



# Cardiovascular Drug Use and Risk of Actinic Keratosis: A Case-Control Study

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## ABSTRACT

**Introduction:** Actinic keratosis (AK) is a pre-cancerous skin lesion. Currently, many experts treat actinic keratosis as squamous cell carcinoma in situ. It is well established that exposure of the skin to ultraviolet radiation is a major risk factor for the development of actinic keratosis. Some studies suggest an association between keratinocyte cancers and photosensitizing cardiovascular drugs. The aim of this study was to establish an association between cardiovascular drug use and the presence of AK.

**Methods:** A total of 400 patients were enrolled into the study (200 with AK; 200 healthy persons in the control group). The group of patients with AK consisted of 106 women and 94 men (mean age 71 years). The control group included 102 women and 98 men (mean age 69 years). An analysis of the risk factors for developing actinic keratosis was performed in

all patients with AK on the basis of a detailed, standardized interview.

**Results:** The statistical analysis showed that features independently associated with increased risk of AK included: age > 80 years (OR 4.14; 95% CI 2.4–7.3), positive cancer history (OR 1.94; 95% CI 1.0–3.6), positive history of sunburns when < 18 years old (OR 2.18; 95% CI 1.3–3.7) and taking angiotensin-converting enzyme inhibitors (OR 2.28; 95% CI 1.2–4.3), angiotensin receptor AT<sub>1</sub> blockers (OR 2.90; 95% CI 1.1–7.9) and calcium channel blockers (OR 2.4; 95% CI 1.0–5.3).

**Conclusion:** In conclusion, our study presented an association between cardiovascular drug use and the risk of developing AK.

**Keywords:** Actinic keratosis; Cardiovascular drug; Photosensitizing drug

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### Key Summary Points

Some studies suggest an association between non-melanoma skin cancers and photosensitizing cardiovascular drugs

Actinic keratosis is a precancerous skin lesion leading to non-melanoma skin cancers. Currently, actinic keratosis is treated by many experts as squamous cell carcinoma in situ. However, an association between the incidence of actinic keratosis and photosensitizing cardiovascular drugs was not reported in the literature

In the presented study the recognized features independently associated with increased risk of actinic keratosis are: age > 80 years, positive cancer history, positive history of sunburns under the age of 18 and prolonged use of angiotensin-converting enzyme inhibitors, angiotensin receptor AT1 blockers and calcium channel blockers

## INTRODUCTION

Actinic keratosis (AK) is a precancerous skin lesion. Currently, many experts treated it as squamous cell carcinoma (SCC) in situ [1]. The lesions of AK are usually multiple and cover a large area of skin, also including seemingly healthy skin. Such extensive lesions are termed “field cancerization” [2]. The presence of lesions within the seemingly healthy skin causes diagnostic difficulties and may lead to delay in treatment. The increasing prevalence of AK and skin cancers is the reason for the research on detecting new risk factors. It is well established that exposure of the skin to ultraviolet radiation (UVR) is a major risk factor for the development of AK and non-melanoma skin cancer; however, there are other possible risk factors including ionizing radiation, chemical exposures, genetic predisposition and immunosuppression [3].

Some studies suggest an association between non-melanoma skin cancers (NMSCs) and photosensitizing cardiovascular drugs [4, 5].

A photosensitivity reaction is an adverse cutaneous reaction that occurs when a certain chemical or drug is applied topically or taken systematically at the same time that a person is exposed to ultraviolet radiation or visible light. That reaction is associated with distinct chemical structures of the drug that allow the absorption of UVR [6, 7]. In phototoxic reactions the drugs may become activated by exposure to sunlight and cause direct tissue and cellular injury. In contrast, photoallergy is a form of a delayed type of immunologically mediated hypersensitivity. In photoallergic reactions, the ultraviolet exposure changes the structure of the drug so that it is recognized as an allergen by the immune system. Medications with a high photosensitivity potential may act as carcinogens by triggering a phototoxic reaction, causing acute DNA damage and a photoallergic reaction, which induces chronic inflammation [5, 7].

