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Angioedema Adverse Drug Reactions Associated with ACE Inhibitor: A Review

Rahmi Marliyeni[1], Widya Kardela[2], Rezlie Bellatasie [3]
[1 2 3]*Department of Pharmacology and Clinical Pharmacy, School of Pharmaceutical Sciences STIFARM PADANG*
Raya Siteba Street, Kurao Pagang, Padang, West Sumatera, Indonesia, 25147

Abstract
Background: *The aim of this literature study is to summarize the angioedema (AE) adverse effect induced by Angiotensin Converting Enzyme (ACE) inhibitors, including sociodemography, risk factors, symptoms and clinical manifestations in patients as well as the most widely prescribed ACE inhibitor drugs that cause angioedema.*
Methods: *Literature searches were carried out on computerized databases such as Science Direct, Google Scholar and PubMed on article published in the last 10 years.*
Conclusion: *Angioedema arising as adverse drug reactions from the use of ACE inhibitor is influenced by the time, duration and dosage consumed. From the patient's characteristic, it was found that ACE inhibitor-related angioedema was more commonly found in women, African-American, age > 25 years old. The most common comorbidities were asthma, hypertension, diabetes mellitus. Symptoms appear in patients such as facial edema, periobital edema, oral edema, angioneurotic edema, facial urticaria, and tongue edema, and it can also increase exponentially followed by mild breathing difficulties. The ACE inhibitor drugs which are widely registered and prescribed that related to angioedema are Lisinopril, Enalapril and Ramipril.*
Keyword: *Adverse Drug Reactions, ACE inhibitors, Angioedema*

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I. Introduction

Adverse drug reactions (ADR) are the most important issue for public health [1]. Adverse drug reactions (ADR) are commonly known as "side effects", or "drug abuse", often cause morbidity in hospitals and public health [2]. The World Health Organization (WHO) defines that ADR is an undesirable or dangerous occurrence associated with medicine at doses that use for prophylaxis, diagnosis, or disease therapy or for modification of physiological functions [3]. The factors that influence ADR are numerous and varied, and there are also those associated with the interaction between drugs. Factors generally considered risky are age, kidney disorders, liver disorders, weakness, polypharmacy, gender, previous history of ADRs, and genetics [2].

ACE inhibitors are a class of drugs used to treat conditions such as hypertension, diabetic nephropathy, and congestive heart failure [4]. ACE inhibitors are a first-line therapy in patients with left ventricular systolic dysfunction [5]. More than 40 million people worldwide are currently receiving an ACE inhibitor [4]. In general, ACE inhibitors have rare side effects during long-term therapy such as hypotension, cough, hyperkalemia, acute renal failure, fetopatic potential, skin rashes, angioedema and others (dysgeusia, neutropenia, glycosuria and hepatotoxisity). Several ACE inhibitors drug interactions, including with the antacid group that can reduce the bioavailability of ACE inhibitors; capsaicin can worsen the cough induced by ACE inhibitors; NSAIDs including aspirin can reduce the antihypertensive response to ACE inhibitors; and potassium-sparing diuretics and potassium supplements may worsen ACE inhibitor-induced hyperkalemia [5]. Cough is the most associated ADR with ACE inhibitors. Based on reports that approximately 5-35% of patients will cough in a matter of months or years after the drug was prescribed [6].

Angioedema is an acute swelling that can occur in localized areas of the body in the head and neck area which can cause airway obstruction [7]. In Caucasians, the incidence rate of angioedema is around 0.1–1%, which could be higher than that of African-Americans [8]. Angioedema caused by ACE inhibitors has a relatively high prevalence [4]. Around 0.1-0.5% patients who are given ACE inhibitor class drugs experience rapid swelling of the nose, throat, mouth, glottis, larynx, lips, and / or tongue, by 0.1-0.5% [5].

The use of ACE inhibitor for more than one episode continuously in long-term therapy could cause an increase in the relapse rate of angiedema with serious morbidity. The use of the drug should be stopped immediately in patient with angioedema and contraindicated in patients with a history of idiopathic angioedema [8]. The purpose of the review is to summarize the adverse effects of angioedema (AE) caused by Angiotensin

Converting Enzyme (ACE) inhibitors including sociodemography, risk factors, symptoms and clinical manifestations in patients as well as identify ACE inhibitor class drugs that cause angioedema.

