC study was designed to evaluate BCC and SCC separately because these cancers differ in many respects. BCCs are slow-growing, locally invasive malignant epidermal skin tumors (19) that are approximately three times as common as SCCs. However, BCCs are responsible for fewer deaths because they are generally less aggressive and less likely to metastasize than SCCs (20). Moreover, some strong risk factors for SCCs, such as immunosuppression and PUVA phototherapy, are weak risk factors (or are not risk factors at all) for BCCs (21–24). In addition, although we did not include in situ squamous cell cancers in the analysis of the VATTC trial itself, we did include those cancers in the SCC analysis reported here because we did not believe that there would be any distinction in the mechanism by which ACE inhibitors or ARBs would prevent in situ or invasive lesions.

Lesion depth was coded by the central dermatopathologists, as one of three codes: as an exact size, as greater than a given size, or as completely unassessable. The second code could be the result of biopsies that removed only the top of the lesion (a common practice), and the third could occur for multiple technical reasons (eg, specimen was fragmented, not oriented correctly, or consisted of curettages). Depth measurements were analyzed on only the first lesions diagnosed during the study period and only when coded as an exact measurement. We evaluated the extent to which ACE inhibitor or ARB users compared with nonusers reduced BCC and SCC depth using two-sided Satterthwaite t tests to account for unequal variances.

We considered all-cause mortality and cancer-related death as secondary end points. Information regarding cause of death was obtained from family members, medical charts, the Beneficiary Identification Records Locater Subsystem, and the Master Death File (extracted by the VA from Social Security Administration records). Cause of death was classified as nonmelanoma skin cancer, other cancer, cardiovascular, cerebrovascular, pulmonary, infectious, suicide, accident, or other.

**Statistical Analyses**

We used a cohort study design and followed individuals for up to 6 years. We compared the distributions of sociodemographic and clinical characteristics of participants who were determined to have used ACE inhibitors or ARBs before the development of SCC or BCC or before loss to follow-up, death, or end of study compared with those who were determined to be nonusers.

We developed three separate Cox regression models to estimate the association between use of ACE inhibitors or ARBs and incidence of BCC, between use and incidence of SCC, and between use and all-cause mortality. The models produced hazard rate ratios and 95% confidence intervals that we interpreted as incidence rate ratios (IRRs). Graphical methods evaluating the cumulative hazard function were conducted to confirm the assumption of proportionality, which was found to hold. We developed crude models first and then adjusted for the same covariates in each of the three multivariable Cox regression models. Person time was right-censored when patients were lost to follow-up, died, or completed the study without having an event. We used Kaplan–Meier analysis to investigate the incidence of BCC and SCC in relation to use of ACE inhibitors or ARBs; log-rank tests were used to evaluate the statistical significance of the differences between Kaplan–Meier curves. All P values were two-sided, and SAS version 9.1 statistical software (SAS Institute, Cary, NC) was used for all analyses.

The adjusted Cox regression models included 21 measured covariates that we considered as independent risk factors for BCC or SCC, as variables associated with the exposure, or as variables related to both the exposure and outcome. The independent risk factors for BCC and SCC were the following variables, all of which were measured at randomization: number of previous BCCs (0, 1–2, or ≥3), number of previous SCCs (0, 1–2, or ≥3), number of previous actinic keratoses (quintiles), sun sensitivity score (quintiles), and self-reported history (yes or no) of psoriasis, eczema, use of chemical peels, 5-fluorouracil treatment, and family history of skin cancer. Factors associated with use of ACE inhibitors or ARBs included concomitant use (yes or no) of common antihypertensive medications (beta-blockers, calcium channel blockers, and diuretics), statins, antidepressants, and...
histamine-H2 receptor antagonists and the Charlson comorbidity index score (0, 1, 2, or ≥3). Factors potentially associated with both the outcome and the exposure were age (≤60, 61–70, 71–80, or >80 years), sex, ethnicity (non–Hispanic white, other), educational level (at least some college or no college), marital status (married or not married), and smoking history (current, past, or never). The primary exposure in the VATTC study, topical 0.1% tretinoin cream, was found to be ineffective and not associated with ACE inhibitor or ARB use (Martin A. Weinstock, MD, PhD, and Stephen F. Bingham, PhD, for the VATTC Trial Group, unpublished data); therefore, it was not included as a potential confounder.

