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## THERAPIES

### HEADING: Pharmacovigilance

## Calcium channel blocker exposure and psoriasis risk: pharmacovigilance investigation and literature data.

*Calcium channel blockers and psoriasis risk.*

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## **Summary**

*Introduction.*- Evidence regarding a possible association between psoriatic manifestations and use of calcium channel blockers (CCBs) is sparse. Currently, psoriatic manifestations are not listed in the summary of product characteristics (SmPC) of CCBs. In this context, we aimed to investigate the association between psoriasis and CCB exposure. *Methods.*- We reviewed spontaneous reports recorded in the French national Pharmacovigilance Database (FPVD) between 1985 and 2019. The association between CCB exposure and risk of psoriasis was assessed using the case/non-case method. We also analyzed literature data. *Results.*- Ninety-four reports of psoriatic manifestations after CCB exposure were recorded in the FPVD. Both induction and exacerbation cases were observed. Time to onset was less than 2 years in 64% of reports and outcome was favorable in 71% of reports after CCB discontinuation. These features were concordant with those of literature reports. The reporting odds ratio (ROR) was 2.45 (95% CI 1.99 – 3.02). Concomitant use of betablockers or angiotensin II receptor blockers did not interact with the association between CCB exposure and psoriasis risk. The ROR for the stratum “use of angiotensin converting enzyme inhibitors” (ACEI) was 2.14 (95% CI 1.29 – 3.55), while the ROR for the stratum ACEI non-use was 0.12 (95% CI 0.10 – 0.15). Large scale epidemiologic studies were focused only on first diagnoses and did not include exacerbations; psoriasis risk was therefore probably underestimated. *Conclusion.*- We found a statistically significant association between CCB exposure and psoriasis risk, which constitutes a safety signal. This risk is a class effect, time to onset is mostly less than 2 years and outcome is favorable after CCB discontinuation. Psoriasis should be mentioned in the SmPCs of all CCBs, and healthcare workers should be aware of this risk. Attention should be paid to patients taking CCB and ACEI concomitantly.

## **KEYWORDS**

Calcium channel blockers, psoriasis, pharmacovigilance

## **Abbreviations**

ACEIs: angiotensin converting enzyme inhibitors

ADR: adverse drug reaction

ARBs: angiotensin II receptor blockers

BBs: betablockers

CCBs: calcium channel blockers

CI: confidence interval

FPVD: French pharmacovigilance database

DHPs: dihydropyridines

MedDRA: medical dictionary for regulatory activities

ROR: reporting odds ratio

SmPC: summary of product characteristics

TRPC channels: canonical transient receptor channels

VGCC: voltage-gated calcium channels

## **Introduction**

Psoriasis is a chronic, non-infectious, disfiguring, disabling and painful disease characterized by the build-up of red, scaly patches on the skin. It can occur at any age, with no predominance of either sex. The estimated prevalence of psoriasis in adults ranges from 0.51% to 11.43% [1]. The pathophysiologic mechanism includes epidermal homeostasis disorders (proliferation and differentiation disorders) and complex inflammatory phenomena [2]. Psoriasis is a multifarious disease and diagnosis is primarily clinical. The most common form, accounting for 90% of all cases, is plaque psoriasis or psoriasis vulgaris. Severe forms, in adults, include pustular psoriasis, psoriatic erythroderma and psoriatic arthritis [3]. Psoriatic lesions occur in a particular genetic

terrain [4]. A variety of triggers have been identified, including infection, stress, and drugs that may induce or aggravate psoriasis [5]. Therapeutic agents may be classified into those with strong evidence for a causal relationship with psoriasis, such as lithium, betablockers (BBs), and antimalarials; and a second, larger group of miscellaneous drugs, including calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), which may possibly be related to psoriasis [6–9].