II. Methods

This review is compiled based on searching articles and literature on various search databases from trusted online journal sites such as the Pub Med, ScienceDirect and Google scholar with keyword "((adverse drug reaction AND (y_10[Filter])) AND (ace inhibitor)) AND (angioedema)" published in the last 10 years. Inclusion criteria for selected articles are orginal articles containing search keywords used, articles that assess causality or severity as well as predictability and preventive measure of ACE inhibitors induce angioedema. As for the exclusion criteria are publication in the form of as systematic review articles, meta analysis and case report.

III. Result

Table 1. Search result in Pubmed

No	Search of terms	Results
1	Adverse drug reaction	52,975
2	Ace inhibitor	13,387
3	Adverse drug reaction AND ACE inhibitor	255
4	Adverse drug reaction AND ACE inhibitor AND angioedema	47

Figure 1. Schematic Result using related keywords

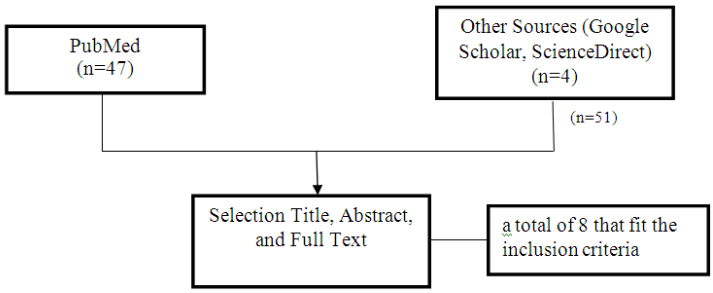


Table 2. Study of Adverse Drug Reaction of Angioedema due to ACE inhibitor.

No	Ref.	Year	Objective	Method	Result
1	[7]	2012	Evaluates the relationship between the increase use of ACE inhibitors and their effect on upper airway AE event rates	Retrospective Study (period 2000-2004 and 2005-2009)	The total number of patients for 10 years with AE associated with ACE inhibitors was 44 patients. a. In 2000-2004 there were 10 patients b. In 2005-2009 there were 34 patients Common symptoms include: • Rash • Tightness • Change voice • Pain • Globulus The most commonly prescribed ACE inhibitors are Enalapril and Ramipril. AE Management: • Steroid • Antihiistamin • Adrenaline inhalation • Steroid + antihistamin

No	Ref.	Year	Objective	Method	Result
					• Steroid + antihistamin + adrenalin • Admission to ICU
2	[9]	2013	Understand the characteristics and clinical manifestations of patients that came to the emergency department (ED) due to AE-ACE inhibitor related	Retrospective	Number of patients 100 people. Demography of patient: • Age : mean 59 years old (25-90 years old) • Female (53%) > male • African American (75%), • Seasonal variation : Springs (April-June 32%). Patient symptoms: • Moderate swelling of the tongue (89%), • Most common mild breathing difficulties (12%) • The need of hospitalization was reported in 66% of patients, ventilatory support 2% (2 patient) The most commonly prescribed ACE inhibitors are: • Lisinopril (86%) • Enalapril (5%) • Benazepril / amlodipine (2%) • Benazepril (2%), lisinopril / HCTZ (2%) • ramipril (2%), moexipril / HCTZ. (1%). Duration of ACEi usage : • Unknown (63%) • <3 months (17%) • 4-6 months (2%) • 7-12 months (3%) • > 12 months (15%) Management of AE-ACEi related: • Corticosteroids (87%), • H-1 antagonists (89%) • H-2 antagonists (74%) • B-2 agonists (4%) • Epinephrine (1%)
3	[10]	2015	Describe the characteristics of angioedema associated with RAS inhibitors in Thai patients.	Retrospective Study (1984-2011)	Total data that meets the inclusion criteria as many as 895 cases. The level of causality probable 65.8%, causality report level 2 (63.6%). Demography of patient: • Age range 1-98 years old (mean 59.9 ± 12.8 years). • Women (66.5%) Edema Category: • Angioedema (55.7%) • Facial edema (39%), • Periorbital edema (11.2%), • Oral edema (7.5%), • Angioneurotic edema (0.4%), • Facial urticaria (0.5%) • Tongue edema (0.2%) The characteristics of angioedema are frequently affected areas: - Face (41.3%)