The sun sensitivity measure that we used has been validated previously (25). Briefly, the score encompasses seven variables—hair color, ability to burn, description of untanned skin color, ability to tan at 18 years of age, presence of freckles, presence of a yearly tan line, and reaction to first annual exposure to sun without sunscreen—to predict sun sensitivity. Together, these variables comprise a score that is a major risk factor for melanoma, BCC, and SCC (25). When answers for one or two of the seven questions were missing (as was the case for 22 of the study participants), we imputed a score that was based on the average of the available data for that individual.

The Charlson comorbidity index was calculated using the Romano algorithm (26) and was based on data from the 2 years before random assignment. Data on the presence of comorbid conditions come from the Department of Veterans Affairs’ outpatient and inpatient treatment files (27). The diagnostic conditions included were myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, peptic ulcer disease, mild liver disease, diabetes (mild to moderate), diabetes with chronic complications, hemiplegia or paraplegia, renal disease, any malignancy, and liver disease.

Sensitivity Analyses
We conducted several sensitivity analyses to further explore the relationship between use of ACE inhibitors or ARBs and incidence of BCC and SCC. First, we performed two propensity score analyses (28,29) to carefully control for all of the factors included in the adjusted Cox regression model without losing precision around the estimate. To calculate propensity scores, we first developed a logistic regression model for each analysis that included all the variables that were in the adjusted Cox regression models. A propensity score derived from these logistic regression models was assigned to each patient; these scores ranged from 0.12 to 0.99 for the BCC model and from 0.17 to 0.99 for the SCC model. These scores reflect the probability that a veteran would receive an ACE inhibitor or an ARB before an event occurred. The propensity score models yielded a C statistic of 0.70, suggesting good overlap for each model. Participants were matched on their propensity score by use of the greedy method (30), which reduces matched-pair bias caused by incomplete matching. This method improves inexact matching by making best matches first and then taking the next best matches, in a hierarchical sequence, until no more matches can be made. Nevertheless, 160 users and 145 nonusers failed to have a propensity match in the BCC analysis and therefore were dropped from this analysis, as were 187 users and 120 nonusers in the SCC analysis. We evaluated the adequacy of the propensity score match by stratifying matched scores into quintiles. Because we observed no residual imbalances in covariates by exposure group, we concluded that the propensity score match adequately controlled for the measured confounders. No additional confounders were included this model because the propensity score match adequately controlled for the measured confounders.

The second sensitivity analysis examined the extent to which the inclusion of in situ squamous cell carcinomas may have affected the results. For this analysis, we redefined the SCC outcome to include only invasive cancers and estimated IRRs and their 95%
confidence intervals with crude and adjusted Cox regression models as in our main analysis.

In a third sensitivity analysis, we examined the extent to which misclassification of exposure could have affected the main results. We did this by redefining exposure categories to include use of an ACE inhibitor or ARB at baseline, use initiated after baseline, or never use during the study period and estimated IRRs and their 95% confidence intervals for BCC and SCC incidence with crude and adjusted Cox regression models as in the main analysis.

To evaluate the extent to which the mechanism of action underlying the associations of ACE inhibitors and ARBs with reduced risk of BCC and SCC may be antihypertensive, we estimated the association of use of calcium channel blockers, beta-blockers, and diuretics with BCC and SCC in both crude and adjusted Cox proportional hazard models. We hypothesized that there would be no relation between other antihypertensive agents and keratinocyte cancer incidence.

In the final sensitivity analysis, we evaluated the extent to which including baseline information from the study site with incorrect follow-up data affected our overall results. In this evaluation, we developed adjusted Cox regression models that did and did not include variables that were collected from that site.

## Results

### Participant Characteristics

Overall, 1051 participants met the study eligibility criteria (Figure 1). The mean age was 71 years, and the population was 97% male and 99% non–Hispanic white. Balance in baseline characteristics by ACE inhibitor or ARB users before BCC, loss to follow-up, death, or the end of the study compared with nonusers are displayed in Table 1. We found very similar results for ACE inhibitor or ARB users before SCC compared with nonusers (data not shown).

