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# The association between ACE inhibitors and the complex regional pain syndrome: Suggestions for a neuro-inflammatory pathogenesis of CRPS

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ABSTRACT

Antihypertensive drugs interact with mediators that are also involved in complex regional pain syndrome (CRPS), such a neuropeptides, adrenergic receptors, and vascular tone modulators. Therefore, we aimed to study the association between the use of antihypertensive drugs and CRPS onset. We conducted a population-based case-control study in the Integrated Primary Care Information (IPCI) database in the Netherlands. Cases were identified from electronic records (1996–2005) and included if they were confirmed during an expert visit (using IASP criteria), or if they had been diagnosed by a medical specialist. Up to four controls per cases were selected, matched on gender, age, calendar time, and injury. Exposure to angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, β-blockers, calcium channel blockers, and diuretics was assessed from the automated prescription records. Data were analyzed using multivariate conditional logistic regression. A total of 186 cases were matched to 697 controls (102 confirmed during an expert visit plus 84 with a specialist diagnosis). Current use of ACE inhibitors was associated with an increased risk of CRPS ($OR^{adjusted}$: 2.7, 95% CI: 1.1–6.8). The association was stronger if ACE inhibitors were used for a longer time period ($OR^{adjusted}$: 3.0, 95% CI: 1.1–8.1) and in higher dosages ($OR^{adjusted}$: 4.3, 95% CI: 1.4–13.7). None of the other antihypertensive drug classes was significantly associated with CRPS. We conclude that ACE inhibitor use is associated with CRPS onset and hypothesize that ACE inhibitors influence the neuro-inflammatory mechanisms that underlie CRPS by their interaction with the catabolism of substance P and bradykinin.



## 1. Introduction

The complex regional pain syndrome (CRPS) can occur in one or more extremities as a painful complication of a fracture, surgery or various other types of physical injuries [30]. Its incidence in the Netherlands is estimated between 20 and 26 per 100,000 person years, while women are affected 3.4 times more frequently than men [9,10]. In the absence of a sensitive and specific biomarker, the diagnosis is based on clinical criteria as established by the International Association for the Study of Pain (IASP) [27]. The mechanisms underlying CRPS have been studied increasingly over the past decade, and parts of the pathogenesis become slowly unraveled. Both inflammatory and neurogenic (autonomic and somatic) disturbances contribute to CRPS, and are represented in the clinical presentation. Most patients display classic inflammatory signs like pain, swelling, redness, and warmth in the initial phase of the disease [30]. Autonomic disturbances, neuropathic pain, and motor impairment are other important features, causing ongoing discomfort and functional disability [3].

Mediators of inflammation in CRPS include classic pro-inflammatory cytokines, such as IL-1β, IL-6, and TNFα, which are elevated in blister fluid [17], spinal liquor [1], and venous blood (mRNA levels) [28] of CRPS patients. Additionally, neuropeptides, such as calcitonin gene-related protein (CGRP) and substance P (SP), play a role in CRPS [4,5], contributing to vasodilatation, long-lasting erythema, and plasma protein extravasation [6,7,21,35]. Substance P also stimulates other immunological responses [23] and, when released by terminal nerve endings in the dorsal horn, it mediates central sensitization [26]. Bradykinin, which is involved in acute and chronic inflammatory responses [8] and in peripheral nociceptor sensitization [32], was measured systematically elevated in CRPS patients in a single study [5].

In addition to inflammatory markers, CRPS patients also have elevated systemic levels of catecholamines [14], whereas local levels are decreased [33]. Catecholamines are considered to be mediators in sympathetic hyperactivity, to which many signs of CRPS have

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been attributed. Under certain circumstances, catecholamines can also induce pro-inflammatory responses, mediated through the interaction with α-receptors expressed on immune cells [15,34].

Some of the above-mentioned inflammatory mediators that are elevated in CRPS patients also play a role in the mechanism of action of antihypertensive drugs. In particular, ACE inhibitors are of interest, as they might block the ACE-dependent degradation of substance P and bradykinin [11,15]. Therefore, ACE inhibitors could be hypothesized to increase the risk of CRPS onset. On the other hand, β-blockers attenuate the effects that are mediated by catecholamines, and therefore may decrease the symptoms of CRPS. Calcium channel blockers cause vasodilatation, thereby improving peripheral blood circulation and counteracting potential CRPS symptoms. Based on these mechanisms of action, we hypothesized that antihypertensive drugs could influence the occurrence of CRPS. This study therefore aimed to investigate whether antihypertensive drugs, and in particular ACE inhibitors, are associated with the risk of developing CRPS.

## 2. Methods

### 2.1. Design and setting

A retrospective case-control design was used, comparing antihypertensive drug use in CRPS patients to that in controls selected from the same general population. The study was nested in the Integrated Primary Care Information (IPCI) database, which is a longitudinal general practice (GP) database that currently contains the electronic records of more than 800,000 persons in the Netherlands. The IPCI population reflects the age and gender distribution of the general Dutch population. In the Dutch Health Care System, all persons are registered with one GP independent of their health status. The GP acts as a gatekeeper for further medical care and as a central receiver of information from secondary care. Therefore, the electronic records can be assumed to contain complete medical information of each patient [24]. GPs participating in the IPCI project do not keep additional paper records, except for specialist and discharge letters. Details on the database have been described previously [29].