No	Ref.	Year	Objective	Method	Result
					- Periorbital area (including the eyelids (13.6%)) - Mouth (including tongue (9.7%)) - Others (2.7%) - Not specific (48.7%) Comorbidity : • Hypertension (55.6%), • Diabetes mellitus (7.6%) • Dislipidemia (7.5%) History of allergies was reported in 15.3 % of cases. Concomitant therapy: • Hydrochlorothiazide(22,8%) • Aspirin (19,9%) • Amlodipine (15,6%) • Simvastatin (15,2%) • Metformin (12,1%) The RAS blockers that caused angioedema the most were ACE inhibitors in 87.7% of cases and the most commonly prescribed drug was enelapril (83.3%) at a dose of 10.1 + 9.8 mg / day, followed by perindopril (1.3%).), Quinapril (1.2%), Ramipril (0.9%), Captopril (0.8%), Lisinopril (0.1%), and Delapril (0.1%).
4	[11]	2016	Describes and determinant the incidence of ACE inhibitor intolerance related to AE in patients starting therapy with ACE inhibitors in primary health care.	Cohort Study (2007-2014)	The number of ace inhibitor patients was 276977, >45 years old, Angioedema reported 416 cases. Determinants of AE related to ACE inhibitor, ranging from co-morbidity that appears until the onset of angioedema and Co-medication occurs within 3 months of the use of ACE inhibitors before the date of AE is reported. ACE inhibitor related AE characteristic: a. Age > 65 years old (OR 1.36, 95% CI 1.07, 1.73) b. Co-Morbidity - Allergies (OR 1.53, 95% CI 1.19, 1.96) c. Co-Medication: ●Use of calcium channel blockers (OR 1.57, 95% CI 1.23; 2.01), ●Use of antihistamines (OR 21.25, 95% CI 16.44, 27.46) ●Use of systemic corticosteroids (OR 4.52, 95% CI 3.26, 6.27). The most widely used cases of angioedema related to ACE inhibitor drugs are: • Ramipril (57.7%) • Lisinopril (28.0) • Perindropil (13.5%) • Enalapril (2.2%).

No	Ref.	Year	Objective	Method	Result
5	[12]	2017	Identifying the incidence and risk factors of angioedema related to ACE inhibitor using large integrated electronic health record(EHR).	Studi Kohort Retrospektif (1 January 2000 - 30 September 2008)	The total number of patients prescribed ACE inhibitors was 134,945 patients, the incidence of angioedema was reported in 888 patients (0.7%). Patient characteristics: **a.** Mean age 61.5 years **b.** Race (black, hispanic) **c.** Male (48.9%) **d.** Comorbidity - Coronary artery disease (3.2%) - Hypertension (27.0%) - Congestive heart failure (0.6%) - Proteinuria / nephrotic syndrome (0.3%) **e.** Allergy : NSAIDs allergy (7.1%) **f.** Co-medication : NSAIDs (33.7%) Time of occurrence of angioedema (after ACE inhibitor prescription) • 7 days (4.3%, n= 38) • 14 days (6.8%, =60) • 21 days (8.2%, n=73) • 30 days (10.2%, n =91) Manifestations in patients: • Bronchospasm or wheezing • Cough • Hive and rash Commonly prescribed ACE inhibitors associated with AE including: • Lisinopril/ Prinivil/ Zestril (87,2%), • Enalapril/ Vasotec (4,3%), • Quinapril/ Accupril (2,6%), • Kaptopril/ Capoten (1,4%), • Benazepril/ Lotensin (3,0%), • Ramipril/ Altace (1,1%) • Trandolapril/ Mavik (0,6%)
6	[13]	2017	To assess AE related to ACE inhibitor angioedema in 105 patients with consideration of demographics, risk factors, family history of angioedema, hospitalization, airway outcome, and use of ACE inhibitors for the condition.	Study Kohort Retrospektif (1995-2014)	Total AE related to ACE inhibitor : 105 patients Sociodemography • Gender (female 67 and male 38 {ratio F: M 1.8}), • The highest number of patients is in the range of 60-69 years, an average age of 63 years (sample age range 26-86 years). • Race 104 patients (caucasian 99%) Risk factors • Family history of positive angioedema (6.7%) • History of allergic disease (22.0%) • Smoking (24.8%) • Patients are most commonly referred > 1episode due to relapse (9.5%) after the

