



Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors – a nationwide registry-based cohort study

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Abstract. Rasmussen ER, Pottegård A, Bygum A, von Buchwald C, Homøe P, Hallas J (University of Copenhagen, Denmark; University of Southern Denmark, Denmark; Odense University Hospital, Denmark; Zealand University Hospital, Denmark). Angiotensin II receptor blockers are safe in patients with prior angioedema related to angiotensin-converting enzyme inhibitors – a nationwide registry-based cohort study. *J Intern Med* 2019; **285**: 553–561.

Background. It has long been suggested that angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (AT2s) have some degree of ‘cross-reactivity’ in causing angioedema. Therefore, caution has been advised when switching patients with ACEi-related angioedema to an AT2.

Objectives. To clarify whether AT2s can be used safely in patients with a history of angioedema during ACEi treatment and to estimate the incidence rate of angioedema in patients subsequently treated with other antihypertensive drugs (beta-adrenergic blockers, calcium channel blockers, thiazides and analogues) or no antihypertensives.

Methods. This is a nationwide retrospective registry-based cohort study of the Danish population during the period 1994 to 2016, and it uses Danish health registries. Propensity score adjusted and conventional proportional hazards regression models have been employed.

Results. A total of 1 106 024 ACEi users were identified. In total, 5 507 (0.5%) of these patients had experienced angioedema during ACEi treatment and were included in the study. The highest risk of angioedema recurrence was associated with continued ACEi use at an adjusted hazard ratio of 1.45 (95% CI, 1.19 to 1.78). An inverse association was found between AT2s and angioedema (adjusted hazard ratio, 0.39; 95% CI, 0.30 to 0.51) compared with other antihypertensives (adjusted hazard ratios, 0.77 to 0.97).

Conclusions. Compared with other antihypertensive drugs, AT2s do not increase the incidence of angioedema in patients with previous ACEi-related angioedema.

Keywords: Angioedema, angiotensins, angiotensin-converting enzyme, hypertension, therapeutics.

Introduction

Angiotensin-converting enzyme inhibitors (ACEis) are widely used to treat hypertension, heart failure and diabetic nephropathy in both young and elderly patients. Approximately 30% of patients are unable to tolerate ACEis. This is usually due to

symptomatic hypotension and the presence of a dry cough, but more severe adverse reactions, including angioedema and renal failure, can also occur [1–3]. Angioedema caused by ACEis involves the upper airways in up to 54% of patients and can produce a life-threatening risk of suffocation [4]. Laryngeal angioedema is thus a risk factor for

hospital admission from the emergency department [5]. In 50% of patients, the first episode of angioedema occurs within the first month of treatment. However, there is often a substantial latency period following initiation of treatment, and this delays a correct diagnosis because causality is not always obvious [6]. Previous studies found that the risk of angioedema during ACEi treatment was 0.2–2.5%, but incidence studies are often limited by short follow-up periods [7–9]. A systematic review on angioedema incidences estimated the risk of ACEi-AE to vary between 7 and 26 in 100 000 patients [10]. Worldwide, approximately 35–40 million individuals are being treated with an ACEi, so although the absolute risk of angioedema for each individual is low, the general health impact is considerable [11]. In a US study, 18 of 136 (13%) angioedema-related deaths in which a pharmaceutical was implicated specifically identified an ACEi as the drug responsible [12].

Patients intolerant of ACEis due to angioedema attacks will usually need treatment with another drug. Whether angiotensin II receptor blockers (AT2s) increase the risk of angioedema in ACEi-intolerant patients has long been debated [3]. It has been a clinical dogma that ACEi and AT2 have some degree of ‘cross-reactivity’ in causing angioedema; therefore, caution is advised when switching an ACEi-intolerant patient to an AT2 due to a presumed increased risk of recurrent angioedema [13,14]. However, only a few clinical studies have addressed this issue; the reported risk of angioedema in patients switched to an AT2 as a result of swelling episodes during ACEi treatment is 7.7–8.9% [15,16].