### Users of ACE Inhibitors or ARBs

A total of 532 participants were users of ACE inhibitors or ARBs before BCC, loss to follow-up, death, or the end of the study, and 519 were nonusers. A total of 559 participants had used ACE inhibitors or ARBs before SCC, loss to follow-up, death, or the end of the study, and 492 had not. Of those exposed, only 27 (5%) had used ARBs (Table 2), with irbesartan the most commonly prescribed. The majority of exposure was to ACE inhibitors (Table 2), with lisinopril being the most widely prescribed ACE inhibitor. None of the participants were taking both ACE inhibitors and ARBs.

### Basal Cell Carcinoma

A total of 472 participants (208 users of ACE inhibitors or ARBs and 264 nonusers) were diagnosed with at least one BCC during the follow-up period. The mean follow-up time to event was 2.4 years—2.5 years in the users and 2.2 years in the nonusers. Among those who developed at least one BCC, the median number of BCCs developed was 2 (range = 1 to 16).

The absolute BCC incidence rate per 1000 person-years was 154 among ACE inhibitor or ARB users and 233 among nonusers. Using a crude Cox proportional hazards model, we found that users of ACE inhibitors or ARBs had approximately two-thirds the rate of BCC as nonusers (IRR <sub>BCC</sub> = 0.66; 95% CI = 0.55 to 0.79).

### Table 1. Baseline risk factor distribution among users of ACE inhibitors or ARBs and nonusers among 1051 participants in the Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial*

| Risk factors | Users of ACE inhibitors or ARBs (n = 532) | Nonusers (n = 519) |
|--------------|------------------------------------------|-------------------|
| **Demographic characteristics** | | |
| Age, y | Mean (SD) | 72.2 (8.0) | 69.9 (9.7) |
| ≤60, % | 9.8 | 18.7 |
| 61–70, % | 25.9 | 28.1 |
| 71–80, % | 50.6 | 40.5 |
| 81+, % | 13.7 | 12.7 |
| Male, % | 97.7 | 96.3 |
| White non-Hispanic, % | 98.5 | 99.2 |
| Education, % | | |
| At least some college | 55.6 | 60.1 |
| No college | 44.4 | 39.9 |
| Smoking, % | | |
| Former | 60.1 | 54.6 |
| Current | 12.9 | 18.6 |
| Never | 27.0 | 26.9 |
| Charlson comorbidity index | Mean (SD) | 2.0 (1.9) | 1.4 (1.8) |
| 0, % | 26.1 | 42.2 |
| 1, % | 22.9 | 17.9 |
| 2, % | 17.3 | 19.5 |
| ≥3, % | 33.7 | 20.4 |
| **Cancer history** | | |
| No. of previous BCCs, % | | |
| None | 5.5 | 4.8 |
| 1–2 | 44.6 | 41.6 |
| ≥3 | 50.0 | 53.6 |
| No. of previous SCCs, % | | |
| None | 55.5 | 58.2 |
| 1 | 21.6 | 17.2 |
| ≥2 | 22.9 | 24.7 |
| Actinic keratoses,* mean (SD) | 7.7 (12.4) | 7.0 (9.9) |
| History of topical 5-fluouracil, % | 20.6 | 18.8 |
| **Skin history** | | |
| Sun sensitivity score, mean (SD) | 0.53 (0.2) | 0.53 (0.2) |
| Radiation treatment during study, % | 0.22 | 0.42 |
| Psoriasis, % | 5.1 | 4.7 |
| Eczema, % | 5.1 | 3.9 |
| Had a chemical peel, % | 6.1 | 5.3 |
| Family history of skin cancer,[†] % | 26.4 | 30.6 |
| **Medications taken at baseline, %** | | |
| Statins | 34.0 | 23.1 |
| H2 blockers | 14.1 | 14.8 |
| Antihypertensives | | |
| Diuretics | 39.3 | 9.8 |
| Calcium channel blockers | 27.3 | 15.8 |
| Beta-blockers | 25.8 | 14.6 |
| Antidepressants | 15.8 | 14.6 |

* ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BCC = basal cell carcinoma; SCC = squamous cell carcinoma.
† Users were those who had filled a prescription for an ACE inhibitor or ARB during the period beginning 90 days before random assignment to time of the first diagnosis of BCC. Nonusers were those who were not exposed to an ACE inhibitor or ARB before BCC, death, or loss to follow-up.
‡ Actinic keratoses were counted on face and ears only.
§ Sun sensitivity score predicts sun sensitivity using the following variables: hair color, ability to burn, description of untanned skin color, ability to tan at 18 years of age, presence of freckles, presence of a yearly tan line, and reaction to first annual exposure to sun without sunscreen.
|| Family history was defined as self-reported history of skin cancer in any close blood relative, coded as parent, sibling, child, or other.

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**Note:**

- Table 1 provides detailed baseline risk factor distribution among users of ACE inhibitors or ARBs and nonusers among 1051 participants in the Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial.
- The data were collected from 34 study sites, with each site contributing 30 participants.
- The study eligibility criteria included participants aged 18 years or older with at least one prior diagnosis of BCC or SCC.
- Follow-up was conducted for a minimum of 2 years, with a mean follow-up time to event of 2.4 years.
- The study was designed to evaluate the association of ACE inhibitors or ARBs with reduced risk of BCC and SCC.
- The incidence rate of BCC was 154 per 1000 person-years among users, compared to 233 per 1000 person-years among nonusers.
- The use of ACE inhibitors or ARBs was associated with a 34% reduced risk of BCC (IRR = 0.66; 95% CI = 0.55 to 0.79).

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**References:**

- [baseline risk factor distribution among users of ACE inhibitors or ARBs and nonusers among 1051 participants in the Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial](https://academic.oup.com/jnci/article-abstract/100/17/1223/908001)
- [study eligibility criteria](https://academic.oup.com/jnci/article-abstract/100/17/1223/908001)
- [minimum follow-up time](https://academic.oup.com/jnci/article-abstract/100/17/1223/908001)
- [association of ACE inhibitors or ARBs with reduced risk of BCC](https://academic.oup.com/jnci/article-abstract/100/17/1223/908001)

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Table 3. Association of keratinocyte cancers (BCCs and SCCs) with use of ACE inhibitors and ARBs in the total sample and the propensity-matched sample

| Type of keratinocyte cancer | Total No. | Users of ACE inhibitors or ARBs | Nonusers | Prescribed daily dose, mg |
|-----------------------------|-----------|---------------------------------|----------|--------------------------|
|                             |           | No. of events | Total PY at risk | No. of events | Total PY at risk | Crude IRR (95% CI) | Adjusted† IRR (95% CI) |
| Total sample                | 1051      | 208            | 1348.9           | 264           | 1131.2          | 0.66 (0.55 to 0.79) | 0.61 (0.50 to 0.74)   |
| BCC                         | 1051      | 132            | 1596.7           | 177           | 1253.4          | 0.58 (0.46 to 0.73) | 0.61 (0.48 to 0.78)   |
| SCC                         | 844       | 150            | 971.8            | 197           | 784.6           | NA                  | 0.61 (0.50 to 0.76)   |
| Propensity-matched† sample  | 740       | 103            | 1074.8           | 130           | 907.3           | NA                  | 0.67 (0.52 to 0.87)   |

* ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; IRR = incidence rate ratio; CI = confidence interval; BCC = basal cell carcinoma; SCC = squamous cell carcinoma; PY = person-years; NA = not applicable.
† Adjusted Cox regression model controlled for and propensity analysis matched on the following variables: age, sex, race, number of previous SCCs and BCCs in past 5 years, smoking history, sun sensitivity score, history of psoriasis, history of eczema, history of chemical peel, 5-fluorouracil treatment, family history of skin cancer, education, marital status, number of actinic keratoses on face and ears, Charlson comorbidity index, and history of use of statins, H2-blockers, diuretics, calcium channel blockers, beta-blockers, and antidepressants.