No	Ref.	Year	Objective	Method	Result
					termination of ACEi. Manifestations of AE: a. Localization of angioedema a. head and neck (95.2%) b. Peripherals (13.3%) c. Abdominal (2.9%) b. Concomitant rash (18%) c. Airway management (intubation=3.8% and tracheostomy=0.9%) Management of acute angioedema: • Antihistamines (62.5%) • Corticosteroids (63.3%) • Adrenaline (15.0%) • Icatibant (66.7%)
7	[14]	2019	Angiotensin receptor blocker II (AT2) can be used safely in patients with AEs associated with ACE inhibitors and the incidence of AEs treated with other antihypertensive drugs (beta-adrenergic blockers, calcium channel blockers, thiazides and analogues) or without anti-hypertension.	Nationwide Retrospective Registry-based Cohort Study (periode 1994-2016)	The total number of ACE inhibitor users : > 1 million population Total AE reported : 5,507 patients (0.5%), mean age 64 years old. The angioedema comorbidities associated with ACE inhibitors are: 1. Cerebrovascular disease (61.3%), 2. Hypertension (37.2%), 3. Ischemic heart disease (21.3%), 4. Musculoskeletal disease (19.7%), etc. Lifestyle disease, including: 1. Type 2 diabetes (13.8%) 2. Smoking (10.3%) Patients who are intolerant to ACE angioedema-related inhibitors typically require treatment with other medications such as Angiotensin Receptor Inhibitor II (AT2s) hazard ratio (HR) = 1.45 (95% CI, 1.19-1.78).
8	[4]	2019	Calculation of angioedema associated with ACE inhibitors reported case, risk factors and risk differences for each ACE inhibitor	Observational Retrospective Cohort (1994-2015)	The number of patients 176 (71 men, 105 women) divided into 2 groups: 1. In 2003-2015 there were 105 patients (38 male, 67 female), 2. In 2014-2016 there were 71 patients (diagnosed after 2009). The total number of cases reported was 1.1%, other cases 98.9% were not reported. The most frequently prescribed drugs were Enalapril (40.3%) and Ramipril (42.6%). The most commonly reported ACE inhibitor related AE group were Enalapril (53.9%) and Ramipril (17.0%)

IV. Discussion

Identification of adverse drug reactions is very important in reducing unwanted risk from medication. This review aim to identify factors associated with the occurrence of adverse effect angioedema in patients using ACE inhibitors. The main database for collecting articel use in this review is PubMed, and additional databases are ScienceDirect, and Google Scholar. On the initial search, we found 51 articles related to the keyword angioedema cause by adverse drug reaction of ACE inhibitor. After screening the title, abstract and full

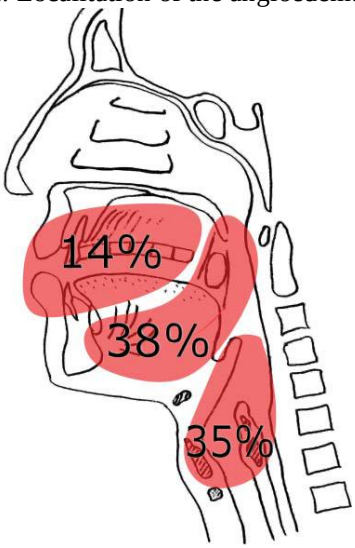
text, there were 8 articles qualified and used in the review. The study use varied research methods, such as retrospective studies [7], [9], [10], [14], Retrospective Cohort Study [12], [13], Cohort Study [11], Observational Retrospective Cohort [4].

In 1960, Ferreira and coalleagues suggested that snake venom could improve the vasodilator response of bradykinin. Bradykinin is a peptide that inhibits kininase II, an enzyme that inactivates bradykinin. Erdos and colleagues also suggested that ACE and kininase II are the same enzyme that catalyze the synthesis of angiotensin II and the destruction of bradykinin. In his findings there was nonapeptide teprotide (snake venom that can inhibit peptides from kininase II and ACE) which then synthesized and tested in humans, because it can lower blood pressure and have an effect on heart failure patients [5].