From a pharmacological perspective, cross-reactivity should not be expected. The ACEi-related angioedema is a consequence of metabolites of bradykinin that accumulate as a downstream consequence of ACE inhibition [17]. Conversely, AT2s inhibit the renin–angiotensin system at the target receptor level and do not interfere with bradykinin metabolism. A number of studies have investigated whether AT2s are associated with angioedema in general, and these essentially found no association between the two [18,19]. However, it is conceivable that genuine cross-reactivity could have been overlooked in these studies. Few ACEi users experience angioedema, and cross-reactive AT2-related angioedema is probably exceedingly rare. To our knowledge, there are no studies that specifically investigate a population of AT2 users

who have developed angioedema during ACEi treatment. Such an approach would better address the clinical question at hand, whether AT2 could be prescribed safely to patients who have had angioedema during ACEi treatment.

The primary objective of this study was to determine whether AT2 can be used safely to treat patients with a history of angioedema during ACEi treatment. The secondary objective was to calculate the hazard ratios for recurrent angioedema following ACEi-related angioedema in patients who had been treated subsequently with other antihypertensive drugs. We hypothesized that the incidence rate of angioedema in response to AT2 treatment would not be higher than that observed in response to treatment with other antihypertensive drugs or with no antihypertensives.

Material and methods

This was a nationwide retrospective cohort study of the Danish population during the period 1994–2016. We identified all subjects who had experienced a registered episode of angioedema (defined as the 10th revision of the International Statistical Classification of Diseases and Related Health Problems [ICD-10] code T78.3 angioneurotic oedema/Quincke’s oedema/giant urticaria) whilst being treated with an ACEi. This ICD-10 code was chosen based on our previous study of diagnostic coding of ACEi angioedema incidents [1], and these patients were followed up after their index episode of angioedema. In Denmark, all patients collect their antihypertensive medication at a pharmacy and trial doses dispensed at a hospital are rarely used.

Data sources

We used three data sources for this analysis. These were the Danish National Patient Registry, the Danish National Prescription Registry and the Danish Civil Registration System. The Danish National Patient Registry has recorded all secondary care contacts for Danish residents since 1977. Outpatient diagnoses have been available since 1994. Diagnoses were encoded according to ICD-8 between 1977 and 1993 and according to ICD-10 thereafter. ICD-9 was never used in Denmark [20,21]. The Danish National Prescription Registry has recorded all prescription drugs dispensed since 1995 [22]. The Danish Person Registry contains each individual’s unique central

personal registration number (the civil registration number/CPR number) as well as data on deaths, births and migrations [23]. We used this data source to follow subjects and censor data in the event of death or emigration. The study period was 1 January 1994 until 31 December 2016.

Prescription data

Medication exposure data were obtained from the Danish National Prescription Registry. The data for each dispensed prescription are a person identifier, the date of dispensing, the identity of the prescriber and a full account of the dispensed product, including the active substance, ATC code, quantity, drug form and route of administration. The indication and the prescribed daily doses are not recorded.

For prescriptions in each of the five categories, thiazides, beta-blockers, calcium channel blockers, ACEis and AT2s, we defined treatment episodes according to the method described by Pottegård and Hallas, but without excluding incident users, since our objective was not to measure the duration of treatment [24]. This method models the time–distance between prescriptions to establish which ones can reasonably be assumed to belong to the same treatment episode. To define treatment episodes, we set the waiting time parameter to 0.9, otherwise using the same algorithm as Pottegård and Hallas [24].

Population

We retrieved data for all hospital contacts (admissions, emergency department and outpatient department visits) from the Danish National Patient Registry and for all medication prescribed to every patient treated with an ACEi ($n = 1\ 106\ 024$) using the Danish National Prescription Registry. We identified every patient who had a registered episode of angioedema whilst being treated with an ACEi. For patients who had more than one episode of angioedema during ACEi treatment, the first episode registered since 1995 was identified. This was defined as the index angioedema episode and was the starting point for the subsequent follow-up (i.e. the cohort entry date). Comorbidity and co-prescribed medication data obtained from all previous hospital contacts and prescriptions preceding the index date by less than 4 months were used to characterize every patient.

Follow-up

All subjects were followed from 30 days after their index episode until any of the following events: a new episode of angioedema, death, emigration or the end of the study period. The 30-day quarantine period was introduced to avoid confusing hospitalizations caused by the index episode with new episodes of angioedema. We categorized all follow-up events in a time-dependent manner relative to any combination of the five main categories of antihypertensive drugs described above. Subjects may have used more than one antihypertensive drug during the follow-up period, and the groups are therefore not mutually exclusive. The nonusers category included patients who at some time during follow-up did not take any antihypertensive drug prescribed, according to our algorithm.