The IPCI project complies with the European Union guidelines on the use of medical data for research, and has been proven to be valid for pharmacoepidemiological studies [31]. The present study has been approved by the Scientific and Ethical Advisory Group of IPCI and by the Medical Ethical Board of the Erasmus Medical Center (protocol number 2006-099).

### 2.2. Source population

The source population comprised all persons with at least 1 year of valid history in the IPCI database during the study period (January 1996–June 2005) to ensure sufficient baseline information on all subjects. This meant that the practice had been contributing data to the IPCI database for at least 1 year, and that the patient had been registered with the GP for at least 1 year. Follow-up started on the first of January 1996 or on the date that 1 year of valid history was available, whichever date was the latest. Follow-up was ended upon transferring out of the practice, the date of last data supply by the GP, death, diagnosis of CRPS or at the end of the study period, whichever came first. The source population was restricted to all practices that were still active in the IPCI database in 2006.

### 2.3. Cases

Potential incident CRPS cases were identified in the database using a sensitive string search algorithm. Subsequently, short questionnaires were mailed to the GPs, in which they were asked to reconfirm whether the person indeed had suffered from CRPS and to provide copies of all available specialist letters. A more detailed description of the case identification and validation process up to this point has been given in our study on the incidence of CRPS in the Netherlands [9].

In a subsequent step, all confirmed cases were invited to our study. Cases who consented to participate were visited by the primary investigator, a physician with clinical experience in diagnosing CRPS (M.M.). Preceding this visit, patients received a questionnaire wherein potential CRPS-related complaints were listed. Patients were required to indicate which of the complaints applied to them presently or in the past. Moreover, patients were asked which types of physicians they visited for CRPS, how they were treated, and how well they recovered. The results regarding treatment patterns and recovery will be reported elsewhere. Patients completed the questionnaire by themselves (maximum time load approximately 1 h), and during the visit the investigator and patient together solved incomplete answers. A physical examination of the affected and contra-lateral unaffected extremity was also performed. Subjective (questionnaire and interviews) and objective (physical examination) features of CRPS were noted on a standard assessment form, as used in TREND, the Dutch research consortium in which this study was embedded (http://www.trendconsortium.nl).

Patients were included as cases in the analysis if they were judged to have ever fulfilled the diagnostic criteria for CRPS as established by the International Association for the Study of Pain (IASP) [27], using the combined information from the visit, electronic journal and specialist letters (if available). We used the IASP diagnostic criteria for patient inclusion instead of the more specific criteria by Harden and Bruehl [13], because they require, more than the IASP criteria, detailed information regarding objective symptoms during the disease course. Such detailed information was not available for all patients in the GP journals or specialist letters. However, combining multiple sources of information did provide sufficient clinical information to apply the IASP criteria. Patients who could not be visited but who had a specialist diagnosis of CRPS were included as a case in the primary analysis, but were excluded in a secondary analysis. The index date was chosen as the date on which CRPS was first mentioned in the medical records.

### 2.4. Controls

Per case, up to four gender and age (year of birth)-matched controls were selected from the IPCI database, with the requirement that each control had encountered a similar type of injury as its matching case within 2 years prior to the date of CRPS diagnosis of the case. This meant that cases with CRPS following a fracture were matched to controls with a fracture, cases with CRPS following a soft tissue injury were matched to controls with a soft tissue injury, etc. If the CRPS had occurred in a case spontaneously (no initiating injury), the control was not required to have had an injury either. For each control, the index date was established as the date of the injury plus the time between injury and CRPS onset in its matched case.

### 2.5. Use of antihypertensive drugs

Drug prescriptions were retrieved from the IPCI database. The available data comprised Anatomical Therapeutical Chemical (ATC) classification code [2], prescription start date, quantity, strength, indication, and prescribed daily dose. The following groups of antihypertensives were included (according to the Dutch multidisciplinary guidelines for cardiovascular risk management,

also listed in Table 2): ACE inhibitors, angiotensin II (AT2) receptor antagonists, β-blockers, calcium channel blockers, and diuretics (alone or in combination with other antihypertensives). AT2 receptor antagonists were analyzed separately from the ACE inhibitors since they do not affect SP and bradykinin degradation, and therefore they were not suspected of affecting CRPS occurrence. The duration of a prescription was calculated as the quantity of prescribed units (mostly tablets) divided by the daily intake of units. Episodes of use per drug were created by combining consecutive prescriptions and correcting for overlap. A person was classified as a current user of a certain drug if the prescribed duration of the most recent prescription plus 7 days covered the index date. If the last prescription ended more than 7 days prior to the index date, persons were classified as past users. In the current users, we assessed the duration of use as the number of days that the drug was used during the last year before the index date. The prescribed daily dose was expressed as the number of dose equivalents of the defined daily dose (DDD) for the last prescription [2]. In order to evaluate the accuracy of the GP prescription data, pharmacy dispensing lists were requested for a subset of patients and compared to the prescription data.