Since the 1970s, CCBs are used in various indications such as hypertension, angina pectoris and management atrial arrhythmias. They are often classified into 2 major categories: dihydropyridines (DHPs, e.g. amlodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nimodipine, nitrendipine) and non-dihydropyridines (non-DHPs, e.g. verapamil, diltiazem, bepridil) [10]. CCBs are associated with a wide spectrum of cutaneous reactions [11]. The first reports of psoriatic manifestations with CCBs date back to late 1980s/early 1990s [12–14]. Two decades later, data from epidemiological studies regarding psoriasis risk with CCB use remain conflicting [15–17]. Currently, psoriatic manifestations are not listed in the summary of product characteristics (SmPC) of CCBs, and more information may be warranted in order to judge whether it is necessary to include a mention of psoriasis in the SmPC. In this context, we aimed to investigate the association between CCB exposure and risk of psoriasis, by analyzing data from the French national pharmacovigilance database (FPVD) and data from the literature.

## Methods

### **French national pharmacovigilance database (FPVD) Data**

#### Data Source

The FPVD was set up in 1985 to allow online input of spontaneous adverse drug reaction (ADR) reports from 31 regional pharmacovigilance centres. French legislation requires healthcare

professionals to report all ADRs to their regional pharmacovigilance centre. Reports are validated by qualified personnel before anonymous storage in the FPVD. ADRs are coded according to the medical dictionary for regulatory activities (MedDRA®) [18]. An ADR is considered serious if it leads to death, is life-threatening, causes hospitalization or prolongation of an existing hospitalization, persisting significant disability or incapacity, congenital anomaly/birth defects, or other serious medical situation. Causality between ADRs and drugs is assessed according to the French causality method [19].

### Descriptive analysis

We performed a retrospective, descriptive analysis. All spontaneous notifications of psoriasis with CCB exposure from the inception of the database in 1985 to 31 December 2019 were reviewed. For each CCB marketed in France (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nimodipine, nitrendipine, verapamil, diltiazem and bepridil), a broad search in the FPVD was performed using a query with the following high level terms: “psoriatic conditions” and “psoriatic arthropathy” (MedDRA® version 20.1). Only notifications in which CCBs were considered as “suspect” were included in the study. For each notification, we systematically recorded variables related to the patient (i.e., age, gender, and medical history); related to the drug (international nonproprietary name and action taken against the ADR); and related to the ADR (i.e., preferred term, time to onset, seriousness and outcome). For each case, we verified inconsistencies between the completed fields and the clinical description.

### Case/non-case study

We assessed the association between psoriasis and CCB exposure using a case/non-case approach, which evaluates the disproportionality of combinations of a drug with a particular ADR in pharmacovigilance databases. Cases are all reports of the ADR of interest (in this study, psoriasis).

Non-cases are all other ADRs reported in the database during the same period of time (in this study, cutaneous ADRs except psoriasis). This method allows comparison of drug exposure (in this case, to CCBs) among cases and non-cases by calculation of the reporting odds ratio (ROR) and its 95% confidence interval (CI). This is a validated method of safety signal detection [20–21]. For each CCB, the ROR was calculated using the following formula:  $(a/c)/(b/d)$ , where (a) is number of psoriasis reports with the suspected CCB, (b) is the number of cutaneous ADRs except psoriasis with the suspected CCB, (c) is the number of psoriasis reports with all other suspected drugs, and (d) is the number of cutaneous ADRs except psoriasis with all other suspected drugs. The 95% CI was calculated using the Woolf method [22]. To validate our results, we chose lithium as a positive control [23]. BBs, ACEIs and ARBs were taken into account as a potential confounders, and the stratification method was applied. For each stratum (e.g. BB use stratum and BB nonuse stratum), the ROR and 95% CI were calculated, and homogeneity between the stratified RORs was tested using the Breslow-Day test [24]. If RORs were not significantly different, they were pooled to calculate the adjusted Mantel–Haenszel ROR; significance of the adjusted ROR was assessed using the Cochran–Mantel–Haenszel test [25]. Statistical analysis was performed using SAS 9.4 Software (SAS Institute Inc., Cary, NC, USA).

## **Review of the literature reports**

We reviewed published articles dealing with psoriasis risk with CCB use from the following databases: Medline®, Cochrane®, Scopus®, ScienceDirect®, and Google Scholar®. For each CCB (amlodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nimodipine, nitrendipine, verapamil, diltiazem and bepridil), the search was conducted as follows: (CCB name) AND [‘psoriasis’ OR ‘pustular psoriasis’ OR ‘psoriatic erythroderma’ OR ‘psoriatic arthritis’ OR ‘psoriasiform dermatitis’].