ACE is part of the renin-angiotensin system which converts angiotensin I to angiotensin II, and additionally responsible for bradykinin degaradation, resulting in a high molecular weight kininogen by kallikrein. Bradykinin has two receptors that can affect vascular permeability and stimulate the release of substance P from ACE (kininase II) which causes vasodilation and plasma extravasation [15]. The use of ACE inhibitor drugs related to angioedema must be stopped immediately, suitable pharmacological treatment other than the antihistamines, steroids and epinephrine [16]. ACE inhibitors can alter the balance between vasoconstriction, salt-retention, hypertrophic of angiotensin II (Ang II) and vasodilatory, natriuretic property of bradykinin and also can change from a number of other metabolic vasoactive substances [17].

ACE inhibitors are commonly used for mild, moderate, or severe hypertension, including those used for hypertension with congestive heart failure, diabetes, dyslipidemia, left ventricular hypertrophy, coronary heart disease and obesity [18]. Cough was the most frequently reported adverse reaction for ACE inhibitor drugs (5.3%), followed by angioedema (0.7%), hyperkalemia (0.4%), and bronchospasm / wheezing (0.3%), Hives or other rash (0.3%), renal toxicity (0.2%), gastrointestinal upset (0.1%), dizziness (0.1%), and headaches (0.1%) [12]. Around 19-30% of ACE inhibitor drug use was discontinued due to its has common side effects such as persistent dry cough. In addition there are also other adverse effects of ACE inhibitors such as angioedema (AE) that can be potentially life-threatening [11]. The manifestation of localized AE in different body parts seen in figure 1.

Figure 1. Localitation of the angioedema [7]



Description

Type 1 (14%): angioedema limited to the face and oral cavity, but not the floor of the mouth.

Type 2 (38%): angioedema involving the floor of mouth and/or oropharynx including the base of the tongue.

Type 3 (35%): angioedema with oro-pharyngeal involvement and extension to supraglottic and glottic structures 13% had normal findings at the time of

The main target of ACE inhibitor is the renin-angiotensin-aldosterone system which causes decreased of angiotensin II production, decreased of aldosterone secretion, decreased of vasopressin activity, and beneficial as antihypertensive activity. The mechanism of ACE inhibitor-induced angioedema is related to the kallikrein-kinin system, which works antagonistically to the renin-angiotensin-aldosterone system. Kallikrein is a protease that replaces kininogens with high molecular weight into kinins especially bradykinin, because it is considered a very strong vasodilator that mediates its release such as nitric oxide, substance P, prostacyclin, and endothelial hyperpolarization factors that bind to the bradykinin B1 and B2 receptors [19]. Another mechanism which cause angioedema occurs due to the release of chemical structures of the ACE inhibitor drug group for example, the sulphydryl compounds (captopril, zofenapril), the carboxyalkyldipeptides (enalapril, lisinopril) and the phosphoric acid compounds (fosinopril) [20].

The reporting rate of angioedema related to ACE inhibitor cases is low, only 1.1% and other unreported cases are 98.9% [4]. Some other studies report that about 50-60% patients experiencing angioedema in the first week of using ACE inhibitor drugs, there are also some rare cases where angioedema occurs after 5

years of starting treatment [9]. Holm et al reported that over a 10-year period (2000-2009), there are significant increase in ACE inhibitor-related angioedema inhibitors (67%) [7]. Based on the duration of ACE inhibitor use, angioedema reported within < 3 months (17%), 4-6 months (2%), 7-12 months (3%), > 12 months (15%), and unknown (63%) [9].

The trigger of angioedema in the use of ACE inhibitors is influenced by several risk factors. From sociodemography, reported patients mostly woman older than 25 years old [9], [13], and African Americans (75%), because black African / Caribbean American people have a prevalence 3 to 4 times higher than white people [19]. In terms of Co-morbidity, some of the most common conditions such as coroner's artery disease, congestive heart failure, proteinuria/ nephrostatic syndrome [12], cerebrovascular disease, hypertension, ischemic heart disease, musculoskeletal disease [14], and some are dependent on lifestyles such as type 2 diabetes, dislipidemia, and disease related to smoking [10], [14]. Usual co-medication are statins, calcium channel inhibitors, use of antihistamines as well as simultaneous use of NSAID and the use of systemic corticosteroids (OR 4.52, 95% CI 3.26, 6.27) [11]. Other risk factors of ACE inhibitor-related angioedema caused history of allergy (OR1.53, 95% CI 1.19, 1.96), [11].Angioedema patients associated with the use of ACE inhibitor drugs tend to have a history of NSAIDs and other drug allergies involving aspirin / NSAIDs or mast cell degranulators that are the causative factors, either immunologically (IgE-mediated) or non-immunologic due to increased production of leukotrien from inhibition of cyclolooksigenase [12].