### 2.6. Covariables

The medical history prior to the onset of CRPS was extracted from the electronic medical records. Smoking and disorders related to antihypertensive drug use, including hypertension, hypercholesterolemia, cardiovascular diseases (for example, angina pectoris and myocardial infarction) and diabetes mellitus (DM) type II, were considered as potential confounders. Additionally, diseases that were found to be associated with CRPS onset in a previous study conducted within the IPCI database were taken into account, namely osteoporosis, migraine, asthma, and menstrual cycle-related disorders [10]. Current use of drugs that might be associated with either antihypertensive use or CRPS was also evaluated as potential confounder (NSAIDs, corticosteroids, statins, SSRIs, tricyclic antidepressants, anti-epileptics, and drugs for migraine).

### 2.7. Statistical analyses

Conditional logistic regression analyses were performed to study the association between current and past use of antihypertensive drugs and CRPS onset, calculating crude and adjusted odd ratios (OR) with 95% confidence intervals (CI). Since two or even three antihypertensive drugs are frequently co-prescribed, antihypertensive drug monotherapy was analyzed separately, whereby (concomitant) users of other antihypertensives than the one of interest were classified into a separate category. Covariates were included in the model if they altered the OR for current use of ACE inhibitors by more than 10%. Sensitivity analyses were conducted to estimate the effect of outcome misclassification, including only the cases who were validated by a visit (using IASP criteria), thereby excluding the unvisited cases who were diagnosed by specialist. To investigate effect modification by gender stratified analyses were performed and interaction terms for gender and antihypertensive drug use were tested in the regression model.

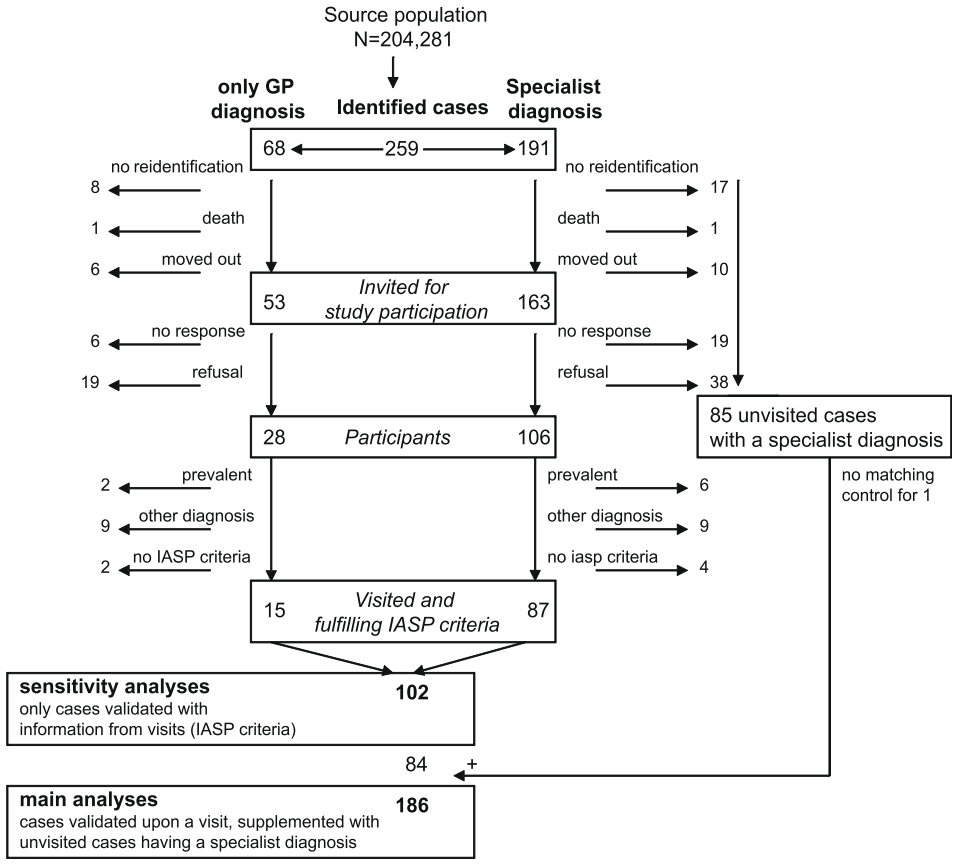


**Fig. 1.** Inclusion of cases for main and sensitivity analyses. *Re-identification* means the process of decoding the patient number in the IPCI database. The first decoding step is performed by the IPCI gatekeeper, who subsequently contacts the GP. Only the GP can retrieve the patient names and addresses for contacting purposes, and all patient contacts are mediated through the GP. Reasons for failure of re-identification are changes in software systems or retirement of the GP. In *prevalent* cases, CRPS onset occurred before start of follow-up time in the database. Since we were interested in drug use before CRPS onset, these patients were excluded from the analyses.

