Use of Angiotensin Receptor Blockers and the Risk of Cancer

Björn Pasternak, MD, PhD; Henrik Svanström, MSc; Torbjörn Callréus, MD, PhD; Mads Melbye, MD, DrMedSci; Anders Hviid, MSc, DrMedSci

Background—A recent meta-analysis of randomized trials suggested that use of angiotensin receptor blockers (ARBs) may be associated with a modestly increased risk of incident cancer, particularly lung cancer.

Methods and Results—We linked individual-level data from Danish registries on filled drug prescriptions, diagnostic information, and covariates. In a nationwide cohort of new users of ARBs and angiotensin-converting enzyme inhibitors ≥35 years of age during 1998 to 2006, we compared incidence rates of all cancer, cancer subgroups by anatomic site, and cancer mortality. Among 107,466 ARB users, 3954 cases of cancer were detected during 312,753 person-years of follow-up compared with 6214 cases during 435,207 person-years of follow-up in 209,692 angiotensin-converting enzyme inhibitor users (adjusted rate ratio, 0.99; 95% confidence interval, 0.95 to 1.03). Cancer risk did not increase with increasing duration of ARB exposure (increase in rate ratio per year, 0.99; 95% confidence interval, 0.99 to 1.00) and was similar across individual ARBs. In subgroup analyses, there was a significant association between ARB use and cancer of male genital organs (rate ratio, 1.15; 95% confidence interval, 1.02 to 1.28), but no significantly increased risk of any of the other 15 cancer subgroups, including lung cancer (rate ratio, 0.92; 95% confidence interval, 0.82 to 1.02).

Conclusion—In this large nationwide cohort, use of ARBs was not significantly associated with increased risk of incident cancer overall or of lung cancer. (Circulation. 2011;123:1729-1736.)

Key Words: angiotensin II ■ epidemiology ■ product surveillance, postmarketing ■ neoplasms ■ safety

Angiotensin receptor blockers (ARBs) are in widespread use for hypertension, heart failure, and diabetic nephropathy.1–3 A recent meta-analysis of 9 randomized trials found that the use of ARBs was associated with a modestly increased risk of incident cancer overall (rate ratio [RR], 1.08; 95% confidence interval [CI], 1.01 to 1.15) compared with placebo or comparator drugs.4 Among the specific cancers examined, there was significantly increased risk of lung cancer (RR, 1.25; 95% CI, 1.05 to 1.49), whereas no significant risk of cancer mortality was detected. These findings prompted the Food and Drug Administration and the European Medicines Agency to initiate a review of ARB safety.5,6

Clinical Perspective on p 1736

Because previous studies have failed to detect an increased risk of cancer associated with use of angiotensin-converting enzyme (ACE) inhibitors,7–11 results of the meta-analysis4 imply that mechanisms specific to ARBs, ie, inhibition of the angiotensin II type 1 receptor and associated unopposed stimulation of the type 2 receptor, may influence the development of cancer. On the other hand, the body of experimental data favors possible beneficial effects of ARBs, including inhibition of tumor growth, angiogenesis, and metastasis in cancer models.12,13

The trials included in the meta-analysis were not designed to investigate cancer as a primary outcome, and the meta-analysis lacked individual-level data, which precluded time-to-event analyses.4 Only 3 small observational studies have examined the association between ARBs and specific cancers, finding no significant risk of melanoma, breast cancer, or renal cancer.14–16

In a nationwide registry-based cohort in Denmark, we evaluated the hypothesis that ARB use is associated with incident cancer in a comparison of new users of ARBs and ACE inhibitors.

Methods

We identified the source population for the study from the Civil Registration System,17 including all individuals living in Denmark and ≥35 years of age between January 1, 1998, and December 31, 2006. Using participants’ unique personal identification numbers, we linked individual-level information from nationwide registries on
filled drug prescriptions, cancer diagnoses, and potential confounders. We established a cohort of new users of ARBs and ACE inhibitors, including those who filled a new prescription during the study period. The primary outcome measure was risk of incident cancer overall in new users of ARBs compared with new users of ACE inhibitors. Secondary outcomes included cancer subgroups by anatomic site (including a specific analysis of lung cancer because of previous findings) and specific ARBs, analyses by sex, and cancer mortality. The study was approved by the Danish Data Protection Agency. Ethics approval is not required for registry-based research in Denmark.