Analyses

The cohort study data were analysed using a conventional propensity score adjusted method. We chose propensity scores to adjust for confounding variables because we anticipated few angioedema episodes in our follow-up and therefore a risk of overfitting the models. We constructed five different propensity score models, one for each of the five main categories of antihypertensive drug. In the propensity score models. We analysed predictors of using a particular drug versus not using that drug during follow-up. These drug-specific models were used as appropriate when analysing the risk of angioedema for a given drug. For example, when analysing the risk associated with beta-blocker use, we employed the propensity score model for beta-blockers versus that for not using beta-blockers at any time. Propensity scores were calculated relative to the profile at cohort entry date (the date of the index angioedema episode). The covariates included in the propensity score models are listed in Table 1.

Confidence intervals (CIs) for the crude incidence rates were calculated using exact Poisson limits. In the proportional hazards regression model, we either used age and sex as the only covariates (crude analysis) or we used age, sex and the drug-specific propensity score (adjusted analysis) (Table 3). In all instances, we contrasted current use of any given drug with being a nonuser of the same drug, in an entirely time-dependent manner. We applied the ‘asymmetric trimming’ technique,

Table 1 Demographics, comorbidities and recent drug dispensing history amongst 5 507 patients who experienced an episode of angioedema whilst being treated with ACEis. The study subjects were divided into subgroups according to subsequent antihypertensive therapy or complete withdrawal (nonusers) during the follow-up period. Subjects may have used more than one antihypertensive, and the groups are therefore not mutually exclusive. The nonuser category includes all subjects who at any time during the follow-up period did not receive any antihypertensive drug. Percentages are shown in parentheses. Comorbidities were retrieved by use of ICD-10 codes in the Danish National Patient Registry