**Table 1**
Characteristics of the study population.

| | Cases $N = 186$; $n$ (%) | Controls $N = 697$; $n$ (%) | OR* |
|---|---|---|---|
| Age | | 51 (16) | Matched |
| Gender (female) | | 677 (77) | Matched |
| *General* | | | |
| Smoking | 36 (19.4) | 127 (18.2) | 1.1 (0.7–1.7) |
| *Co-morbidity* | | | |
| Hypertension | 28 (15.1) | 119 (17.1) | 0.8 (0.5–1.3) |
| Hypercholesterolemia | 16 (8.6) | 58 (8.3) | 1.1 (0.6–2.0) |
| Cardiovascular disorders | 9 (4.8) | 25 (3.6) | 1.3 (0.6–3.0) |
| Diabetes mellitus type II | 6 (3.2) | 27 (3.9) | 0.8 (0.3–2.1) |
| Heart failure | 2 (1.1) | 3 (0.4) | 3.2 (0.4–23.4) |
| Asthma | 14 (7.5) | 32 (4.6) | 2.0 (0.9–3.3) |
| Migraine | 13 (7.0) | 22 (3.2) | **2.4 (1.2–5.0)** |
| Osteoporosis | 13 (7.0) | 24 (3.4) | **2.4 (1.2–5.1)** |
| Menstrual cycle-related dis. | 14 (7.5) | 33 (4.7) | 1.8 (0.9–3.6) |
| *Co-medication (current)* | | | |
| NSAIDs | 16 (8.6) | 23 (3.3) | **2.8 (1.4–5.7)** |
| Corticosteroids | 0 | 2 | n.a. |
| Statins | 7 (3.8) | 35 (5.0) | 0.8 (0.3–1.8) |
| SSRIs | 5 (2.7) | 20 (2.9) | 1.0 (0.4–2.7) |
| TCAs | 2 (1.1) | 5 (0.7) | 1.3 (0.2–7.5) |
| Anti-epileptics | 1 (0.5) | 4 (0.6) | n.a. |
| Anti-migraine drugs | 4 (2.2) | 4 (0.6) | 4.0 (1.0–16.0) |

NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
The bold values mean significance at $p < 0.05$.
* Matched on gender, year of birth, calendar time (2-year band), and type of injury.

**Table 2**
Associations between the use of antihypertensive drugs and the risk of CRPS.

| | | Cases $N = 186$ | Controls $N = 697$ | OR* (95% CI) | OR$^{adj\#}$ (95% CI) | OR$^{adj\wedge}$ (95% CI) |
|---|---|---|---|---|---|---|
| Ace inhibitors | Never | 171 | 656 | Ref | Ref | Ref |
| | Current | 11 | 21 | 1.9 (0.9–4.1) | **2.8 (1.1–6.8)** | **2.7 (1.1–6.8)** |
| | Past | 4 | 20 | 0.8 (0.3–2.3) | 1.2 (0.3–4.2) | 1.1 (0.3–4.1) |
| Ace inhibitors monotherapy† | Never | 137 | 532 | Ref | Ref | Ref |
| | Current | 7 | 7 | **3.3 (1.1–9.8)** | **5.0 (1.5–16.9)** | **4.7 (1.4–16.3)** |
| | Past | 1 | 8 | **n.a.** | **n.a.** | **n.a.** |
| | Concomitant | 41 | 150 | 1.0 (0.7–1.6) | 1.3 (0.8–2.1) | 1.2 (0.7–2.1) |
| AT2 antagonists | Never | 183 | 679 | Ref | Ref | Ref |
| | Current | 2 | 13 | 0.6 (0.1–2.6) | 0.7 (0.2–3.4) | 0.7 (0.1–3.4) |
| | Past | 1 | 5 | n.a. | n.a. | n.a. |
| AT2 antagonists monotherapy† | Never | 137 | 532 | Ref | Ref | Ref |
| | Current | 1 | 2 | n.a. | n.a. | n.a. |
| | Past | 0 | 4 | n.a. | n.a. | n.a. |
| | Concomitant | 48 | 159 | 1.1 (0.8–1.6) | 1.3 (0.8–2.2) | 1.3 (0.8–2.2) |
| β-Blockers monotherapy† | Never | 160 | 598 | Ref | Ref | Ref |
| | Current | 8 | 47 | 0.7 (0.3–1.5) | 0.7 (0.3–1.6) | 0.7 (0.3–1.7) |
| | Past | 18 | 52 | 1.3 (0.7–2.3) | 1.4 (0.7–2.5) | 1.4 (0.8–2.7) |
| β-Blockers | Never | 137 | 532 | Ref | Ref | Ref |
| | Current | 2 | 27 | 0.3 (0.1–1.3) | 0.3 (0.1–1.4) | 0.3 (0.1–1.4) |
| | Past | 12 | 33 | 1.4 (0.7–2.8) | 1.6 (0.8–3.4) | 1.7 (0.8–3.5) |
| | Concomitant | 35 | 105 | 1.2 (0.8–1.9) | 1.5 (0.8–2.6) | 1.4 (0.8–2.5) |
| Calcium antagonists | Never | 174 | 658 | Ref | Ref | Ref |
| | Current | 8 | 22 | 1.3 (0.5–3.0) | 1.5 (0.6–3.8) | 1.4 (0.6–3.8) |
| | Past | 4 | 17 | 0.8 (0.3–2.6) | 0.9 (0.3–2.8) | 1.0 (0.3–3.1) |
| Calcium antagonists monotherapy† | Never | 137 | 532 | Ref | Ref | Ref |
| | Current | 3 | 6 | 1.3 (0.3–6.5) | 1.6 (0.3–8.7) | 1.8 (0.3–9.8) |
| | Past | 3 | 5 | 2.0 (0.5–8.9) | 2.1 (0.5–9.6) | 2.4 (0.5–11.2) |
| | Concomitant | 43 | 154 | 1.1 (0.7–1.6) | 1.3 (0.8–2.2) | 1.2 (0.7–2.0) |
| Diuretics | Never | 161 | 620 | Ref | Ref | Ref |
| | Current | 10 | 28 | 1.5 (0.7–3.2) | 2.1 (0.9–5.0) | 2.0 (0.8–4.8) |
| | Past | 15 | 49 | 1.1 (0.6–2.0) | 1.2 (0.6–2.3) | 1.1 (0.6–2.1) |
| Diuretics monotherapy† | Never | 137 | 532 | Ref | Ref | Ref |
| | Current | 2 | 6 | 1.4 (0.3–6.8) | 1.6 (0.3–8.2) | 1.6 (0.3–8.5) |
| | Past | 9 | 27 | 1.0 (0.4–2.4) | 1.1 (0.5–2.6) | 0.9 (0.4–2.2) |
| | Concomitant | 38 | 132 | 1.1 (0.7–1.7) | 1.4 (0.8–2.5) | 1.5 (0.8–2.6) |