## **Results**



## French pharmacovigilance data

During the study period, 829,761 spontaneous ADR reports were registered in the FPVD, 2,120 were psoriatic conditions of which 94 occurred with CCBs. The mean age of patients was  $68 \pm 11$  years (range 34 – 93 years), the male/female ratio was 3.4 (72 men and 21 women). Thirty four reports (36%) were considered serious; the seriousness criteria were “hospitalization or prolongation of existing hospitalization” (n = 20) and “other serious medical situations” (n = 14). The indications for CCB use, where completed (n = 54), were hypertension (n = 48), angina pectoris (n = 2), arrhythmia (n = 1), ischaemic cardiomyopathy (n = 1), facial neuralgia (n = 1) and ischaemic heart disease prophylaxis (n = 1). Sixty five percent of reports (n = 61) were coded as “psoriasis” (without further detail), 34% as “psoriasiform dermatitis” (n = 32), one case as “erythrodermic psoriasis”. A personal history of psoriasis was mentioned in 27% of reports (n = 25); these reports were classified as exacerbation of psoriasis. Time to onset, where mentioned (n = 50), ranged from 1 day to 30 years; the average was 36 months. In 64% (n = 32) of the reports where time to onset was available, it was less than 2 years. DHPs accounted for 73% of suspected CCBs (n=69). The most commonly implicated CCBs were: amlodipine (n = 22), nifedipine (n = 18) and verapamil (n = 14). In 71% (n = 67) of reports, other antihypertensive drugs were taken concomitantly: BBs (n = 34), diuretics (n = 24), ACEIs (n = 19) or ARBs (n = 18). The action taken with the suspected CCB was as follows: drug withdrawal in 33% of reports (n = 31), decreased dose in one report, unchanged dose in 46% of reports (n = 43) and unknown in 20% of reports (n = 19). After CCB discontinuation, the outcome was favorable in 71% of reports (n = 22) [Table 1].

There were 33 psoriatic manifestations with lithium, the ROR was 3.68 (95% CI 2.59 – 5.48). The ROR for psoriasis with a CCB was 2.45 (95% CI 1.99 – 3.02), the highest values were observed with nifedipine (n = 18, ROR 4.62, 95% CI 2.87 – 7.43), lercanidipine (n = 11, ROR 9.68, 95%CI 5.20 – 18.03) and lacidipine (n = 3, ROR 12.35, 95% CI 3.71 – 41.18) [Table 2].

The ROR adjusted for concomitant BB use was 1.86 (95% CI 1.50–2.31), the Cochran–Mantel–Haenszel test was significant (P-value <0.01). Regarding ACEIs, the ROR for the ACEI use stratum was 2.14 (95% CI 1.29 – 3.55), and for the stratum ACEI non-use 0.12 (95% CI 0.10 – 0.15). The test of homogeneity was significant (P-value <0.01), and thus, the stratified RORs were

not pooled. The ROR adjusted for ARB concomitant use was 2.06 (95% CI 1.67 – 2.55), the Cochran–Mantel–Haenszel test was significant (P-value <0.01) [Table 3].

## Literature data

The first articles dealing with CCB exposure and psoriasis risk date back to late 1980s /early 1990s. Lavrijsen et al. noted that patients with psoriasis may be at special risk for eruptions while using diltiazem [12]. Stern et al. reported 2 psoriasis-type reaction cases with nifedipine and diltiazem [13]. Kitamura et al. reported 8 cases of psoriasiform eruptions with CCBs (3 males and 5 females); the average age was  $67.1 \pm 9.7$  years (range 56 to 78 years). Time to onset ranged from 9 days to 10 years, with an average of 34.7 months. Time to onset was less than 2 years in 75% of cases. The causative drugs were: nifedipine (n = 2), nisoldipine (n = 1), verapamil (n = 2), diltiazem (n = 1) and nifedipine (n = 3). Eruptions developed after starting a CCB and resolved with its discontinuation in 3 cases, eruptions developed after starting a CCB but persisted to a lesser degree in 2 cases, lesions worsened after starting a CCB in 3 cases. One case developed psoriasiform eruptions with nifedipine, eruptions waned after its discontinuation but reappeared after nisoldipine introduction [14].

