

Supplementary Material 1

Supplementary Material 1: Information requested from the Danish ADR Database, when applying for a data export

Notes: The application to the DKMA was written in Danish (left column). A translated list of the requested information was written afterwards (right column)

Abbreviations: ADR, adverse drug reaction; CPR, personal identification number; DKMA, Danish Medicines Agency

Danish (original)	English (translation)
Om der er indberettet en bivirkning (ja/nej).	If an ADR has been reported (yes/no)
Hvem der har indberettet bivirkningen.	Who reported the ADR
Hvorfra bivirkningen er indberettet (hospital, afdeling, egen læge, speciallæge-praksis)	Where the ADR was reported from (hospital, department, general practitioner, specialist)
Andel af anonyme indberetninger i bivirkningsdatabasen	Share of anonymous reports in the ADR database
Modtagedato	Date of receiving the report
Lægemiddelnavn	Name of medication
Bivirkning	Name of ADR
Organklasse	Which organs are affected
Er patienten kommet sig?	Has the patient recovered
Alvorlighed	Severity
Dødsfald	Whether the ADR was fatal
Køn	Gender
Fødselsår	Birthdate
CPR nr.	CPR number
Alder i år	Age in years
Beregnet alder	Calculated age
Aldersgruppe	Age group
Lægemiddel startdato	Date of initiating treatment
Indikation	Indication for treatment
Bivirknings startdato	Date of ADR start
Spontan indberetning	Whether the report was spontaneous
Medicinsk bekræftet	Whether the ADR has been medically confirmed

Supplementary Material 2

Supplementary Material 2: Terms used to search the Danish ADR Database for angioedema related ADR reports

Notes: List made using MedDRA. Highlighted terms returned results.

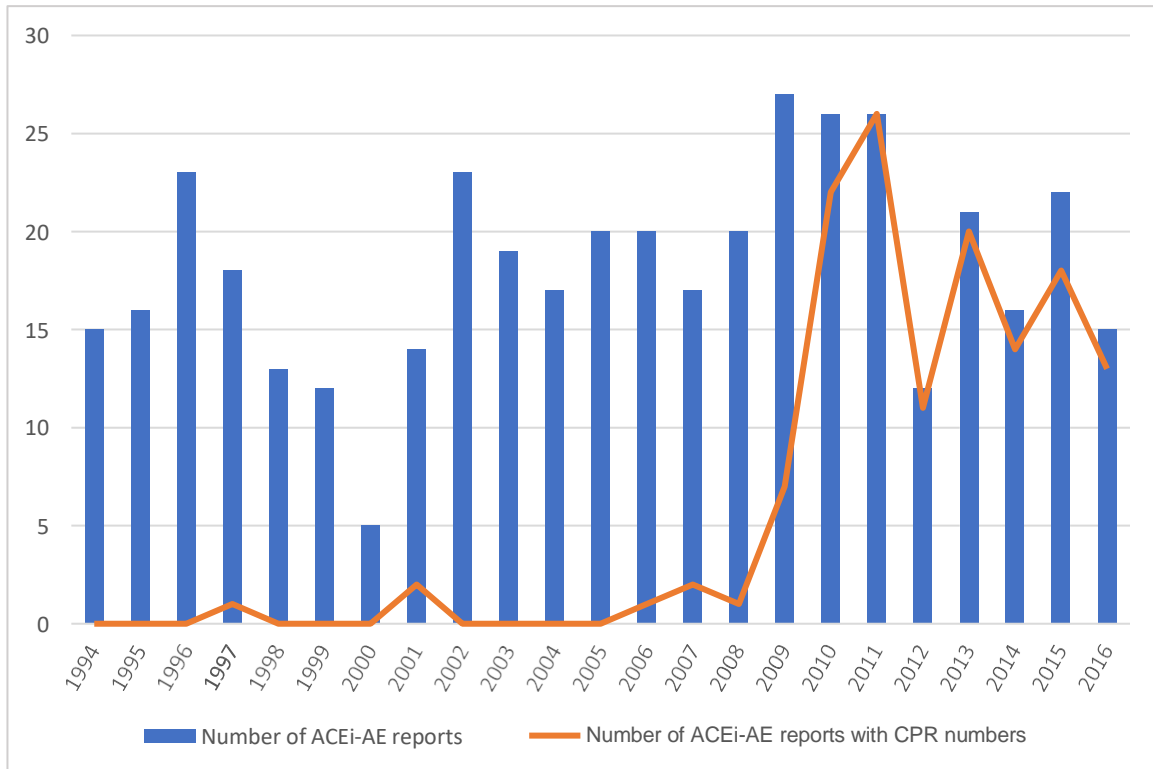
Abbreviations: ADR, adverse drug reaction