The bold values mean significance at $p < 0.05$.
† Concomitant users of other antihypertensives are classified into a separate group.
* Matched on gender, year of birth, calendar time (2-year band), and type of injury.
# Adjusted for hypertension, hypercholesterolemia, DM, and cardiovascular disorders.
^ Additionally adjusted for the current use of NSAIDs and statins.

## 3. Results

Two-hundred and fifty-nine cases were identified and reconfirmed by the GP in the source population of 204,281 persons: 191 (74%) with a specialist diagnosis and 68 (26%) with only a GP diagnosis. The procedure for final case inclusion in the main and sensitivity analyses is presented in Fig. 1. The final case set comprised cases who were validated upon a visit ($n$ = 102) supplemented with the specialist diagnosed cases amongst the non-visited patients ($n$ = 84). Thus, the total study population comprised 883 patients, including 186 cases and 697 age, gender and injury-matched controls (up to four per case).

Characteristics of the study population are displayed in Table 1. The mean age on the index date in the study population was 51 years, 77% was female, and CRPS patients had more often migraine and osteoporosis in their medical history, and they were more frequently current users of NSAIDs.

For 166 patients (19% of the total study population), complete pharmacy dispensing lists were available for comparison with GP prescription records. The sensitivity for current use of an antihypertensive drug in the GP records was 82%, while the specificity was 99%. This was non-differential between cases and controls.

Associations between antihypertensive drug use and the risk for CRPS are displayed in Table 2. No significant associations were observed between CRPS and current use of β-blockers, AT2 antagonists, calcium channel blockers or diuretics. Current use of ACE inhibitors was associated with an increased risk of CRPS (OR: 1.9, 95% CI: 0.9–4.1). This association became stronger upon adjustments for potential confounders (OR: 2.7, 95% CI: 1.1–6.8). The association further strengthened if monotherapy with ACE inhibitors was analyzed separately from combinations of ACE inhibitors and other antihypertensives (OR: 3.3, 95% CI: 1.1–9.8). A stratified analysis by gender displayed an even stronger effect of ACE inhibitor use in women (OR: 4.6, 95% CI: 1.6–13.2 in 143 cases and 534 controls), while in men the association disappeared (OR: 0.5, 95% CI: 0.1–4.9 in 43 cases and 163 controls). However, the multiplicative interaction term in the regression model was non-significant. Hypertension was the primary indication for ACE inhibitor prescriptions in 9 of the cases (81.1%) and 17 of the controls (81.0%).

Long-term use of ACE inhibitors, as well as a high dose, was associated with a stronger association with CRPS than short-term use and a low dose (OR: 3.0, 95% CI: 1.1–8.1 and OR: 4.3, 95% CI: 1.4–13.7, respectively) (Table 3). The association between CRPS and current use of ACE inhibitors remained in a sensitivity analysis that was restricted to the cases who were confirmed CRPS upon expert visitation.