	ACEi users	AT2 users	BB users	CCB users	TZD users	Nonusers
<i>N</i>	790	1 018	1 502	2 011	1 688	2 713
Men	399 (50.5)	509 (50.0)	762 (50.7)	965 (48.0)	756 (44.8)	1 166 (43.0)
Women	391 (49.5)	509 (50.0)	740 (49.3)	1 046 (52.0)	932 (55.2)	1 547 (57.0)
Age, median (IQR), in years	66 (58–74)	67 (59–74)	68 (60–75)	67 (59–75)	68 (59–75)	64 (55–73)
Diagnoses, history of						
Hypertension	294 (37.2)	431 (42.3)	676 (45.0)	852 (42.4)	647 (38.3)	77 (2.8)
Ischaemic heart disease	168 (21.3)	211 (20.7)	417 (27.8)	369 (18.3)	265 (15.7)	32 (1.2)
Heart failure	82 (10.4)	132 (13.0)	216 (14.4)	148 (7.4)	95 (5.6)	36 (1.3)
Renal disease	39 (4.9)	82 (8.1)	125 (8.3)	148 (7.4)	79 (4.7)	15 (0.6)
Smoking-related diseases	81 (10.3)	154 (15.1)	216 (14.4)	278 (13.8)	198 (11.7)	46 (1.7)
Asthma	47 (5.9)	69 (6.8)	87 (5.8)	133 (6.6)	100 (5.9)	14 (0.5)
Allergy or anaphylaxis	80 (10.1)	96 (9.4)	140 (9.3)	200 (9.9)	159 (9.4)	37 (1.4)
Diabetes type 1	51 (6.5)	76 (7.5)	99 (6.6)	106 (5.3)	78 (4.6)	12 (0.4)
Diabetes type 2	109 (13.8)	159 (15.6)	221 (14.7)	262 (13.0)	195 (11.6)	39 (1.4)
Osteoporosis	21 (2.7)	43 (4.2)	58 (3.9)	85 (4.2)	58 (3.4)	14 (0.5)
Cancer	90 (11.4)	113 (11.1)	184 (12.3)	242 (12.0)	203 (12.0)	36 (1.3)
Osteoporosis with fracture	11 (1.4)	11 (1.1)	16 (1.1)	22 (1.1)	15 (0.9)	(<i>n</i> < 5)
Peptic ulcer	48 (6.1)	55 (5.4)	91 (6.1)	117 (5.8)	101 (6.0)	15 (0.6)
Cerebrovascular disease	484 (61.3)	653 (64.1)	1 040 (69.2)	1 254 (62.4)	981 (58.1)	152 (5.6)
Vascular disease	80 (10.1)	129 (12.7)	184 (12.3)	230 (11.4)	174 (10.3)	28 (1.0)
Musculoskeletal disease	156 (19.7)	215 (21.1)	334 (22.2)	443 (22.0)	341 (20.2)	55 (2.0)
Dementia	10 (1.3)	5 (0.5)	21 (1.4)	27 (1.3)	21 (1.2)	6 (0.2)
Schizophrenia	5 (0.6)	6 (0.6)	10 (0.7)	14 (0.7)	12 (0.7)	(<i>n</i> < 5)
Mood disorders	24 (3.0)	20 (2.0)	52 (3.5)	67 (3.3)	53 (3.1)	6 (0.2)
Anxiety or stress-related disease	9 (1.1)	10 (1.0)	16 (1.1)	20 (1.0)	13 (0.8)	(<i>n</i> < 5)
Neurological disease	65 (8.2)	86 (8.4)	156 (10.4)	188 (9.3)	141 (8.4)	32 (1.2)
Organ transplant	9 (1.1)	13 (1.3)	28 (1.9)	29 (1.4)	9 (0.5)	(<i>n</i> < 5)
Drug use, recent dispensing of						
Antidiabetics	150 (19.0)	184 (18.1)	252 (16.8)	323 (16.1)	254 (15.0)	43 (1.6)
Systemic corticosteroids	60 (7.6)	89 (8.7)	128 (8.5)	161 (8.0)	126 (7.5)	36 (1.3)
Traditional NSAIDs	136 (17.2)	159 (15.6)	242 (16.1)	319 (15.9)	288 (17.1)	44 (1.6)
Antihistamines	113 (14.3)	111 (10.9)	174 (11.6)	251 (12.5)	220 (13.0)	52 (1.9)
Leukotriene antagonists	8 (1.0)	18 (1.8)	14 (0.9)	23 (1.1)	19 (1.1)	(<i>n</i> < 5)
DPP4 inhibitors	5 (0.6)	16 (1.6)	13 (0.9)	18 (0.9)	16 (0.9)	(<i>n</i> < 5)
Thrombocyte inhibitors	291 (36.8)	363 (35.7)	629 (41.9)	761 (37.8)	577 (34.2)	84 (3.1)
Statins	235 (29.7)	385 (37.8)	596 (39.7)	701 (34.9)	552 (32.7)	58 (2.1)
Fibrates	11 (1.4)	19 (1.9)	29 (1.9)	34 (1.7)	30 (1.8)	(<i>n</i> < 5)

Table 1 (Continued)

	ACEi users	AT2 users	BB users	CCB users	TZD users	Nonusers
COPD drugs	134 (17.0)	205 (20.1)	278 (18.5)	405 (20.1)	319 (18.9)	65 (2.4)
Osteoporosis drugs	93 (11.8)	123 (12.1)	192 (12.8)	257 (12.8)	227 (13.4)	20 (0.7)
Opioids	157 (19.9)	185 (18.2)	276 (18.4)	376 (18.7)	302 (17.9)	63 (2.3)
Antidepressants	133 (16.8)	148 (14.5)	243 (16.2)	329 (16.4)	257 (15.2)	60 (2.2)
Antipsychotic drugs	28 (3.5)	28 (2.8)	50 (3.3)	75 (3.7)	58 (3.4)	14 (0.5)
Antiepileptic drugs	36 (4.6)	42 (4.1)	67 (4.5)	85 (4.2)	60 (3.6)	15 (0.6)
Benzodiazepine	85 (10.8)	89 (8.7)	154 (10.3)	192 (9.5)	159 (9.4)	33 (1.2)
Warfarin	18 (2.3)	30 (2.9)	52 (3.5)	40 (2.0)	30 (1.8)	6 (0.2)
Digoxin	34 (4.3)	40 (3.9)	64 (4.3)	61 (3.0)	44 (2.6)	17 (0.6)
Drugs for benign prostate enlargement	16 (2.0)	21 (2.1)	36 (2.4)	41 (2.0)	31 (1.8)	(<i>n</i> < 5)
Anti-obesity drugs	11 (1.4)	15 (1.5)	20 (1.3)	23 (1.1)	24 (1.4)	(<i>n</i> < 5)

ACEi, angiotensin-converting enzyme inhibitor; AT2, angiotensin II receptor blocker; BB, beta-blocker; CCB, calcium channel blocker; TZD, thiazides; NSAID, nonsteroidal anti-inflammatory drug; DPP4, dipeptidyl peptidase IV; COPD, chronic obstructive pulmonary disease.