The Prescription Drug Registry contains individual-level information on all prescriptions filled at all Danish pharmacies, including the personal identification number, dispensing date, anatomic therapeutic chemical code, and number of defined daily doses in the prescription. We included all ARBs (ATC-code C09CA) and ACE-inhibitors (C09AA) in use in Denmark, including combinations with thiazide diuretics (C09DA and C09BA, respectively): losartan, eprosartan, valsartan, irbesartan, candesartan, telmisartan, and olmesartan; and captopril, enalapril, lisinopril, perindopril, ramipril, quinapril, benazepril, fosinopril, trandolapril, and moexipril. Those who had filled a prescription for ARBs or ACE inhibitors during a washout period of 2 years before cohort entry were excluded. This design allowed selective inclusion of new users, which reduces the potential for prevalent user bias and allows estimation of exposure duration.

After cohort entry, defined by the date of filling the first prescription for an ARB or ACE inhibitor, we allowed for a 180-day lag period. During the lag period, participants did not contribute person-time. Those diagnosed with cancer or meeting other censoring criteria (defined below) during the lag period were disregarded from further analyses, thereby limiting the inclusion of participants with incipient cancer (the development of which might not have been affected by drug treatment during a short period of time).

Patients were assigned as users if they had filled a minimum of 2 consecutive prescriptions for an ARB or ACE inhibitor, and follow-up was started on the day the second prescription was filled. If the second prescription was filled during the lag period, participants did not contribute person-time until after the end of the lag period.

Patients were followed up continuously for their current drug exposure status throughout the follow-up. Within each treatment episode, a gap between prescriptions of up to 50% of the duration of the preceding prescription (in defined daily doses) was accepted to leave room for variations in drug intake habits. If 2 prescriptions overlapped, the overlap was disregarded and exposure time was counted from the dispensing day of the most recent prescription. Users of ARBs or ACE inhibitors who subsequently stopped treatment were recategorized to a distinct group of patients—past users—and contributed person-time to this group from the day the maximum gap time after a prescription was exceeded. The past user group thus consisted of unexposed person-time from patients previously exposed to ARBs or ACE inhibitors who had stopped treatment. However, if they later refilled a prescription and fulfilled criteria for use, past users could again be recategorized and contribute person-time to the user group. Thus, each participant could contribute several distinct use and past use episodes that, when added together, represented this participant’s total person-time of use and past use, respectively.

Diagnoses of incident cancer were identified via the Danish Cancer Registry, which documents all cases of cancer in the country with high completeness and validity; cancers are classified according to the International Classification of Diseases. We grouped cancers according to anatomic site (International Classification of Diseases codes in Table 1 in the online-only Data Supplement) and subdivided the respiratory group into lung and nonsmall. We also performed exploratory analyses of lung cancer by histological type: small-cell carcinoma, adenocarcinoma, squamous cell carcinoma, and other/unspecified types. Individuals diagnosed with any cancer before cohort entry (back to 1978) were excluded. Cancer causes of death were derived from the Cause of Death Registry.

**Statistical Analyses**

Participants were censored at the date of a first diagnosis of cancer, end of follow-up (December 31, 2006), death, disappearance, or emigration, whichever occurred first. Applying a Poisson regression model (log-linear regression of the counts of cancer using the logarithm of the follow-up time as offset), we estimated the RR for incident cancer or cancer mortality comparing ARB and ACE inhibitor users (SAS version 9.1). We compared only those who did not use ARBs and ACE inhibitors simultaneously and had not switched between the 2 drugs. In subgroup analyses of specific ARBs, switching between different ARBs was allowed. We also analyzed cancer risk according to total duration of ARB use (estimated by cumulative received defined daily doses) compared with the overall risk associated with ACE inhibitor use. In these analyses, 365 defined daily doses were defined as equivalent to 1 year, and the cumulative received doses were counted starting after the lag period.

Effect measures were adjusted for sex, age in 5-year intervals, calendar year, socioeconomic class, degree of urbanization, and use of other antihypertensives (β-blockers [C07A], calcium channel blockers [C08CA, C08D], and thiazides [C03A]). To adjust for comorbidity, we used diagnostic information from the National Patient Registry, which documents all hospitalizations and outpatient hospital visits in the country, and calculated the Charlson comorbidity index (cancer diagnoses were not included) on the basis of data registered before cohort entry. We also adjusted for the number of hospitalizations in the last 3 years before cohort entry. We did not have data on smoking. In subgroup analyses, we did not correct for multiple comparisons.