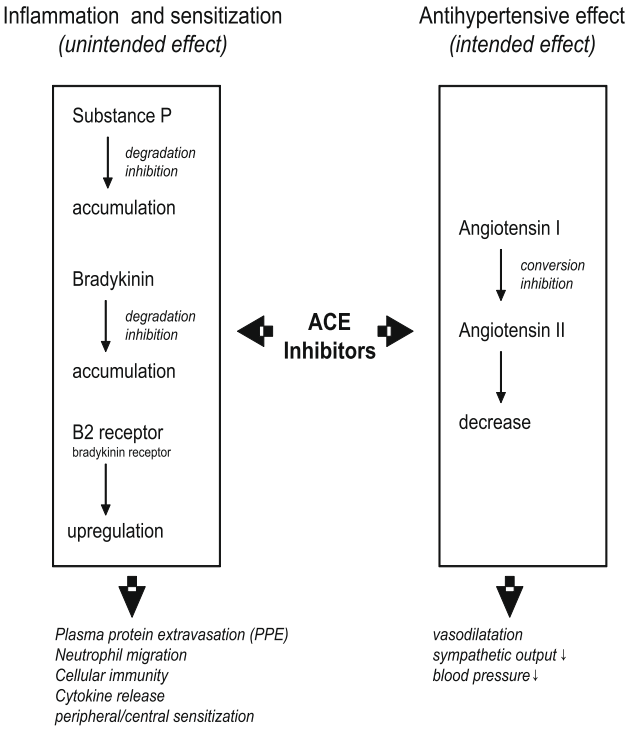


**Fig. 2.** The intended effect of ACE inhibitors is to block the conversion of angiotensin I into angiotensin II in order to decrease blood pressure. However, as unintended effect, ACE inhibitors prevent the degradation of substance P and bradykinin, causing accumulation of these peptides. In addition to this, ACE inhibitors upregulate the bradykinin (B2) receptor, thereby further potentiating bradykinin activity. Both substance P and bradykinin are important mediators in neuro-inflammatory responses and sensitization, and probably in the pathogenesis of CRPS.

## 4. Discussion

In this nested population-based case-control study, we observed a dose- and duration-dependent association between use of ACE inhibitors and the risk of CRPS. Other classes of antihypertensive drugs were not associated with either a significant reduced or increased risk of CRPS.

The observed association between ACE inhibitors and CRPS was a-priori hypothesized due to its biological plausibility (Fig. 2). ACE is one of the most important kininases involved in the inactivation of SP [25] and bradykinin [11] and ACE inhibition therefore would increase the levels of these pro-inflammatory peptides. Both SP and bradykinin are well-known mediators in inflammation and

**Table 3**
Associations between the duration and the dosage of ACE inhibitor use and CRPS in the main analysis and in a sensitivity analysis that excluded unvisited cases.

| Ace inhibitors | Main analysis Including cases verified upon a visit + (unvisited) specialist diagnosed cases | | | Sensitivity analysis Including only cases verified upon a visit | | |
|---|---|---|---|---|---|---|
| | Cases $N$ = 186 | Controls $N$ = 697 | OR*#^ (95% CI) | Cases $N$ = 102 | Controls $N$ = 381 | OR*#^ (95% CI) |
| Never | 171 | 656 | Ref | 95 | 359 | Ref |
| ≤180 days | 2 | 3 | 1.9 (0.3–23.9) | 0 | 0 | n.a. |
| >180 days | 9 | 18 | **3.0 (1.1–8.1)** | 6 | 11 | **4.6 (1.1–19.3)** |
| Past | 4 | 20 | 1.1 (0.3–4.0) | 1 | 11 | 0.5 (0.0–5.4) |
| Never | 171 | 656 | Ref | 95 | 359 | Ref |
| ≤1DDD | 4 | 12 | 1.6 (0.4–5.8) | 2 | 7 | 1.7 (0.2–13.4) |
| >1DDD | 7 | 9 | **4.3 (1.4–13.7)** | 4 | 4 | **9.7 (1.7–54.2)** |
| Past | 4 | 20 | 1.1 (0.3–4.0) | 1 | 11 | 0.5 (0.0–5.6) |

*#^ Matched on gender, year of birth, calendar year (2-year band), and type of injury; adjusted for hypertension, hypercholesterolemia, cardiovascular diseases, diabetes mellitus, and current use of NSAIDs and statins.

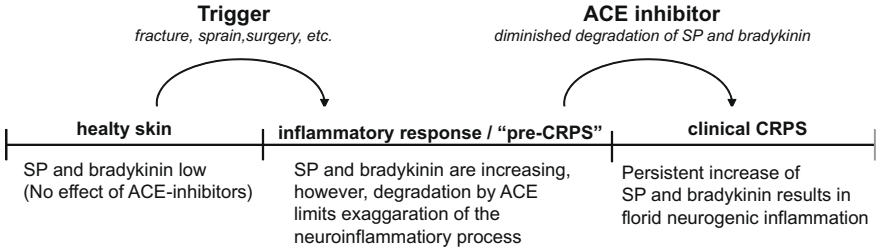


**Fig. 3.** ACE inhibitors do not facilitate neurogenic inflammation in healthy skin [19]. However, hypothetically ACE inhibitors may enhance an existing neuro-inflammatory response that has been initiated by a previous trigger, by preventing the degradation of SP and bradykinin. In some cases, this may cause a physiological inflammatory reaction ('pre-CRPS') to develop towards a florid neurogenic inflammation, resulting in the clinical picture of CRPS.

sensitization, two important mechanisms underlying CRPS, and both peptides have actually been demonstrated involved in CRPS pathology [5,12,22].