Allergic oedema	Lip oedema
Angioedema	Lip swelling
Circumoral oedema	Mouth swelling
Conjunctival oedema	Oculo-respiratory syndrome
Corneal oedema	Oedema mouth
Epiglottic oedema	Oropharyngeal oedema
Eye oedema	Oropharyngeal swelling
Eye swelling	Palatal oedema
Eyelid oedema	Palatal swelling
Face oedema	Periorbital oedema
Gingival oedema	Pharyngeal oedema
Gingival swelling	Scleral oedema
Gleich's syndrome	Swelling face
Hereditary angioedema	Swollen tongue
Idiopathic angioedema	Tongue oedema
Idiopathic urticaria	Tracheal oedema
Intestinal angioedema	Urticaria
Laryngeal oedema	Urticaria cholinergic
Laryngotracheal oedema	Urticaria chronic
Limbal swelling	Urticaria papular

Supplementary Material 3

Supplementary Material 3: Total number of ACEi-AE reports to the DKMA and number of reports to the DKMA including full CPR numbers each year, respectively

Abbreviations: ACEi-AE, ACE-inhibitor related angioedema; DKMA, Danish Medicines Agency; CPR, personal identification number

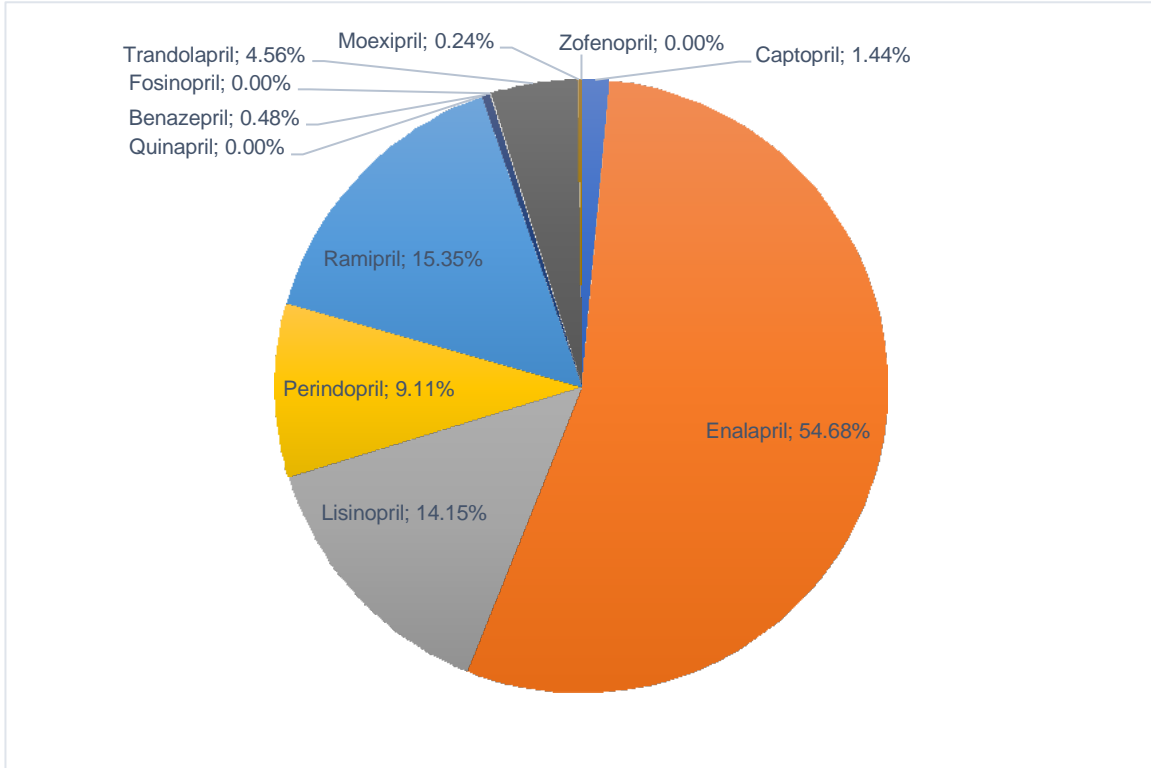


Supplementary Material 4

Supplementary Material 4: Distribution of ACEi substances related to ACEi-AE reports to the DKMA (1994-2016)