In their case-control study, published in 2001, Cohen et al. highlighted a significant association between CCB exposure and psoriasis risk. One hundred fifty patients hospitalized for psoriasis or psoriasiform eruptions and 150 matched controls were included in the study between 1989 and 1999. Thirteen patients hospitalized for psoriatic manifestations had taken CCBs (9 males, 4 females; mean age was  $64.1 \pm 8.9$  years). Two patients had new-onset psoriasis and 11 had exacerbation of pre-existing psoriasis. The CCBs involved were: nifedipine (n = 10), felodipine (n = 2) and amlodipine (n = 1). Seven patients were taking BBs concomitantly. Time to onset ranged from 4 months to 143 months, with an average of 38.4 months. Time to onset was less than 2 years in 50% of cases. The OR was 3.5 (95%CI 1.3 – 16.6). The authors suggested that a further large population study was needed to conclude on this possible association [15]. In another case-control study, conducted between 1994 and 2005 on the UK general practice research database, 36,702 cases with a first-time psoriasis diagnosis and 36,702 matched controls were included; 3202 cases were on CCBs. In this publication, the findings of Brauchli et al. did not support the hypothesis that

CCB use was associated with an increased risk of psoriasis (OR 0.97, 95% CI 0.88 – 1.07) [16]. Finally, in a prospective cohort study using the Nurses' Health Study data, conducted from June 1996 to June 2008, 843 incident psoriasis cases among 77,728 participants were documented; 96 cases had taken CCBs. No association was found between CCBs and risk of psoriasis even after more than 6 years of exposure (HR 1.08, 95%CI 0.80 – 1.45) [17].

## Discussion

In the FPVD, we found a total of 94 spontaneous reports of psoriatic manifestations after CCB exposure. To the best of our knowledge, this is the largest case series described with this therapeutic class. CCBs were mainly used in hypertension management. The mean age of about 65 years and the male predominance are compatible with epidemiological data regarding hypertension [26]. CCBs inhibit L-type voltage-gated calcium channels (VGCC), and among them, both DHPs and non-DHPs have the same capacity to lower blood pressure. DHPs have vascular smooth muscle cell tropism and act mainly through vasodilatation, while non-DHPs have cardiomyocyte tropism and act mainly via a negative inotropic effect [10]. Depending on the cardiovascular risk factors and blood pressure levels, hypertension management may require double or triple therapy, with CCBs preferentially associated with diuretics, ACEIs, ARBs or BBs [27].

More than half of all reports were considered as non-serious. However, psoriasis has a significant negative impact on patients' quality of life. It is associated with various psychological impairments, such as embarrassment, lack of self-esteem, anxiety and increased prevalence of depression [28].

Psoriasis has an unpredictable course of symptoms and several triggers, but the causal relation between psoriasis and drug intake is often difficult to prove [29]. These features lead us to believe that psoriatic manifestations with CCBs are probably underreported. Underreporting is the major limitation of studies based on spontaneous reporting. It is estimated that 94 % of ADRs are not reported to health authorities [30].

The data from the FPVD and literature reports, especially the case series described by Katamura et al. [14], are congruent. Almost all CCBs were involved, DHPs as well as non-DHPs,

suggesting a class effect. The time to onset was generally less than 2 years, and outcome was favorable after drug discontinuation. Typical psoriatic lesions as well as psoriasiform lesions were described. Psoriasiform lesions differ from typical psoriatic lesions in terms of size, shape and anatomical distribution [31]. Both induction and exacerbation cases were observed.

Data from epidemiological studies regarding the association between CCB use and psoriasis risk are conflicting. Only one study highlighted a significant association. This study included first diagnoses as well as exacerbation cases, but was limited by its small size [15]. No association was found between CCBs and psoriasis in the studies conducted using the UK general practice research database and the nurses' health study data; even after long exposure [16,17]. These large population-based studies were focused only on first diagnoses and did not include exacerbations; psoriasis risk with CCBs was therefore probably underestimated.