The role of ACE in CRPS and neurogenic inflammation has been investigated before from a genetic and experimental perspective yielding quite contradictory results. A Japanese study revealed an increased prevalence of the ACE polymorphism DD genotype in 16 CRPS patients compared to the general population (43% versus 20%) [18]. The DD genotype however is known to be associated with higher ACE levels, and thereby with supposedly lower SP and bradykinin levels. Therefore, the DD genotype would be expected to correlate with a low risk of CRPS, instead of a high risk as was observed in the Japanese study. However, only a small study population ($n$ = 16) was included, and the findings were not confirmed in a larger German study (48 sporadic and 12 familial patients) [16].

An experimental study using healthy skin showed no facilitation of electrical C-fiber stimulation induced neurogenic inflammation by the ACE inhibitor captopril [19], although this was expected because ACE inhibition would lead to SP and bradykinin accumulation. However, healthy skin is different from the inflamed tissue that is present in the early phase or pre-stadium of CRPS. ACE inhibitors do not facilitate neurogenic inflammation in healthy skin probably because there the levels of its substrates, SP and bradykinin, are low [19]. On the contrary, inflamed skin holds increased levels of SP, released by primary afferents under the influence of cytokines [36], and bradykinin. Normally, SP and bradykinin should be degraded by ACE, but ACE inhibitors may block their catabolism, resulting in the further accumulation of these peptides. In this view, ACE inhibitors may not affect the initiation of the neuro-inflammatory response that underlies CRPS, but they can facilitate its progression once it has been triggered by other causes. Eventually, this may cause an initially functional inflammatory response to develop towards a point that it becomes pathological, as in CRPS (Fig. 3).

It has also been shown that under certain circumstances, ACE inhibitors facilitate the degradation of CGRP [20], another neuropeptide that has been found increased in CRPS patients [5]. As ACE inhibitors may diminish the CGRP levels, they could also have been found to protect against CRPS, the opposite of what we observed. However, the interaction between ACE inhibitors and CGRP is indirect, and occurs only when the main metabolizer of CGRP, an enzyme called neutral endopeptidase (NEP), is blocked [20]. SP and bradykinin are direct substrates for ACE, and our observation that ACE inhibitors increase, instead of decrease, the risk of CRPS suggests that SP or bradykinin or both are important mediators in CRPS. CGRP may be important in CRPS as well, but its actual relevance cannot be derived from the present study, since the interaction between ACE and CGRP is more complex.

Strengths of our study include the unique population-based setting and design, wherein controls had an injury similar to the cases. The availability of prescription records with accurate information on prescription dates allowed us to study the role of drugs in the onset of CRPS. However, the study also has some limitations. Misclassification of the CRPS diagnosis, a general problem in CRPS research, may also have occurred in our study, since the final verification of the diagnosis had to be performed retrospectively. However, assuming that misclassification of the diagnosis was unrelated to the use of antihypertensive drugs this would only have resulted in an underestimation of the associations of interest. This was confirmed by a sensitivity analysis that was limited to the cases that were verified during a visit (more valid diagnosis) and showed an even stronger association between ACE inhibitor use and CRPS onset. Also, some non-differential misclassification of the exposure (current use of antihypertensives) was present, for example where antihypertensive drugs were prescribed by physicians other than the GP. Potential selection bias was reduced by including the specialist diagnosed cases who were not visited (including refusers and untraceable patients). In addition, antihypertensive drug use did not differ between participants and non-participants (derived from the prescription records in the database). Confounding was addressed as far as possible by the inclusion of various comorbidities and drugs in the model, but residual confounding cannot be ruled out.

In conclusion, we found a positive dose and duration-dependent association between the use of ACE inhibitors and the risk of CRPS. This points to the important role of SP or bradykinin or both in the pathogenesis of CRPS, as these inflammatory peptides are metabolized by ACE and increase during ACE inhibition. We hypothesize that ACE is one possible modulator of the neuro-inflammatory mechanisms that underlie CRPS.

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## References


[1] Alexander GM, van Rijn MA, van Hilten JJ, Perreault MJ, Schwartzman RJ. Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. Pain 2005;116:213–9.

[2] Anonymous. ATC and DDD values. Geneva: WHO; 1996.

[3] Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes – analysis of 145 cases. Acta Neurol Scand 2000;101:262–9.

[4] Birklein F, Schmelz M, Schifter S, Weber M. The important role of neuropeptides in complex regional pain syndrome. Neurology 2001;57:2179–84.

[5] Blair SJ, Chinthagada M, Hoppenstehdt D, Kijowski R, Fareed J. Role of neuropeptides in pathogenesis of reflex sympathetic dystrophy. Acta Orthop Belg 1998;64:448–51.

[6] Brain SD, Tippins JR, Morris HR, MacIntyre I, Williams TJ. Potent vasodilator activity of calcitonin gene-related peptide in human skin. J Invest Dermatol 1986;87:533–6.

[7] Brain SD, Williams TJ, Tippins JR, Morris HR, MacIntyre I. Calcitonin gene-related peptide is a potent vasodilator. Nature 1985;313:54–6.

[8] Couture R, Harrisson M, Vianna RM, Cloutier F. Kinin receptors in pain and inflammation. Eur J Pharmacol 2001;429:161–76.