Based on a review of the literature, cardiovascular drugs can be divided into photosensitizing (alpha-2 receptor agonists and thiazide diuretics), non-photosensitizing (alpha-blockers, beta-blockers, angiotensin receptor blockers [ARBs]) or undetermined (angiotensin-converting enzyme [ACE] inhibitors, calcium channel blockers) [5, 6].

Statins have been rarely reported as photosensitizers [8]. Simvastatin may cause chronic actinic dermatitis [9], and atorvastatin may cause erythema with edema [10].

Among the angiotensin-converting enzyme inhibitors, captopril, ramipril, quinapril and enalapril have been reported to cause photosensitive reactions [11]. Captopril has been reported to cause a follicular mucinosis as a photoallergic manifestation [12], while valsartan was the only angiotensin receptor AT<sub>1</sub> blocker triggering photosensitivity [13].

In the group of calcium channel blockers, amlodipine and nifedipine have been found to cause photodistributed facial telangiectasia [14] and diltiazem photodistributed hyperpigmentation, photosensitivity and photoallergic dermatitis [15].

Thiazides are widely used diuretics that have been implicated in many photosensitive reactions. In a series of 62 cases of photosensitivity due to thiazides, hydrochlorothiazide was the most commonly implicated agent, and the most common presentation was eczematous lesions in a photodistributed pattern [16].

The aim of the present study was to determine the association between cardiovascular drug use and presence of AK.

## METHODS

Two hundred consecutive patients with histologically confirmed actinic keratosis treated at the out-patient department were included in the study. Individuals in the control group were selected from healthy persons (without the clinical features of AK, SCC and basal cell carcinoma, BCC) during check-up visits and matched for age and gender with analyzed patients.

The analysis of risk factors for AK development was performed in all patients with AK on the basis of a detailed, standardized interview. Clinical data regarding age, gender, sunscreen use, history of sunburns when under and above 18 years of age, history of cancers and long-term (not less than 5 years) usage of cardiovascular medications and other drugs during the last 10 years were collected.

The statistical analysis included a chi-squared test, Fisher's exact test, multivariate logistic regression model and Hosmer-Lemeshow goodness-of-fit test. All hypotheses were tested with a statistical significance of 0.05.

The study was approved by the Research Ethics Committee for the Protection of Persons and Animals of Central Clinical Hospital of the MSWiA in Warsaw, Poland. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

## RESULTS

A total of 400 subjects were enrolled in the study: 200 patients with actinic keratosis and 200 of age- and sex-matched healthy controls. The group of patients with AK consisted of 106

women and 94 men; the mean age was 71 (46–93) years. The control group included 102 women and 98 men with a mean age of 69 (45–90) years. Among patients with AK, 65 (32.5%) patients were > 80 yearsold and 54 (27%) patients in the control group. There was no statistically significant difference with respect to mean age and gender. The studied population included only Caucasians with Fitzpatrick phototypes I–III.

In our study 29.5% (59/200) of patients with AK and 23.5% (47/200) in the control group reported having had < 5 sunburns when < 18 years of age. These differences were statistically significant ( $p < 0.004$ ). There was no significant association between AK and sunburns for those > 18 years old. Patients with AK reported no sunscreen usage more often (57%; 114/200) compared to patients in the control group (48.5%; 97/200) or usage of sunscreens with a lower sun protection factor (SPF) [SPF < 15: 26.5% (53/200) vs. 24.5% (49/200); SPF 15–29: 5.5% (11/200) vs. 24.5% (22/200); SPF 30–49: 9% (18/200) vs. 12.5% (25/200), SPF  $\geq$  50: 2% (4/200) vs. 3% (6/200)]. However, these differences were not statistically significant.

Patients with AK had a positive personal cancer history significantly more often than those in the control group (20.5%, 41/200 vs. 10%, 20/200;  $p < 0.05$ ).