Note: Danish legislation prohibits reporting counts that are less than five.

thus eliminating everyone with PS outside of the interval defined by the 2.5th percentile of propensity score for the treated and the 97.5th percentile of propensity score for the untreated [25]. This approach has been shown to provide some safeguard against unmeasured confounders [25]. To assert the robustness of our approach, we also conducted a nonpropensity score-based analysis, simply including all baseline characteristics listed in Table 1 as covariates in a conventional multivariable Cox regression model. All results are presented with 95% CI as appropriate.

Ethical approval

The study was approved by the Danish Data Protection Agency (journal number 2008-58-0035). Being a purely registry-based study, the local ethics committee did not need to approve this study.

Results

A total of 1 106 024 users of ACEi were identified. In total, 5 507 subjects were found to have a diagnosis of angioedema during ACEi treatment. Clinical and demographical data regarding those subjects were retrieved from the national registries. The follow-up period consisted of 40 739 person-years. The risk of ACEi angioedema was 0.5%. We found no correlations between age, sex

or general health and any of the five antihypertensive drugs used subsequently to ACEi (Table 1).

Subjects who at some point in time received no antihypertensive drug after an episode of angioedema were generally younger (mean age, 64), female (57%), had a low prevalence of comorbidities and a low usage of other drugs compared with those using any of the five antihypertensive drugs (Table 1).

The most common comorbidities in patients with ACEi-related angioedema were cerebrovascular disease, hypertension and ischaemic heart disease (Table 1). Lifestyle-dependent diseases, including type 2 diabetes (overall 11.2%) and smoking-related diseases (overall 11.7%), were also prevalent. In addition to drugs that reduce the cardiovascular disease risk profile (i.e. statins and thrombocyte aggregation inhibitors), the study patients had a relatively high usage of antihistamines (overall 10.7%) and systemic corticosteroids (overall 6.9%). The amount of follow-up for each category, the number of angioedema episodes occurring and the crude incidence rates are presented in Table 2. In total, 790 subjects (14.3%) used ACEis at some point after their index episode of angioedema, and the incidence rate of angioedema during follow-up in these patients (61/1000 person-years) was higher than that in any other patient category (Table 2).

The highest risk of recurrent angioedema was observed in patients who used ACEis after the cohort entry date (propensity score adjusted hazard ratio, 1.45; 95% CI, 1.19 to 1.78) (Table 3). No elevated risk was observed when ACEis were substituted with calcium channel blocking drugs; the propensity score adjusted hazard ratio of recurrent angioedema was 0.97 (95% CI, 0.83 to 1.14) or other antihypertensives (hazard ratios ranging from 0.75 to 0.94) (Table 3). A decreased risk of recurrent angioedema was found in patients treated with AT2s at follow-up (adjusted hazard ratio, 0.39; 95% CI, 0.30 to 0.51) (Table 3).

Our nonpropensity score-based analysis with all baseline characteristics included as covariates agreed very well with the propensity score-based analysis (data not shown).

A subgroup analysis was performed in patients receiving an AT2 after the index angioedema episode. The results can be seen in Table 4. Female sex, age ≥ 65 , diabetes and congestive heart failure were the factors most prominently associated with a low risk of angioedema recurrence.

Discussion

We tested the hypothesis that in ACEi-intolerant patients, angioedema is not more prevalent in those who switch to an AT2 compared with any other antihypertensive drug. Our results support this hypothesis and show an adjusted hazard ratio of 0.39 (95% CI, 0.30 to 0.51) in patients who had switched to an AT2. The underlying reason for this

Table 3 Crude and propensity score adjusted hazard ratios (with 95% CIs) for the use of different antihypertensives relative to the development of angioedema are shown. The study population included the 5 507 subjects who had experienced angioedema whilst being treated with ACEis