[9] de Mos M, de Bruijn AG, Huygen FJ, Dieleman JP, Stricker BH, Sturkenboom MC. The incidence of complex regional pain syndrome: a population-based study. Pain 2007;129:12–20.

[10] de Mos M, Huygen FJPM, Dieleman JP, Koopman JSHA, Stricker BHC, Sturkenboom MCJM. Medical history and the onset of complex regional pain syndrome (CRPS). Pain 2008;139:458–66.

[11] Dendorfer A, Wolfrum S, Wellhoner P, Korsman K, Dominiak P. Intravascular and interstitial degradation of bradykinin in isolated perfused rat heart. Br J Pharmacol 1997;122:1179–87.

[12] Gradl G, Finke B, Schattner S, Gierer P, Mittlmeier T, Vollmar B. Continuous intra-arterial application of substance P induces signs and symptoms of experimental complex regional pain syndrome (CRPS) such as edema, inflammation and mechanical pain but no thermal pain. Neuroscience 2007;148:757–65.

[13] Harden RN, Bruehl S. Diagnostic criteria: the statistical derivation of the four criterion factors. In: Wilson PR, Stanton-Hicks M, Harden RN, editors. CRPS: current diagnosis and therapy. Seattle: IASP Press; 2005. p. 45–58.

[14] Harden RN, Rudin NJ, Bruehl S, Kee W, Parikh DK, Kooch J, et al. Increased systemic catecholamines in complex regional pain syndrome and relationship to psychological factors: a pilot study. Anesth Analg 2004;99:1478–85 [table of contents].

[15] Heijnen CJ, Rouppe van der Voort C, Wulffraat N, van der Net J, Kuis W, Kavelaars A. Functional alpha 1-adrenergic receptors on leukocytes of patients with polyarticular juvenile rheumatoid arthritis. J Neuroimmunol 1996;71:223–6.

[16] Huhne K, Leis S, Schmelz M, Rautenstrauss B, Birklein F. A polymorphic locus in the intron 16 of the human angiotensin-converting enzyme (ACE) gene is not correlated with complex regional pain syndrome I (CRPS I). Eur J Pain 2004;8:221–5.

[17] Huygen FJ, De Bruijn AG, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators Inflamm 2002;11:47–51.

[18] Kimura T, Komatsu T, Hosada R, Nishiwaki K, Shimada Y. Angiotensin-converting enzyme gene polymorphism in patients with neuropathic pain. In: Proceedings of the ninth World Congress in pain. Seattle, WA: IASP Press; 2000. p. 471–6.

[19] Kramer HH, Schmidt K, Leis S, Schmelz M, Sommer C, Birklein F. Inhibition of neutral endopeptidase (NEP) facilitates neurogenic inflammation. Exp Neurol 2005;195:179–84.

[20] Kramer HH, Schmidt K, Leis S, Schmelz M, Sommer C, Birklein F. Angiotensin converting enzyme has an inhibitory role in CGRP metabolism in human skin. Peptides 2006;27:917–20.

[21] Leis S, Weber M, Isselmann A, Schmelz M, Birklein F. Substance-P-induced protein extravasation is bilaterally increased in complex regional pain syndrome. Exp Neurol 2003;183:197–204.

[22] Leis S, Weber M, Schmelz M, Birklein F. Facilitated neurogenic inflammation in unaffected limbs of patients with complex regional pain syndrome. Neurosci Lett 2004;359:163–6.

[23] O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. J Cell Physiol 2004;201:167–80.

[24] Schrijvers AJP. Health and Healthcare in the Netherlands. A critical self-assessment of Dutch experts in medical and health sciences. Utrecht: De Tijdstroom; 1997.

[25] Skidgel RA, Erdos EG. Angiotensin converting enzyme (ACE) and neprilysin hydrolyze neuropeptides: a brief history, the beginning and follow-ups to early studies. Peptides 2004;25:521–5.

[26] Snijdelaar DG, Dirksen R, Slappendel R, Crul BJ. Substance P. Eur J Pain 2000;4:121–35.

[27] Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–33.

[28] Uceyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. Pain 2007;132:195–205.

[29] van der Lei J, Duisterhout JS, Westerhof HP, van der Does E, Cromme PV, Boon WM, et al. The introduction of computer-based patient records in the Netherlands. Ann Intern Med 1993;119:1036–41.

[30] Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–6.

[31] Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339–44.

[32] Wang H, Ehnert C, Brenner GJ, Woolf CJ. Bradykinin and peripheral sensitization. Biol Chem 2006;387:11–4.

[33] Wasner G, Heckmann K, Maier C, Baron R. Vascular abnormalities in acute reflex sympathetic dystrophy (CRPS I): complete inhibition of sympathetic nerve activity with recovery. Arch Neurol 1999;56:613–20.

[34] Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. Physiol Rev 2002;82:981–1011.

[35] Weber M, Birklein F, Neundorfer B, Schmelz M. Facilitated neurogenic inflammation in complex regional pain syndrome. Pain 2001;91:251–7.

[36] Woolf CJ, Safieh-Garabedian B, Ma QP, Crilly P, Winter J. Nerve growth factor contributes to the generation of inflammatory sensory hypersensitivity. Neuroscience 1994;62:327–31.