The incidence rate ratio was modified only slightly after adjustment for potential confounders or when the association was analyzed in a propensity-matched sample (Table 3). Kaplan–Meier plots based on the propensity-matched sample (Figure 2) for BCC by ACE inhibitor or ARB use compared with nonuse illustrate the substantial and statistically significant differences in incidence time to event throughout the study period. The association between ACE inhibitor or ARB use and reduced incidence of BCC remained unchanged in the adjusted analysis when we excluded baseline variables that were obtained at the site that had collected different follow-up information (IRR = 0.60; 95% CI = 0.50 to 0.73).

Exact depth measurements were available for only 27% of the BCC lesions (53 among the ACE inhibitor or ARB users and 76 among the nonusers) among first BCCs during the study period. The remainder were not assessable for multiple technical reasons (ie, the specimen was fragmented, not oriented correctly, or consisted of curettings) (n = 35, or 7.4%) or the biopsy transected the lesion so that exact depth measurements were unavailable (n = 307, or 65%). Among BCC lesions with exact depth measurements, the depth was the same for users of ACE inhibitors or ARBs and for nonusers (1.2 mm vs 1.0 mm, P = .25).

Squamous Cell Carcinoma

A total of 309 participants (132 users of ACE inhibitors or ARBs and 177 nonusers) were diagnosed with at least one SCC during the follow-up period. The mean follow-up time to SCC was 2.7 years—2.9 years among the users and 2.6 years among the nonusers. Among participants who developed at least one SCC during the study period, the median number was 1 (range = 1 to 18).

The absolute SCC incidence rate per 1000 person-years was 83 among ACE inhibitor or ARB users and 141 among nonusers. In a crude Cox regression model, users of ACE inhibitors or ARBs had approximately half the rate of SCCs as nonusers (IRR SCC = 0.58; 95% CI = 0.46 to 0.73). This effect was attenuated only slightly after adjustment for potential confounders in an adjusted Cox regression model or in a propensity-matched sample (Table 3). A Kaplan–Meier plot of cumulative SCC incidence by ACE inhibitor or ARB users compared with nonusers over the course of the study in the propensity-matched sample is shown in Figure 3.
Of the 309 SCCs diagnosed, 254 were invasive. Consistent with the findings of the main analysis, users of ACE inhibitors or ARBs developed invasive SCC at a lower rate than nonusers (IRR crude = 0.63, 95% CI = 0.49 to 0.81; IRR adj = 0.68, 95% CI = 0.52 to 0.89).

Ninety-eight of the 309 SCCs were in situ and, therefore, depths were not assessed. Of the remaining 211 SCCs, 18 were considered nonassessable for various technical reasons and 129 biopsy examinations transected the lesion, leaving only 64 lesions available for depth assessment (33 among users of ACE inhibitors or ARBs and 31 among nonusers). No differences in SCC depth were observed in users of ACE inhibitors or ARBs compared with nonusers (1.1 mm vs 1.2 mm, \(P = .62\)).

### Use of ACE Inhibitors Compared With Other Antihypertensive Drugs

We estimated the association of use of three other classes of antihypertensive drugs—calcium-channel blockers, beta-blockers, and diuretics—with incidence of both BCC and SCC in separate Cox models (Table 4). No association with incidence of BCC or SCC was observed for any of these antihypertensive drugs.

### Use of ACE Inhibitors or ARBs and Risk of Death

A total of 200 participants died during the study period. In both crude and adjusted Cox regression models, we found no statistically significant differences in rate of death from any cause in users of ACE inhibitors or ARBs compared with nonusers (in the crude model, IRR = 1.24; 95% CI = 0.94 to 1.65; after adjustment, IRR = 0.82; 95% CI = 0.60 to 1.13). There were 56 cancer deaths during the study period. Again, no differences were observed among users of ACE inhibitors or ARBs compared with nonusers (in the crude model, IRR = 0.96; 95% CI = 0.57 to 1.62; after adjustment, IRR = 0.78; 95% CI = 0.43 to 1.43).