Drug	HR (crude)	HR (adjusted)
ACEis	1.61 (1.34–1.94)	1.45 (1.19–1.78)
AT2s	0.49 (0.38–0.63)	0.39 (0.30–0.51)
Beta-adrenergic blockers	0.93 (0.79–1.10)	0.77 (0.63–0.94)
Calcium channel blockers	1.18 (1.03–1.35)	0.97 (0.83–1.14)
Thiazides and analogues	1.05 (0.90–1.22)	0.87 (0.73–1.04)

ACEis, angiotensin-converting enzyme inhibitors; AT2s, angiotensin II receptor blockers; HR, hazard ratio.

moderate inverse association is currently unknown. It should not be interpreted as an indication that AT2s generally protect against angioedema because our study population was highly selected and based on a history of ACEi-related angioedema. One factor contributing to the inverse association could be that physicians are more cautious when using an AT2 to treat patients who have experienced angioedema during ACEi treatment (due to the hypothesized cross-reaction). As a result, patients with very severe and/or recurrent episodes of angioedema would be more likely to have another antihypertensive prescribed, and this would lower the recurrence rate of angioedema in patients being treated with AT2s.

Table 2 Follow-up for each drug category, number of angioedema episodes and crude incidence rates of angioedema during treatment. The study population included the 5 507 subjects who had experienced angioedema whilst being treated with ACEis

Drug class	N	Follow-up in person-years	Number of angioedema episodes during follow-up	Incidence rate of angioedema during follow-up/1000 person-years (95% CI)
ACEis	790	2 069	127	61.4 (51.2 to 73.0)
AT2s	1 018	3 569	64	17.9 (13.8 to 22.9)
Beta-adrenergic blockers	1 502	5 313	175	32.9 (28.2 to 38.2)
Calcium channel blockers	2 011	6 979	292	41.8 (37.2 to 46.9)
Thiazides and analogues	1 688	5 717	214	37.4 (32.6 to 42.8)
No antihypertensive	4 359	17 092	593	34.7 (32.0 to 37.6)

ACEis, angiotensin-converting enzyme inhibitors; AT2s, angiotensin II receptor blockers; CI, confidence interval. N, number of patients.

Table 4 Subgroup analysis for the association between use of AT2s and the risk of angioedema. Propensity score adjusted hazard ratios are shown (with 95% CIs)

Subgroup	Hazard ratio
Males	0.48 (0.34–0.69)
Females	0.30 (0.20–0.47)
Aged 65 years or over	0.30 (0.20–0.44)
Aged under 65 years	0.51 (0.35–0.74)
A diagnosis of hypertension	0.38 (0.24–0.59)
No diagnosis of hypertension	0.40 (0.29–0.57)
A diagnosis of congestive heart failure	0.26 (0.10–0.66)
No diagnosis of congestive heart failure	0.40 (0.30–0.54)
Diabetes (diagnosis or drug use)	0.25 (0.13–0.48)
No diabetes (diagnosis or drug use)	0.43 (0.32–0.58)

A subgroup analysis of the AT2 patients indicated that there was a sex- and age-dependent difference in the levels of risk but also that certain comorbidities were associated with a lower risk of angioedema during subsequent AT2 treatment (Table 4). Previous studies have shown that type 2 diabetes can protect against ACEi-related angioedema, although the underlying mechanism is not fully understood [1]. One possible explanation is that poor blood glucose control and high levels of HbA1c might increase the level of dipeptidyl peptidase IV, which degrades the vasoactive peptides bradykinin and substance P [26].

We observed a relatively high level of anti-allergic drug prescriptions (i.e. antihistamines and corticosteroids) in our study population, which supports previous results suggesting that ACEi-related angioedema is often misdiagnosed as an allergic (i.e. histamine-related) reaction [1]. This is problematic because the ACEis may not be withdrawn, and anti-allergic drugs can cause adverse reactions, especially if patients are treated with long-term corticosteroids (e.g. fractures and metabolic disease) or with epinephrine (e.g. myocardial infarction) [27,28].

Data regarding comorbidities are subject to bias due to the potential lack of comprehensive registration of secondary diagnoses from hospitals, whereas the principal diagnosis is a requirement

for reimbursement. However, in Denmark, an economic incentive is implemented since hospitals receive additional reimbursement for patients with comorbidities and not just based on the current reason for the visit/admission.