**Results**

From a source population of 3,312,484 individuals, we excluded 117,012 with a history of cancer and 169,681 with previous ARB or ACE inhibitor use. A total of 438,728 individuals filled a new ARB or ACE inhibitor prescription during the study period. The mean duration of a prescription was 97 days (SD, 64 days) for ARBs and 116 days (SD, 96 days) for ACE inhibitors, and the mean interval between prescriptions was 72 days (SD, 79 days) for ARBs and 71 days (SD, 89 days) for ACE inhibitors. During the 180-day lag period after a first prescription of an ARB or ACE inhibitor, an additional 13,443 individuals were censored owing to death, end of follow-up, disappearance, emigration, or a cancer diagnosis. The final study cohort thus included 425,285 persons. Among these, 107,466 and 209,692 fulfilled criteria for ARB and ACE inhibitor use, respectively, and had no simultaneous or previous use of the other drug; descriptive characteristics are presented in Table 1. Among ARB users, 894 (0.8%) had filled only 2 prescriptions and 106,572 (99.2%) had filled at least 3 prescriptions. Among ACE inhibitor users, 3,156 (1.5%) had filled only 2 prescriptions and 206,536 (98.5%) had filled at least 3 prescriptions. The mean duration of ARB and ACE inhibitor use was 2.9 years (SD, 2.2 years) and 2.1 years (SD, 1.9 years), respectively.

ARB use was not significantly associated with increased risk of incident cancer overall (crude RR, 0.89; 95% CI, 0.85 to 0.92) compared with ACE inhibitor use (Table 2). There was no significantly increased risk of cancer associated with ARB use after adjustment only for age (RR, 0.93; 95% CI, 0.90 to 0.97) or after adjustment for age, sex, year, socioeconomic class, degree of urbanization, comorbidity, hospital-
### Table 1. Baseline Characteristics of Angiotensin Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor Users in a Nationwide Cohort in Denmark, 1998 to 2006

<table>
<thead>
<tr>
<th></th>
<th>ARB Users* (n=107 466)</th>
<th>ACE Inhibitor Users† (n=209 692)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>63 (12)</td>
<td>65 (13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>58 665 (55)</td>
<td>95 286 (45)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Socioeconomic class, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
| Employment with unknown, basic, or no qualifications | 27 118 (25) | 52 270 (25) |\
| Employment with medium-level qualifications | 8694 (8) | 13 157 (6) |\
| Employment with high-level qualifications | 10 334 (10) | 15 237 (7) |\
| Self-employed/coworking spouse | 6979 (6) | 12 485 (6) |\
| Outside labor market | 16 510 (15) | 31 847 (15) |\
| Pensioned | 37 831 (35) | 84 869 (40) |\
| Degree of urbanization, n (%) |                |                                   | <0.01|
| Population density ≤49 inhabitants per 1 km² | 7301 (7) | 14 666 (7) |\
| Population density 50–99 inhabitants per 1 km² | 31 391 (29) | 63 363 (30) |\
| Population density 100–199 inhabitants per 1 km² | 23 183 (22) | 46 629 (22) |\
| Population density ≥200 inhabitants per 1 km² | 10 144 (9) | 18 819 (9) |\
| Copenhagen suburbs | 27 005 (25) | 47 377 (23) |\
| Copenhagen | 64 842 (8) | 18 838 (9) |\
| Comorbidity, n (%)§ |               |                                   | <0.01|
| Myocardial infarction | 1096 (1) | 4492 (2) | <0.01|
| Congestive heart failure | 360 (0) | 1894 (1) | <0.01|
| Peripheral vascular disease | 1107 (1) | 3152 (0) | <0.01|
| Cerebrovascular disease | 688 (1) | 1587 (1) | <0.01|
| Dementia | 42 (<0.1) | 144 (<0.1) | <0.01|
| Chronic pulmonary disease | 1992 (2) | 4503 (2) | <0.01|
| Rheumatic disease | 911 (1) | 1955 (1) | 0.02|
| Peptic ulcer disease | 1119 (1) | 2602 (1) | <0.01|
| Mild liver disease | 350 (0.3) | 780 (0.4) | 0.04|
| Diabetes mellitus without chronic complications | 2095 (2) | 9036 (4) | <0.01|
| Diabetes mellitus with chronic complications | 509 (0.5) | 2679 (1) | <0.01|
| Hemiplegia or paraplegia | 47 (<0.1) | 129 (<0.1) | 0.04|
| Renal disease | 186 (0.2) | 358 (0.2) | 0.88|
| Moderate or severe liver disease | 48 (<0.1) | 67 (<0.1) | 0.08|
| HIV/AIDS | 13 (<0.1) | 36 (<0.1) | 0.28|
| Charlson comorbidity index, mean (SD) | 0.12 (0.43) | 0.19 (0.56) | <0.01|

(Continued)