Literature reviews dealing with drug provoked psoriasis agree on the fact that lithium intake has a strong association with psoriasis, although the mechanism of this phenomenon is not yet elucidated [6–9]. We chose lithium as a positive control for the case/non-case study using the FPVD reports. The significant ROR value obtained with lithium validated our methodology. We highlighted a statistically significant association between CCB exposure and risk of psoriasis, which constitutes a potential safety signal. DHPs as well as non-DHPs were concerned. Among the DHPs, nifedipine, nicardipine and lacidipine had a higher ROR value than the positive control. Among the non-DHPs, only verapamil had a significant association with psoriasis. As a class effect is presumed, the risk of psoriasis should be mentioned in the SmPC of all CCBs. A calcium gradient exists across the epidermis, and plays a crucial role in keratinocyte differentiation/proliferation and inflammation processes. In psoriatic skin, the calcium gradient is defective leading to impaired keratinocyte differentiation, enhanced keratinocyte proliferation and increased release of pro-inflammatory cytokines. Canonical transient receptor channels (TRPC channels) are important in the formation of the calcium gradient. Reduced expression of TRPC channels is observed in psoriatic keratinocytes [32]. L-type VGCCs are also expressed in keratinocytes and play a role in the maintenance of the calcium gradient [33]. CCBs could therefore diffuse to the epidermis and disrupt the calcium gradient. The different levels of association observed with psoriasis could be explained by differences in the ability to diffuse to keratinocytes, and the ability to bind L-type VGCC or TRPC channels.

Cohen et al. [15] suggested that patients concomitantly taking BB and CCB may be at higher risk of psoriasis. Our data did not support this hypothesis; the concomitant use of BB or

ARB did not interact with CCB exposure and psoriasis risk. In contrast, RORs stratified for ACEI use were significantly different, whereby patients concomitantly taking ACEI and CCB were at higher risk of psoriasis. We recently reported a significant association between ACEI exposure and psoriasis risk using the FPVD reports [34]. Time to onset was less than 1 year, and outcome was favorable after ACEI discontinuation. Physicians would therefore be wise to heighten their vigilance with patients taking ACEI and CCB concomitantly.

## **Conclusion**

This case/non-case study using data from the French national Pharmacovigilance database highlights a statistically significant association between the risk of psoriasis, and CCB exposure, which constitutes a potential safety signal. This risk is a class effect, time to onset is generally less than 2 years, and outcome is favorable after drug discontinuation. Both onset and exacerbation, and both typical psoriatic eruptions and psoriasiform eruptions are involved. A critical gap exists in identifying the causes of psoriasis flares, especially the potential role of drugs. Health authorities should sensitize healthcare workers to the risk of psoriasis with CCBs. Particular attention should be paid to patients taking CCB and ACEI concomitantly. Given the suggestive reports in the FPVD and in the literature, the SmPC of all CCBs should mention this risk.

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## **Disclosure of interest**

The authors declare that they have no competing interest.

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**Table 1.** Preferred terms, international non-proprietary names, actions taken against the psoriatic manifestations and outcomes after drug discontinuation in the French pharmacovigilance database reports of psoriasis occurring with calcium channel blockers between 1985 and 2019.

Variable	Frequency (%)
Preferred Term	
<ul style="list-style-type: none"> <li>• Psoriasis (without precision)</li> <li>• Psoriasiform dermatitis</li> <li>• Erythrodermic psoriasis</li> </ul>	61 (65%) 32 (34%) 1 (1%)
International non-proprietary name	
Dihydropyridines <ul style="list-style-type: none"> <li>• amlodipine</li> <li>• nifedipine</li> <li>• lercanidipine</li> <li>• nicardipine</li> <li>• lacidipine</li> <li>• manidipine</li> <li>• isradipine</li> <li>• nitrendipine</li> </ul> Non-dihydropyridines <ul style="list-style-type: none"> <li>• verapamil</li> <li>• diltiazem</li> <li>• bepridil</li> </ul>	69 (73%) <ul style="list-style-type: none"> <li>• 22 (23%)</li> <li>• 18 (19%)</li> <li>• 11 (12%)</li> <li>• 11 (12%)</li> <li>• 3 (3%)</li> <li>• 2 (2%)</li> <li>• 1 (1%)</li> <li>• 1 (1%)</li> </ul> 25 (27%) <ul style="list-style-type: none"> <li>• 14 (15%)</li> <li>• 9 (10%)</li> <li>• 2 (2%)</li> </ul>
Action taken with the suspected CCB	
<ul style="list-style-type: none"> <li>• Drug withdrawal</li> <li>• Unchanged dose</li> <li>• Decreased dose</li> <li>• Unknown</li> </ul>	31 (33%) 43 (46%) 1 (1%) 19 (20%)
Outcome after drug discontinuation (n=31)	
<ul style="list-style-type: none"> <li>• Improvement</li> <li>• No improvement</li> </ul>	22 (71%) 9 (29%)