Patients with AK were treated significantly more often ( $p < 0.05$ ) with ACE inhibitors (21.5%; 43/200), calcium channel blockers (16.5%; 26/200) and ARBs (11.5%; 21/200) compared to the control group (9.5%, 19/200; 5.5%, 11/200 and 3.0%, 6/200; respectively). There were no statistically significant differences in statin therapy in patients with AK [16.4% (33/200) individuals, including 19.4% men (18/94) and 14.1% women (15/106)] compared to the control group [8.0% (16/200) individuals, including 5.2% men (4/76) and 9.6% women (12/124)]. Moreover, there were no statistically significant differences in the percentage of patients with AK who were treated with beta blockers (21.5%; 43/200) and thiazide diuretics (17.5%; 35/200) compared to the control group (13.0%; 26/200 and 7.5%; 15/200, respectively).

The statistical analysis showed that features independently associated with increased risk of AK included: age > 80 years (OR 4.14; 95% CI 2.4–7.3), positive cancer history (OR 1.94; 95% CI 1.0–3.6), positive history of sunburns when < 18 years old (OR 2.18; 95% CI 1.3–3.7), and treatment with ACE inhibitors (OR 2.28; 95% CI 1.2–4.3), ARBs (OR 2.90; 95% CI 1.1–7.9) and calcium channel blockers (OR 2.4; 95% CI 1.0–5.3). An influence of age was seen in both men (OR 4.6; 95% CI 1.9–10.9) and women (OR 2.6; 95% CI 1.2–5.7).

The detailed results are presented in Table 1.

Table 2 summarizes the features independently associated with increased risk of actinic keratosis.

## DISCUSSION

In the study we showed that patients > 80 years of age had fourfold higher risk of developing AK than patients under this age. This risk was

higher in both men and women, but in women the risk increased twofold and in men more than fourfold. The study results were in line with the previous ones. Recent epidemiological studies have indicated that prevalence of AK increases with age for both genders, but the increase in men is higher than in women [17]. In a European multicenter clinical trial published in 2016 the authors emphasized that the risk of AK and non-melanoma skin cancer increases with population aging [17]. Massy et al. [18] showed that the prevalence of AK in patients > 60 years of age was 30.6% and was threefold higher than in patients 50–59 years old. Green et al. [19] analyzed and estimated the prevalence of AK in individual age groups at 40% for the 20–69-year age group and at 68.1% for women and 79.4% for men 60–90-year age group.

Our study showed that a significant risk factor for AK was a positive history of sunburns when < 18 years of age, which increased the risk

**Table 1** Risk factors for actinic keratosis

	Patients with AK % (n)	Control group % (n)	p
< 5 sunburns when < 18 years of age	18.0% (36/200)	22.5% (45/200)	0.74
≥ 5 sunburns when < 18 years of age	29.5% (59/200)	23.5% (47/200)	*0.004
< 5 sunburns when > 18 years of age	16.5% (33/200)	19.5% (39/200)	0.92
≥ 5 sunburns when > 18 years of age	14.0% (28/200)	12.5% (25/200)	0.54
Usage of sunscreens with SPF <sup>2</sup> < 15	26.5% (53/200)	24.5% (49/200)	0.76
Usage of sunscreens with SPF 15–29	5.5% (11/200)	11.0% (22/200)	0.24
Usage of sunscreens with SPF 30–49	9.0% (18/200)	12.5% (25/200)	0.18
Treatment with beta blockers	21.5% (43/200)	13.0% (26/200)	0.96
Treatment with angiotensin-converting enzyme inhibitors	21.5% (43/200)	9.5% (19/200)	*0.01
Treatment with thiazide diuretics	17.5% (35/200)	7.5% (15/200)	0.88
Treatment with statins	16.5% (33/200)	8.0% (16/200)	0.46
Treatment with calcium channel blockers	13.0% (26/200)	5.5% (11/200)	*0.03
Angiotensin receptor AT <sub>1</sub> blockers	11.5% (21/200)	3.0% (6/200)	*0.03
Positive cancer history	20.5% (41/200)	10.0% (20/200)	*0.01