### Table 1. Continued

<table>
<thead>
<tr>
<th></th>
<th>ARB Users* (n=107 466)</th>
<th>ACE Inhibitor Users† (n=209 692)</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations in last 3 y, n (%)</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
| 0 | 100 816 (94) | 190 690 (91) |\
| 1–2 | 5612 (5) | 15 340 (7) |\
| 3 | 1038 (1) | 3662 (2) |\
| Use of other antihypertensive drugs in last year, n (%) |               |                                   |
| Thiazides | 39 621 (37) | 76 722 (37) | 0.12|
| β-blockers | 30 089 (28) | 58 270 (28) | 0.21|
| Calcium channel blockers | 27 966 (26) | 48 605 (23) | <0.01|
| Any other antihypertensive drug | 64 568 (60) | 122 623 (58) | <0.01|

ARB indicates angiotensin receptor blocker; ACE, angiotensin-converting enzyme.

*No concomitant use of ACE inhibitors.
†No concomitant use of ARBs.
‡The χ² test for categorical variables and t test for continuous variables.
§As captured by the National Patient Registry (documents hospitalizations and outpatient hospital visits).

The risk of cancer did not increase with increasing duration of ARB use, estimated by cumulative received drug doses, compared with the overall risk associated with ACE inhibitor use (Figure 1); the increase in adjusted RR per year of ARB use was 0.99 (95% CI, 0.99 to 1.00). For instance, the adjusted RR was 1.00 (95% CI, 0.96 to 1.11) compared with past use of ACE inhibitors.

Figure 2 shows associations between ARB use and cancer subgroups by anatomic site. ARB use was significantly associated with a modestly increased risk of male genital cancer (adjusted RR, 1.15; 95% CI, 1.02 to 1.28) and modestly decreased risk of other cancers (ill-defined, secondary, and unspecified sites; adjusted RR, 0.78; 95% CI, 0.65 to 0.94) compared with ACE inhibitor use. There were no significant associations between ARB use and any of the other 14 subgroups of cancer, including lung cancer (adjusted RR, 0.92; 95% CI, 0.82 to 1.02) and squamous cell carcinoma (n=128 among ARB users), 1.24 (95% CI, 1.01 to 1.52) for adenocarcinoma (n=173), 0.86 (95% CI, 0.67 to 1.12) for squamous cell carcinoma (n=87), and 0.80 (95% CI, 0.65 to 0.98) for other/unspecified types (n=136).

Figure 3 shows that none of the specific ARBs was associated with significantly increased risk of incident cancer.
overall compared with ACE inhibitors. We also followed up patients for the outcome of death. ARB use was not associated with increased risk of cancer mortality compared with ACE inhibitor use (adjusted RR, 0.77; 95% CI, 0.72 to 0.82).

In planned sensitivity analyses, we first used an alternative exposure definition; ARB exposure was not associated with cancer overall when we used a conservative definition of ARB and ACE inhibitor use that did not allow any gap between prescriptions (adjusted RR, 1.00; 95% CI, 0.95 to 1.05). Second, the lag period from first prescription to start of follow-up was redefined as 3 years. Among patients who remained in the cohort after this extended lag period, 64,036 ARB users were followed up during 140,562 person-years and compared with 89,259 ACE inhibitor users who were followed up during 163,617 person-years; ARB use was not associated with cancer (adjusted RR, 0.96; 95% CI, 0.90 to 1.02).

Posthoc, the subgroup of male genital cancers was divided into prostate and nonprostate (penis, testicle, other) genital cancer. The adjusted RRs for ARB use were 1.13 (95% CI, 1.00 to 1.26) for prostate cancer and 1.64 (95% CI, 0.93 to 2.89) for nonprostate cancer. When other antihypertensives were used as the comparison group, the adjusted RR for the association between ARBs and prostate cancer was 1.18 (95% CI, 0.99 to 1.41). Analyzing prostate cancer risk according to duration of ARB use, estimated by cumulative received drug doses, we found that nonsignificant increases of RRs appeared to be evenly distributed across time periods (Figure I in the online-only Data Supplement).

### Discussion

This large nationwide cohort study found no significant association between use of ARBs and the risk of incident cancer overall compared with use of ACE inhibitors. Given the narrow CIs, a 4% risk increase associated with ARB exposure could be excluded. Risk estimates were similar for men and women and across specific ARBs and did not increase with increasing duration of exposure.