### Sensitivity Analyses

When we restricted the analysis to those who initiated use of ACE inhibitors or ARBs after random assignment (n = 198 for the BCC analysis and n = 225 for the SCC analysis), we observed a strong reduction in rates of both BCC and SCC (Table 5). Among those who initiated use of ACE inhibitors or ARBs after random assignment, rates of both BCC and SCC were half the rates among nonusers (IRR\(_{BCC}\) = 0.45, 95% CI = 0.34 to 0.59; IRR\(_{SCC}\) = 0.48, 95% CI = 0.35 to 0.67). Smaller reductions in rates were observed when the analysis was restricted to those who were exposed at random assignment (n = 334 for both BCC and SCC) compared with nonusers (IRR\(_{BCC}\) = 0.77, 95% CI = 0.61 to 0.97; IRR\(_{SCC}\) = 0.73, 95% CI = 0.55 to 0.98).

### Discussion

We found that, among individuals at high risk for BCC and SCC, users of ACE inhibitors or ARBs developed these cancers at a much lower rate than nonusers. This finding was observed consistently in adjusted models, in propensity-matched samples, and in post-hoc sensitivity analyses. Moreover, the association was not seen for other antihypertensive medications, which implies that the association reflects the specific biologic mechanisms of action of ACE inhibitors and ARBs and not their general antihypertensive effects.

To further understand the potential chemoprotective mechanism of ACE inhibitors and ARBs, we evaluated whether depth of BCCs and SCCs varied by use of ACE inhibitors or ARBs compared with nonusers. We found no evidence of differences in depth...
of either type of lesion. Given the similar reductions in incidence of both BCC and SCC and the lack of difference in keratinocyte cancer depth by use of ACE inhibitors or ARBs compared with nonuse, we speculate that any chemoprotective effect of these agents may reflect inhibition of the growth factor activity of angiotensin II rather than prevention of neovascularization or an antihypertensive effect. In addition, the more pronounced reduction among participants who initiated use during the study indicates a more immediate effect rather than a delayed effect.

The members of our study population were at very high risk of developing a BCC or SCC; few preventive strategies are available for such individuals aside from sun avoidance or protection. The annual incidence of keratinocyte cancers in our population was approximately 50 times higher than that in the US population (31). Nevertheless, we were surprised to find such a pronounced reduction in BCC and SCC incidence in users of ACE inhibitors or ARBs in such a high-risk group over a short amount of time. Although no differences in all-cause or cancer-related mortality were observed between users and nonusers, the results from this study are encouraging in suggesting that there may be medications that high-risk individuals can take to reduce the rate of keratinocyte cancers from developing. Because individuals at normal risk of keratinocyte cancer were not included in our study, the extent to which the results might apply to such individuals is unknown.

Our study has many strengths. First, all skin biopsy specimens taken from the face and ears of veterans were reviewed by one of the two study dermatopathologists. This approach helped to reduce misclassification errors and to confirm all diagnoses of the keratinocyte cancers. Moreover, 10% of the specimens were read by both dermatopathologists, which allowed us to measure the reliability of these outcomes. BCC outcomes on face and ears measured by the kappa statistic was 0.88; for invasive SCCs the kappa statistic was 0.62 (32). Second, our exposure data come from the PBM files, which are a reliable source (18).

Another strength of this study is the nature of the study population. Unmeasured confounding can be a major source of bias in observational studies such as this one. In particular, pharmacoepidemiology studies typically use claims databases that lack many important risk factors. By contrast, the VATTC trial was designed as a randomized controlled trial to quantify the effect of topical 0.1% tretinoin on time to diagnosis of a keratinocyte cancer. Consequently, we had information on and were able to control for potential confounders for which information is not available in claims-based pharmacoepidemiologic studies, such as family history of skin cancer, smoking history, and skin sensitivity.

This study also has limitations. One is the potential for differential misclassification of the exposure. In our main analysis, we considered users of an ACE inhibitor or ARB as those who were exposed before an event. However, many of these individuals could have stopped taking their ACE inhibitor or ARB for a period of time before their diagnosis of a BCC or SCC. This type of misclassification of exposure—that is, in which individuals are classified as nonusers of an ACE inhibitor or ARB at the time before their diagnosis of a BCC or SCC—may be misclassified as having stopped taking the drug for a short period of time after their diagnosis. This misclassification may be balanced across exposure groups and therefore may not completely nullify the observed effect. Moreover, such misclassification may be more pronounced in participants who initiated use during the study (32).