The characteristics of angioedema are often found in the face (41.3%), periorbital area (including the eyelids (13.6%)), mouth (including the tongue (9.7%)), others (2.7%), and some are not specific (48.7%). Angioedema (55.7%) was the most common term used for reporting followed by facial edema (39%), periorbital edema (11.2%), oral edema (7.5%), angioneurotic edema (0.4%), facial urticaria (0.5%) and tongue edema (0.2%). The number of reports increased exponentially with time [10]. Other manifestations of angioedema are localized (head and neck (95%); peripheral (13.3%); abdominal (2.9%)) and concomitant rash (18%) [13]. Common symptoms in Emergency Department (ED) patients are moderate tongue swelling (89%), followed by mild breathing difficulties (12%) [9].

Win et al reported that the Renin Angiotensin System (RAS) has 4 classes of drugs, of which the RAS blockers that cause angioedema the most are ACE inhibitors drug class (87.7%) with enalapril (83.3%) as the predominant agent (mean dose of 10.1 + 9.8 mg/day), perindopril (1.3%), quinapril (1.2%), ramipril (0.9%), captopril (0.8%), lisinopril (0.1%), and delapril (0.1%). The most common drugs were hydrochlorothiazide (22.8%), aspirin (19.9%), amlodipine (15.6%), simvastatin (15.2%) and metformin (12.1%) [10]. In general, RAS blocker drugs are well tolerated except for angioedema, because they are rare but can be potentially bad. RAS blockers associated with angioedema (RASBA) are sudden and short-lived, swelling within the skin, subcutaneous and / or mucosal level [10], [21]

Prescribed ACE inhibitors were associated angioedema listed is Lisinopril [9], [11], [12], Enalapril [9], [11], [12], Quinapril [12], Captopril [12], Benazepril [9], [12], Ramipril [9], [11], [12], Trandolapril [12], Perindropil [11]. Several combinations are also known to cause angioedema such as benazepril / amlodipine [9], Lisinopril / HCTZ [9], moexipril / HCTZ [9]. In Denmark, the most commonly prescribed ACE inhibitor drugs were enalapril and ramipril, as these drugs represent 2/3 of all ACE inhibitor class drugs sold in Denmark [4], [7].

Based on the literature used in this article, the management of angioedema patients suffering from ACE inhibitors varies. In ED patients, the treatment options used are Corticosteroid, H-1 antagonists, H-2 antagonists, B-2 agonist, and epinephrine. For patient with breathing difficulty, intubation or tracheostomy is given to reduce symptoms in patients [9]. Other article mentioned management of acute angioedema using adrenaline, icatibant [13], combination of steroids plus antihistamines, steroids plus antihistamines and adrenaline, and some need admission to ICU [7]. Patients who are intolerant to ACE angioedema-related inhibitors typically require treatment with other medications such as Angiotensin Receptor Inhibitor II (AT2s). AT2 can safely replace ace inhibitor treatment compared to other hypertensive drugs, as AT2 does not increase the incidence of patient angioedema with ACE inhibitor-related angioedema [14]. Recent study reported that in patient with ADR due to ACE inhibitors, some patients switched to ARB, or to other hypertensive medications. Some patient also quit without replacement therapy and the rest that continue the therapy with ACE inhibitors are at risk for recurrence of angioedema [22].

V. Conclusion

The literature study on Adverse Drug Reaction (ADR) in the hypertensive ACE inhibitor-angioedema class of drugs was reported sociodemographically, the patients were mostly women aged over 25 years, African american black race. Common symptoms that occur in patients include facial edema, periobital edema, oral edema, angioneurotic edema, facial urticaria, and tongue edema and can also increase exponentially followed by mild breathing difficulties. The most common comorbidities that appear are asthma, hypertension, diabetes

mellitus, and others. ACE inhibitor class drugs with adverse drug reactions that are widely registered and prescribed such as Lisinopril, Enalapril and Ramipril.

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