How has the notion of cross-reactivity between ACEi and AT2 emerged? Research by Johnsen *et al.* found an adjusted odds ratio of 10 for the association between ACEi and angioedema [29]; therefore, users of ACEis were approximately 10-fold more likely to experience an episode of angioedema than nonusers. However, this also implies that approximately 10% of angioedema episodes occurring during ACEi therapy are spontaneous and would have occurred even if the patient had not been using an ACEi [30]. The 90% that are truly ACEi-induced are unlikely to recur when the ACEi is discontinued, whereas the 10% that are truly unrelated to ACEis have a high risk of recurrence because the factors that triggered angioedema – whatever they are – have not been removed. In cases of ACEi intolerance, AT2s are frequently used as a replacement, and it is likely that a substantial proportion of the 10% of angioedema episodes that are truly unrelated to ACEis will recur during AT2 treatment and that this will be perceived as cross-reactivity by the clinicians. In fact, the reported proportions of cross-reactivity are fully consistent with this understanding. Warner *et al.* found that in 19 patients with angioedema during AT2 treatment, six patients had previously experienced angioedema and one had developed a cough (a known risk factor for subsequently angioedema if ACEi treatment is continued) during ACEi treatment. This was interpreted as ACEi angioedema being a risk factor for subsequent angioedema during AT2 treatment [13]. However, since no patients receiving other types of antihypertensive drugs or no drugs were used for comparison, no real conclusion can be drawn from this. The reason for recurrent angioedema could be the previous ACEi treatment, as it is known that recurrences can occur, or the patients might be susceptible to angioedema for other reasons than ACEi or AT2s (mostly idiopathic angioedema).

Due to the risk of this severe adverse reaction, it could be discussed whether AT2s should replace ACEis in some circumstances. However, in patients with heart failure ACEis reduces the mortality rate significantly, whereas AT2s do not [31,32]. No head-to-head trials have assessed the effect of

AT2s versus ACEis on morbidity or mortality in patients with diabetic nephropathy. Usage of high-dose ACEi (as opposed to the lower so-called 'renal doses') is associated with a significant reduction in mortality rate [33].

The strengths of this study included the large number of patients (all the ACEi users in Denmark since 1995) and the comprehensive Danish health registries we had access to. However, data on specific treatments given at the hospital during angioedema episodes are not recorded. Another strength of this study is that trial doses from hospitals or general practitioners are very rarely used in Denmark. If they were used no prescription would be registered so the patient would not count as 'exposed' to the drug in question.

One limitation of this study was that subjects were included in the cohort based on the sensitivity (56.3–59.6%) of the ICD-10 T78.3 Quincke's oedema diagnosis code [1]. As a result, 40% of patients with ACEi-related angioedema would not have been included because they would have been coded as something else (e.g. anaphylaxis or allergy) [1]. If genuine angioedemas that are coded correctly do not have different characteristics from those that are coded incorrectly, the imperfect sensitivity will not affect our estimated hazard ratios.

Milder cases of ACEi angioedema might not be registered in the health registries, as they might be managed by a general practitioner, who would then withdraw the ACEi. Thus, the incidence is likely somewhat higher than this study suggests. Also increased awareness from physicians trying out an ARB in an ACEi angioedema patient could mean that mild cases are readily identified and the medication withdrawn without this being registered in the health registries.

In patients suffering from asthma and allergy, who might have a higher risk of angioedema, beta-blocking agents are contraindicated. This could potentially cause the risk of angioedema attributable to these drugs to be underestimated (indication bias).

Another study limitation was that we had to use a complex time-dependent exposure model. Had this research question been addressed using a clinical trial, we would randomize each subject to a single antihypertensive drug which they should take throughout the study period, and we would then

estimate their incidence rate of angioedema. In real-world clinical practice, patients switch between antihypertensives and use multidrug regimes in a highly erratic manner; we had to take this into account during our analysis. Finally, since this is an observational study, we cannot rule out residual confounding by risk factors for angioedema that are not accounted for in our data.

Conclusions

AT2s can safely replace ACEi in patients who experience angioedema during ACEi treatment. We observed a moderate inverse association between AT2s and angioedema in our selected population. The underlying explanation for this is unknown and a potential focus for future studies.

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Conflicts of interest statement

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that Dr Rasmussen has received a research grant from Shire (grant no #IIR-DNK-001219) for her PhD study.

Shire does not produce any antihypertensive drugs; no other relationships or activities have influenced the submitted work.

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