Our finding of no significant association between ARBs and cancer contrasts with that of a recently published meta-analysis of randomized trials by Sipahi et al, who found a modestly increased risk of new cancer among patients treated with ARBs (RR, 1.08; 95% CI, 1.01 to 1.15) compared with placebo or comparator drugs. The meta-analysis also found an increased risk of lung cancer associated with ARB exposure (RR, 1.25; 95% CI, 1.05 to 1.49). In contrast, our study was able to exclude a 3% excess in lung cancer risk (RR, 0.92; 95% CI, 0.82 to 1.02), although an exploratory analysis by histological type found protective associations for small-cell carcinoma and cancer of other/unspecified histological type and an increased risk of adenocarcinoma. The reasons for the differences between our study and the meta-analysis may be due to several factors: we included unselected individuals from a real-world setting who may have differed from participants in clinical trials; the trials included in the meta-analysis were not designed to evaluate cancer as

---

**Table 2. Association Between Use of Angiotensin Receptor Blockers and Risk of Incident Cancer Overall Compared With the Use of Angiotensin-Converting Enzyme Inhibitors in a Nationwide Cohort in Denmark, 1998 to 2006**

<table>
<thead>
<tr>
<th>Follow-Up, Person-y</th>
<th>Incident Cancer Cases, n</th>
<th>Crude Incidence Rate, n/100 000 Person-y</th>
<th>Crude RR (95% CI)</th>
<th>Age-Adjusted RR (95% CI)</th>
<th>Fully Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB†</td>
<td>312 753</td>
<td>3954</td>
<td>1264</td>
<td>0.89 (0.85–0.92)</td>
<td>0.93 (0.90–0.97)</td>
</tr>
<tr>
<td>ACE inhibitor‡</td>
<td>435 207</td>
<td>6214</td>
<td>1428</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
</tbody>
</table>

| Women               |                          |                                          |                   |                          |                             |                             |
| ARB†                | 173 657                  | 2102                                     | 1210              | 0.90 (0.85–0.95)         | 0.94 (0.89–0.99)             | 0.95 (0.90–1.01)            |
| ACE inhibitor‡      | 189 928                  | 2562                                     | 1349              | 1 (Reference)            | 1 (Reference)               | 1 (Reference)              |

| Men                 |                          |                                          |                   |                          |                             |                             |
| ARB†                | 139 096                  | 1852                                     | 1331              | 0.89 (0.85–0.95)         | 0.99 (0.94–1.05)             | 1.01 (0.96–1.07)            |
| ACE inhibitor‡      | 245 280                  | 3652                                     | 1489              | 1 (Reference)            | 1 (Reference)               | 1 (Reference)              |

**Figure 1.** Risk of incident cancer according to duration of angiotensin receptor blocker (ARB) use compared with any angiotensin-converting enzyme inhibitor use in a nationwide cohort in Denmark, 1998 to 2006. Duration of drug use was estimated by cumulative defined daily doses; 365 defined daily doses are equivalent to 1 year. RR indicates rate ratio; CI, confidence interval.
primary outcome, while we used data from the nationwide Danish Cancer Registry; in contrast to the meta-analysis, our study had access to individual-level data, enabling time-to-event analyses; and the meta-analysis was predominantly based on telmisartan, while the most common ARB in our report was losartan. Although it is possible that the average follow-up of 2.9 years for ARB use (following a half-year lag period) in our study may be too short for cancer to develop, a significant risk was detected in the meta-analysis4 (average follow-up, 4 years), but not in our study, during a similar period of time. Furthermore, we did not detect increased risk associated with increasing exposure time; this analysis included a subgroup with >5 years of cumulative exposure (RR, 1.01; 95% CI, 0.94 to 1.08).

Other published observational studies found no significant association between ARBs and melanoma, breast cancer, or renal cell cancer, but had small sample sizes.14–16 Including more than twice the number of studies compared with the Sipahi et al meta-analysis, Bangalore and colleagues25 recently analyzed pooled data from 21 ARB trials and found no evidence of increased risk of cancer on aggregate associated with ARB use compared with comparator drugs or placebo (odds ratio, 1.01; 95% CI, 0.93 to 1.09; fixed-effects model). Our study, which analyzed individual-level data, confirms these findings in a large unselected nationwide cohort and extends them to include a specific analysis of lung cancer and other cancer subgroups. A lower risk of cancer mortality associated with ARB use, as found in our study, is not supported by data from the Bangalore et al meta-analysis (odds ratio, 1.00; 95% CI, 0.87 to 1.15; fixed-effects model; mean follow-up, 3.5 years).25

A carcinogenic effect associated with inhibition of the angiotensin system, if present, would have to be specific for ARBs, and hence for inhibition of the angiotensin II type 1 receptor, because ACE inhibitors are not associated with cancer.7–11 This explanation, however, is unlikely, because increased expression of the type-1 receptor has been detected in several cancer types.12,13,26 Indeed, the body of experimental data suggests that ARB treatment may reduce tumor growth and migration.12,13,26,27 Another possible explanation for a carcinogenic effect of ARBs might be that inhibition of the type 1 receptor by ARBs may lead to unopposed activity...
of angiotensin II on the angiotensin II type 2 receptor. However, type 2 receptor activation would be expected to have antitumor effects, although data are somewhat conflicting. Safety studies in animals have also demonstrated the absence of carcinogenicity with high doses of ARBs.