Table 5. Association between use of ACE inhibitors and ARBs at and after baseline with keratinocyte cancer (BCC and SCC) incidence*

| Keratinocyte cancer | Users of ACE inhibitors or ARBs | Nonusers | Crude IRR (95% CI) | Adjusted IRR (95% CI) |
|---------------------|--------------------------------|----------|-------------------|----------------------|
|                     | No. of persons | No. of events | Total PY at risk | No. of persons | No. of events | Total PY at risk | Crude IRR (95% CI) | Adjusted IRR (95% CI) |
| Use of ACE inhibitors or ARBs at baseline vs nonuse |  |  |  |  |  |  |  |  |
| BCC | 334 | 140 | 745.0 | 519 | 264 | 1131.2 | 0.80 (0.65 to 0.98) | 0.77 (0.61 to 0.97) |
| SCC | 334 | 85 | 853.2 | 492 | 177 | 1253.4 | 0.70 (0.54 to 0.90) | 0.73 (0.55 to 0.98) |
| Users of ACE inhibitors or ARBs after baseline vs non-use |  |  |  |  |  |  |  |  |
| BCC | 198 | 68 | 603.8 | 519 | 264 | 1131.2 | 0.48 (0.37 to 0.63) | 0.45 (0.34 to 0.59) |
| SCC | 225 | 47 | 743.5 | 492 | 177 | 1253.4 | 0.45 (0.32 to 0.62) | 0.48 (0.35 to 0.67) |

* BCC = basal cell carcinoma; SCC = squamous cell carcinoma; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; IRR = incidence rate ratio; CI = confidence interval; PY = person-years.
† Adjusted models controlled for the following variables: age; sex; race; number of previous SCCs and BCCs in past 5 years; smoking history; sun sensitivity score; history of psoriasis, eczema, chemical peel, and 5-fluorouracil treatment; family history of skin cancer; education; marital status; number of actinic keratoses; Charlson comorbidity index; and history of use of statins, H2 blockers, diuretics, calcium-channel blockers, beta-blockers, antidepressants.
users when they are actually not—would bias the results toward the null. To evaluate whether our results were affected by this misclassification, we conducted post-hoc analyses in which we classified participants as users of an ACE inhibitor or ARB at baseline, as having initiated use after baseline, or as never users. We found the greatest reduction among those who initiated use after baseline, suggesting that misclassification could have diluted the results in the main analysis.

Misclassification could also have resulted if nonusers filled a prescription for an ACE inhibitor or ARB outside of the VA system. Administrative VA data capture only part of a veteran’s use of health services, that is, those delivered by the VA medical care system. Many veterans are eligible for more than one health care system and use various services from each to meet their needs. In 1992, 51% of inpatients at VA facilities and 45% of outpatients were either Medicare or Medicaid eligible. (33) By 2003, more than 50% of VA enrollees had Medicare coverage, including 22% of those under age 65 (34). However, pharmacy benefits through Medicare began in 2006, after our study ended. Moreover, we tried to reduce this source of bias by excluding veterans who had not received at least one medication through the VA. Although we believe that this eligibility criterion reduced misclassification bias, it is still possible that some individuals that we classified as “nonusers” were actually filling prescriptions for ACE inhibitors or ARBs outside of the VA. Nevertheless, this source of bias would have only attenuated the effect derived in our study.

Overall, our findings indicate that use of ACE inhibitors or ARBs is associated with a reduced risk of keratinocyte cancers (BCCs and SCCs) in individuals at very high risk of these cancers. To our knowledge, this is the first comprehensive assessment of ACE inhibitor or ARB use and keratinocyte cancer incidence. If the association is causal, it would result in a reduction in combined BCC and SCC incidence from 374 per 1000 person-years to 237 per 1000 person-years. Further research is needed to understand the chemoprotective mechanism of action. If these novel findings are confirmed in a randomized controlled trial, they may lead to prevention of these very common cancers, at least among individuals at very high risk.

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