AK actinic keratosis, SPF sun protection factor

\*p < 0.05

**Table 2** Features independently associated with increased risk of actinic keratosis

Features	Odds ratio	95% CI
Age > 80 years old	4.14	2.4–7.3
Positive cancer history	1.94	1.0–3.6
Positive history of sunburns when < 18 years old	2.18	1.3–3.7
Treatment with angiotensin-converting enzyme inhibitors	2.28	1.2–4.3
Treatment with calcium channel blockers	2.4	1.0–5.3
Treatment with angiotensin receptor AT <sub>1</sub> blockers	2.90	1.1–7.9

of developing AK more than twofold. Similar observations have been described in the literature. Flohil et al. [20] conducted a study on 2061 patients and reported that individuals with a history of sunburns had a threefold higher risk of developing AK. Neale et al. [21] showed that in patients with a history of more than ten sunburns the risk of NMSC is twofold higher [22]. In a cohort study published in 2016, the authors assessed that the risk of NMSC developing in patients with a positive history of sunburns amounts to BCC 1.42 and SCC 1.39 in women and 1.18 and 1.48 in men, respectively [23].

Our study demonstrated that patients with AK did not use sunscreens more often than patients in the control group, and those who did used the sunscreens of lower SPF. It is important to underline that in both groups > 60% of individuals did not use sunscreens or used those with SPF < 15. These results are in line with the previous studies that showed the use of sunscreens not only protects against AK and NMSC but also leads to spontaneous remission of existing lesions [24].

In the literature there are only a few studies concerning the association between pharmacotherapy and a risk of developing skin cancer. In 2018, Su et al. [5] published a large cohort study estimating the association between the use of antihypertensive drugs and risk of SCC. The authors found a 17% increase in the risk of SCC in hypertensive patients who received photosensitizing antihypertensive drugs during follow-up compared to nonusers of antihypertensive drugs. Each class of photosensitizing

antihypertensive drugs showed a small increase in risk, but only thiazide diuretics attained statistical significance. In their meta-analysis of ten observation studies, Tang et al. showed that the use of ACE inhibitors or ARBs was significantly associated with a decreased risk of both BCC (OR 0.53; 95% CI 0.39–0.71) and SCC (OR 0.58; 95% CI 0.42–0.80) [25]. Schmidt et al. showed that long-term low-intensity and long-term high-intensity use of ARBs was associated with melanoma (OR 1.53; 95% CI 1.05–2.23 and 1.44; 95% CI 0.56–3.69, respectively). They also showed that ever use of ACE inhibitors was not associated with a substantial increase in the risk of SCC and BCC [26]. Only one study showed an association between the presence of AK and potentially photosensitizing thiazide diuretics (OR 3.18; 95% CI 1.93–5.26) and potentially photosensitizing cardiac drugs (OR 4.56; 95% CI 2.92–7.13) such as amiodarone and diltiazem [3]. Table 3 summarizes previous study results.

In our study patients with AK used ACE inhibitors and ARBs significantly more often than subjects in the control group. We showed that using ACE inhibitors and ARBs increased AK incidence twofold. Furthermore, in men using ARBs the incidence of AK increased more than five-fold (OR 5.26). Recent experimental data suggested that ACE inhibitors and ARBs had beneficial effects on tumor progression, vascularization and metastasis and that angiotensin receptor AT<sub>2</sub> subtype played a role in the regulation of cell proliferation and neoplastic progression [27, 28]. Grzegorzolka et al. [29] measured the immunohistochemical expression

**Table 3** Results of previous studies on the drug phototoxicity and non-melanoma skin cancer relationship

Study	Results
Su et al. [5]	17% increase in risk of SCC in patients who received photosensitizing antihypertensive drugs. Each class of photosensitizing antihypertensive drugs showed a small increase in risk, but only thiazide diuretics attained statistical significance (aHR 1.32; 95% CI 1.19–1.46)
Tang et al. [25]	Decreased risk of both BCC (OR 0.53; 95% CI 0.39–0.71) and SCC (OR 0.58; 95% CI 0.42–0.80) in patients who received ACE inhibitors or ARBs
Schmidt et al. [26]	Increased risk of melanoma in patients who received long-term low-intensity and long-term high-intensity ARBs (OR 1.53; 95% CI 1.05–2.23 and 1.44; 95% CI 0.56–3.69, respectively) Use of ACE inhibitors was not associated with a substantial increase in the risk of SCC and BCC
Traianou et al. [3]	Increased risk of AK in patients who received photosensitizing thiazide diuretics (OR 3.18; 95% CI 1.93–5.26) and potentially photosensitizing cardiac drugs (OR 4.56; 95% CI 2.92–7.13) such as amiodarone and diltiazem