Some strengths and limitations of our large nationwide cohort study deserve particular mention. We used nationwide registry data to ascertain exposure and outcome independently and included analyses of cancer subgroups by anatomic site and of cancer risk associated with specific ARBs. Use of filled prescriptions as a measure of drug exposure eliminates recall bias and improves the precision of information on specific drugs used. A limitation, however, is that nonadherence to the dispensed drugs would bias results toward the null if one of the drugs were associated with cancer. We used new users of ACE inhibitors as the comparison group. A design that compares initiators of 2 drugs with shared indications has advantages over a design that uses nonusers as a comparison group, reducing the potential for immortal time bias and balancing the treatment groups with regard to patient characteristics not measured in the available register data, in our case, for example, smoking, physical activity, and dietary habits. Furthermore, a comparison to nonusers would have introduced a surveillance bias for cancer because patients under antihypertensive treatment are more likely to be examined by healthcare providers. We cannot, however, exclude the possibility of unmeasured confounding, because differences between ARB and ACE inhibitor users may still exist. Nonetheless, sensitivity analyses comparing ARB users with users of other antihypertensives yielded results similar to those of the main analysis, supporting its validity.

Conclusions
This large nationwide cohort study found no significantly increased risk of cancer overall, in 15 different cancer subgroups, including lung cancer, or in cancer mortality among new users of ARBs compared with new users of ACE inhibitors. The results from the only subgroup analysis associated with increased risk, male genital cancer, must be interpreted with caution, considering the
possibility of a chance finding resulting from multiple comparisons.

Sources of Funding
This work was supported by a research grant from the Danish Medical Research Council.

Disclosures
Dr Callréus is a full-time employee of the Danish Medicines Agency. The views expressed in this article are the personal views of the author, and do not necessarily represent the position of the Danish Medicines Agency. Dr Callréus is a co-opted member of the EU Pharmacovigilance Working Party. The views expressed in this article are the personal views of the author, and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties. The other authors report no conflicts.

References
CLINICAL PERSPECTIVE

A meta-analysis of randomized trials published in June 2010 suggested that use of angiotensin receptor blockers (ARBs) may be associated with an increased risk of cancer, lung cancer in particular. Because millions of patients use ARBs, monitoring their safety is of immediate clinical importance. Using individual-level data from registries in Denmark, including, for example, information on filled drug prescriptions and cancer diagnoses, we conducted a nationwide cohort study to compare the rates of incident cancer among users of ARBs and angiotensin-converting enzyme inhibitors. In an analysis including >100 000 users of ARBs and >200 000 users of angiotensin-converting enzyme inhibitors, we found no evidence of an increased risk of cancer overall associated with ARB use. Confidence intervals were narrow, allowing exclusion of a 4% increase in the risk of cancer. Results were similar when ARBs were compared with other antihypertensive drugs in a sensitivity analysis. In a subgroup analysis, there was no significant association between ARBs and lung cancer. Furthermore, although the angiotensin receptor system is involved in the process of carcinogenesis, experimental data point, if anything, toward beneficial effects of angiotensin signaling inhibition. Strengths of our study include the use of individual-level nationwide registry data and a comprehensive pharmacoepidemiological design. Clinicians can continue to prescribe ARBs without concern about an excess risk of cancer.
Use of Angiotensin Receptor Blockers and the Risk of Cancer
Björn Pasternak, Henrik Svanström, Torbjörn Callréus, Mads Melbye and Anders Hviid

Circulation, published online April 11, 2011;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2011/04/11/CIRCULATIONAHA.110.007336

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2011/04/07/CIRCULATIONAHA.110.007336.DC1
http://circ.ahajournals.org/content/suppl/2011/12/22/CIRCULATIONAHA.110.007336.DC2

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/
Supplementary Table. ICD-10 codes for cancer subgroups.