CCB: calcium channel blocker

**Table 2.** Reporting odds ratio for psoriasis with calcium channel blocker therapy.

	<b>Overall number of notifications</b>	<b>Cases</b>	<b>Non cases</b>	<b>ROR</b>	<b>95% CI</b>
<b>CCBs</b>	14578	<b>94</b>	3731	<b>2.45</b>	<b>(1.99 – 3.02)</b>
• <b>Dihydropyridine</b>	10318	<b>69</b>	2490	<b>2.68</b>	<b>(2.10 – 3.41)</b>
- amlodipine	4278	<b>22</b>	1070	<b>1.95</b>	<b>(1.28 – 2.99)</b>
- nifedipine	1606	<b>18</b>	371	<b>4.62</b>	<b>(2.87 – 7.43)</b>
- lercanidipine	1388	<b>11</b>	108	<b>9.68</b>	<b>(5.20 – 18.03)</b>
- nicardipine	2121	<b>11</b>	446	<b>2.34</b>	<b>(1.28 – 4.26)</b>
- lacidipine	108	<b>3</b>	23	<b>12.35</b>	<b>(3.71 – 41.18)</b>
- manidipine	138	<b>2</b>	81	--	--
- isradipine	134	<b>1</b>	36	--	--
- nitrendipine	293	<b>1</b>	81	--	--
• <b>Non-dihydropyridine</b>	4260	<b>25</b>	1241	<b>1.92</b>	<b>(1.29 – 2.85)</b>
- verapamil	1768	<b>14</b>	421	<b>3.16</b>	<b>(1.85 – 5.39)</b>
- diltiazem	2227	<b>9</b>	760	<b>1.12</b>	<b>(0.58 – 2.16)</b>
- bepridil	265	<b>2</b>	22	--	--
<b>Lithium (positive control)</b>	5487	<b>33</b>	861	<b>3.68</b>	<b>(2.59 – 5.23)</b>
<b>All drugs</b>	829 761	<b>2120</b>	202 667		

CCB: calcium channel blocker; CI: confidence interval; ROR: reporting odds ratio interval

**Table 3.** Stratification by use of beta blockers, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers.

	ROR (95% CI)	Chi-square	DF	P-value
<b>Beta-blockers</b>				
• BB use stratum	2.09 (1.41 – 3.10)	14.06	1	<0.01
• BB non-use stratum	1.80 (1.39 – 2.33)	19.15	1	<0.01
• Homogeneity test	--	0.48	1	0.490
• <b>Mantel-Haenszel analyses</b>	<b>1.86 (1.50 – 2.31)</b>	32.842	1	<b>&lt;0.01</b>
<b>ACEI</b>				
• ACEI use stratum	2.14 (1.29 – 3.55)	9.11	1	<0.01
• ACEI non-use stratum	0.12 (0.10 – 0.15)	431.24	1	<0.01
• <b>Homogeneity test</b>	--	175.8	1	<b>&lt;0.01</b>
<b>ARBs</b>				
• ARB use stratum	1.58 (0.94 – 2.67)	2.98	1	<0.01
• ARB non-use stratum	2.20 (1.74 – 2.77)	46.84	1	<0.01
• Homogeneity test	--	1.29	1	0.256
• <b>Mantel-Haenszel analyses</b>	<b>2.06 (1.67 – 2.55)</b>	46.662	1	<b>&lt;0.01</b>

ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; BB: betablocker; CI: confidence interval; DF: degrees of freedom; ROR: reporting odds ratio.