SCC squamous cell carcinoma, BCC basal cell carcinoma, ACE-inhibitors angiotensin-converting enzyme inhibitors, ARBs angiotensin receptor AT<sub>1</sub> blockers, AK actinic keratosis

of ACE, ACE 2 and Ki-67 antigen in archival samples of normal skin, AK and malignant skin lesions, showing a significantly higher ACE immunoreactivity in normal skin than for BCC and SCC ( $p < 0.01$ ,  $p < 0.0001$ , respectively). Additionally, ACE immunoreactivity was also significantly higher in BCC than SCC ( $p < 0.05$ ). Recently published studies have not shown an association among ACE inhibitors, ARBs and increased incidence of cancer. Some authors have shown that patients treated with ACE inhibitors and ARBs have a slightly higher but significantly increased risk of cancer [30]; however, others have excluded that risk [31–33]. Other authors have noticed that patients with a positive history of cancer taking these medications had reduced mortality and risk of recurrence [34, 35]. In a meta-analysis of randomized controlled trials, Sipahi et al. [36] suggested that ARBs (especially telmisartan) increased the risk of new cancer diagnosis. Qian et al. [30] found that ARBs are associated with a lower risk of breast cancer in Asians and higher risk in Caucasians. A meta-analysis conducted in 2007 by Songa et al. [34] showed that both ACE inhibitors and ARBs decreased the risk of recurrence of cancer and mortality by 40% and 25%, respectively. Mao et al. [35] reported that ACE inhibitors and ARBs reduced the incidence

of prostate cancer. However, based on their meta-analysis, Zhao et al. [33] showed that ACE inhibitors and ARBs neither increased nor decreased the risk of developing cancer. A multicenter European study on the risk factors for developing AK showed that patients taking cardiovascular drugs had a higher incidence of AK, which the researches indirectly attributed to the fact that these drugs are used by older patients [3].

Our study found that calcium channel blockers increased the incidence of AK twofold. These medications were taken statistically significantly more often by the patients with AK than those in the control group. It is difficult to relate this finding to the literature because there have been no studies to date evaluating the association between calcium channel blockers and the incidence of AK and NMSC. Li et al. [37] conducted the study in a group of women aged 65–75 years and showed that using calcium channel blockers increased breast cancer risk (OR 1.5; 95% CI 1.0–2.1). That association was not confirmed by other research. Wilson et al. [38] showed that calcium channel blockers did not increase breast cancer incidence (HR 0.88, 95% CI 0.58–1.33). Azoulay et al.'s study demonstrated an analogous result [39]. In their group of patients, the risk of developing breast

cancer was HR 0.97, and using calcium channel blockers had no association with any cancers.

Further studies are necessary to evaluate the incidence of AK and non-melanoma skin cancer in patients using different classes of cardiovascular drugs.

## CONCLUSIONS

The features connected with an increased risk of AK are: age > 80 years, positive cancer history, positive history of sunburns when < 18 years old and using ACE inhibitors, ARBs and calcium channel blockers. Further studies are necessary to evaluate the incidence of AK and non-melanoma skin cancer in patients using different classes of cardiovascular drugs.

It is important to underline that patients using these classes of medications are very often in older age groups and have a positive history of cancer and sunburns. Thus, they should be educated about skin cancer and the use of sunscreen and regularly undergo dermoscopy for early detection and treatment of AK and skin cancer.

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**Compliance with Ethics Guidelines.** The study was approved by the Research Ethic Committee the Protection Persons and Animals Central Clinical Hospital of the MSWiA in Warsaw. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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