<table>
<thead>
<tr>
<th>Anatomic site</th>
<th>ICD-10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip, oral cavity and pharynx</td>
<td>C00-14</td>
</tr>
<tr>
<td>Digestive organs</td>
<td>C15-26</td>
</tr>
<tr>
<td>Respiratory and intrathoracic organs (non-lung)</td>
<td>C30-33, C35-39, C450</td>
</tr>
<tr>
<td>Lung</td>
<td>C34</td>
</tr>
<tr>
<td>Bone and articular cartilage</td>
<td>C40-41</td>
</tr>
<tr>
<td>Skin†</td>
<td>C43-44</td>
</tr>
<tr>
<td>Mesothelial and soft tissue‡</td>
<td>C45-49</td>
</tr>
<tr>
<td>Breast</td>
<td>C50</td>
</tr>
<tr>
<td>Female genital organs§</td>
<td>C51-58</td>
</tr>
<tr>
<td>Male genital organs§</td>
<td>C60-63</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>C64-68</td>
</tr>
<tr>
<td>Central nervous system including eye</td>
<td>C69-72, C751-753</td>
</tr>
<tr>
<td>Endocrine glands</td>
<td>C73-74, C750, C754-759</td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td>C81-90</td>
</tr>
<tr>
<td>Haematopoietic tissue</td>
<td>C91-96</td>
</tr>
<tr>
<td>Other§</td>
<td>C76-80, C97</td>
</tr>
</tbody>
</table>

*Cancer of anus and anal canal analyzed with skin subgroup if coded as malignant melanoma (morphology code 872-879) and excluded if coded as basal cell carcinoma (morphology code 809).
†Excludes basal cell carcinoma (morphology code 809) and skin cancer with non-specified histology (morphology code 99903 or 99993).
‡Excludes mesothelioma of the pleura (ICD-10 code C450).
§Excludes basal cell carcinoma (morphology code 809).
‖Cancers of ill-defined, secondary and unspecified sites and cancers of independent multiple primary sites.
Supplementary Figure. Risk of prostate cancer according to duration of angiotensin receptor blocker (ARB) use, as compared to any angiotensin converting enzyme-inhibitor use.

<table>
<thead>
<tr>
<th>Duration of ARB use (years)</th>
<th>0-1</th>
<th>1-2</th>
<th>2-3</th>
<th>3-4</th>
<th>4-5</th>
<th>5+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years of follow-up</td>
<td>63 357</td>
<td>49 155</td>
<td>33 360</td>
<td>21 987</td>
<td>16 668</td>
<td>28 644</td>
</tr>
<tr>
<td>Number of ARB-exposed cases</td>
<td>201</td>
<td>158</td>
<td>119</td>
<td>74</td>
<td>65</td>
<td>124</td>
</tr>
</tbody>
</table>

RR: rate ratio
CI: confidence interval
Duration of drug use estimated by cumulative defined daily doses; 365 defined daily doses are equivalent to 1 year
Angiotensin Receptor Blocker의 사용은 암 발생 위험을 증가시키지 않는다

강 덕 현 교수 서울아산병원 심장내과

Summary

배경
Angiotensin receptor blocker(ARB)와 위약을 무작위로 배정한 임상연구들의 메타분석 결과를 Sipahi 등이 2010년 6월에 Lancet Oncology에 발표하였는데, ARB의 사용이 암(특히 패암) 발생 위험의 증가(rate ratio, 1.08; 95% CI, 1.01-1.19)과 연관성을 보였다. 메타분석에 포함된 연구들이 암 발생을 일차 결과변수로 조사하지 않았고, 개인 자료를 제공하지 않아 time-to-event 분석을 시행할 수 없었으므로 연구자들은 덴마크의 전국적인 registry-based 코호트를 이용하여 최근의 메타분석 연구 결과를 검증하였다.

방법 및 결과
덴마크 registry들로부터 암 발생률, 진단 정보와 공변량 등에 관한 개인 자료들을 얻어 상호 연관성을 조사하였다. 1998년부터 2006년까지 ARB 및 angiotensin converting enzyme(ACE) inhibitors를 사용한 쌍방 연구들을 새로운 쌍방 발전 35세 이상의 사람들로 구성된 전국적인 코호트에서 모든 암의 발생률, 장기에 따라 분류된 암의 발생률과 암으로 인한 사망률을 비교하였다. ARB 사용자 107,466 명에서 31,275 환자-년 동안 3,954례의 암이 발생하였고, ACE inhibitor 사용자 209,692명에서 435,207 환자-년 동안 6,214례의 암이 진단되었다(adjusted rate ratio, 0.99; 95% CI, 0.95-1.03). 암 발생 위험은 ARB 사용 기간의 증가에 따라 증가하지 않았고(increase in rate ratio per year, 0.99; 95% CI, 0.99-1.00), 각각의 ARB 간에도 유사하였다. 암 발생 장기에 ARB 사용과의 관계를 조사한 subgroup analysis에서 남성 생식기관암과 ARB 사용 사이에 유의한 연관관계를 보였지만(rate ratio, 1.15; 95% CI, 1.02-1.28), 패암(rate ratio, 0.92; 95% CI, 0.82-1.02)을 비롯한 다른 15 cancer subgroup 모두에서는 위험도가 유의하게 증가하지 않았다 ARB 사용자에서 암과 연관된 사망에 대한 rate ratio는 0.79(95% CI, 0.72-0.82)이었다.

결론
대규모의 전국적인 registry에서 ARB 사용은 전반적인 암 또는 패암 발생 위험의 증가와 유의한 연관성을 보이지 않았다.
Commentary

미국 FDA는 Drug Safety Review 후, 2011년 6월 2일 ARB가 암 위험을 증가시키지 않는다고 발표한 바 있다. 2010년 6월 Sipahi 등이 의해 ARB의 사용이 암 발생 위험을 증가한다고 발표한 연구에서 시행된 5개의 clinical trials 및 62,000명의 메타분석 연구보다 FDA는 비슷한 결과를 보고한 31개의 무작위 배정 연구, 약 156,000명의 메타분석을 시행하였는데, 연구 결과 ARB가 두어온 환자에서 부수적이거나 새로운 암의 위험, 암과 연관된 사망, 유방암, 폐암, 전립선암의 위험도가 증가하지 않았다.

본 연구는 ARB와 ACE inhibitor 사용자를 포함한 코호트 연구로서 무작위 배정 임상시험과 달리 ARB가 사용자와 ACE inhibitor 사용자의 기저 특성이 상이할 수 있지만 실제 진료 상황에 가깝고 time-to-event analysis를 할 수 있는 장점이 있다. 본 연구 결과를 해석할 때 주의할 점으로는 ARB 사용자에서 ACE inhibitor 사용자가 암 위험의 crude RR이 0.89로 낮게 나왔는데, age-adjusted RR은 0.93, fully adjusted RR 0.99로 거의 같게 나왔다. 코호트 연구에서는 비교 대상들 간에 기저 특성이 다를 수 있으므로 보정을 적절하게 해서 비교하는 것이 중요하다. 또한, ARB 사용 환자에서 암 사망의 adjusted RR 0.77(95% CI, 0.72-0.82)로 낮게 나온 결과는 ARB 사용이 암 사망 위험을 낮추다고 설득력이 증명하기보다는 암 사망의 위험도를 증가시키지 않는다고 결론을 내리는 것이 바람직하다. ARB 사용자에서 남성 생식기암의 암 위험도가 유의하게 증가한 것도 multiple testing에 따른 보정을 하면 통계적 유의성을 잃고, ARB 사용기간이 증가해도 전립선암의 위험도가 증가하지 않은 점 및 FDA review에 서도 전립선암의 위험도가 증가하지 않았음으로 미루어 의미를 두기 어렵다.

Sipahi 등이 의해 ARB의 사용이 암 발생 위험을 증가한다는 2010년 6월에 Lancet Oncology에 발표한 이후 여러 논문 및 증단에서 연구 결과의 문제점을 제기한 바 있는데, 메타분석 연구를 통해 보다 많은 환자를 분석함으로써 통계적 판매력을 강화할 수 있지만 메타분석 연구의 가장 지명적인 위험은 결과를 정체 높고 분석에 포함되는 임상연구의 선행 기준을 정할 수 있다는 점이다. 과거 ARB가 급성 심근경색증을 증가시킨다는 메타분석 결과가 불필요한 논쟁만 일으키고 결국 사실이 아닌 것으로 밝혀진 바와 같이 Sipahi 등의 메타분석 연구 역시 심각한 오류를 갖고 있는지 의문점을 갖고, 연구 결과를 해석하는데 보다 주의가 필요하였다. Sipahi 등의 연구가 처음 발표되었을 때 일부 결과분석으로 암 발생을 조사하지 않은 연구들을 대상으로 하였고, 메타 분석에 포함된 임상연구 선행 기준이 적절적인 점들로 인해 분석 결과에 강한 의문이 있었는데, 본 연구는 FDA safety review와 더불어 ARB 사용이 암 위험을 증가시키지 않는다는 사실을 확인하였고, Sipahi 등의 메타분석 연구 결과를 부정하였다.