Notes: Numbers represent calculated means for all years

Abbreviations: ACEi, ACE-inhibitor; ACEi-AE, ACE-inhibitor related angioedema; DKMA, Danish Medicines Agency



Supplementary Material 5

Supplementary Material 5: ACEi substances related to ACEi-AE reports to the DKMA (1994-2016)

Abbreviations: ACEi, ACE-inhibitor; ACEi-AE, ACE-inhibitor related angioedema; DKMA, Danish Medicines Agency

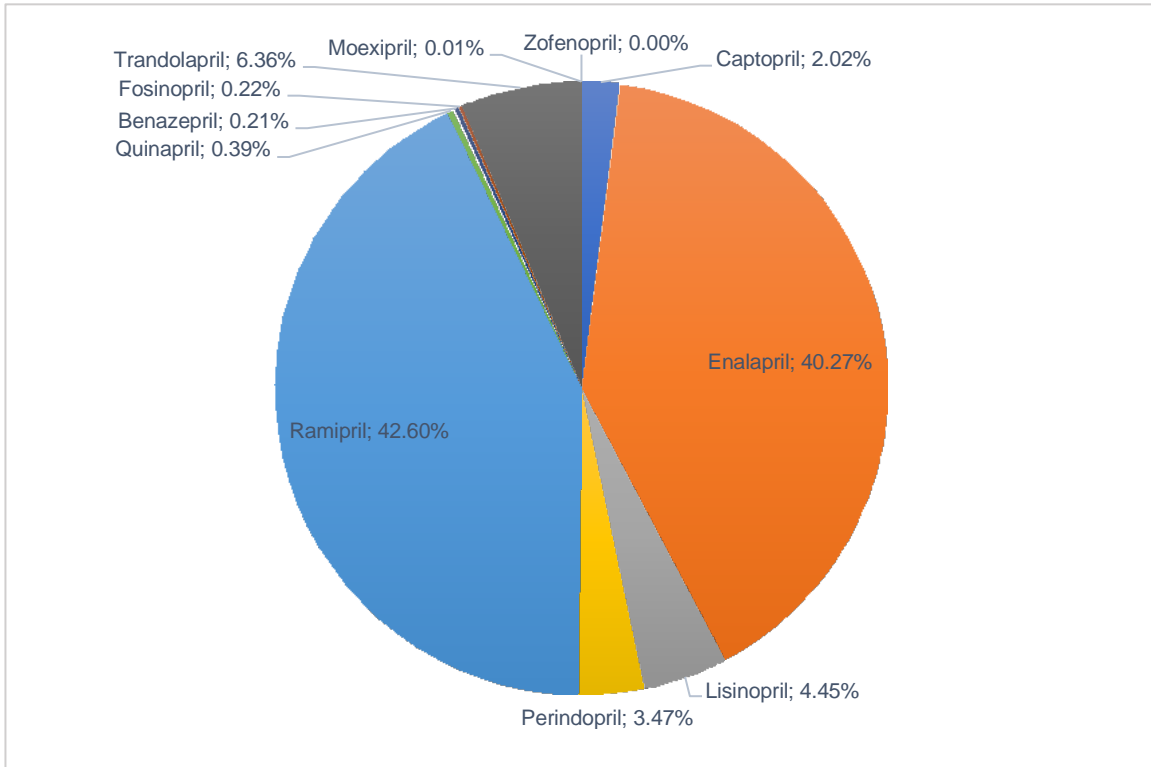
Year	Number of reports								
	Benazepril	Captopril	Enalapril	Lisinopril	Moexipril	Perindopril	Ramipril	Trandolapril	Total
1994		1	7	4		1	1	1	15
1995		1	6	7		1		1	16
1996		1	13	5		1	1	2	23
1997		1	7	4	1	1	2	2	18
1998		1	7	1			2	2	13
1999			3	3		2	3	1	12
2000			1	1		1	1	1	5
2001			4	3		4	3		14
2002		1	15			3	4		23
2003			10	3		2	3	1	19
2004			8	5		1	2	1	17
2005			9	2		3	3	3	20
2006			13	1		5	1		20
2007			10			3	4		17
2008			11	1		5	3		20
2009	2		16	2		2	5		27
2010			16	5		1	3	1	26
2011			14	4			6	2	26
2012			9	2			1		12
2013			11	1		2	7		21
2014			12	2			1	1	16
2015			14	2			6		22
2016			12	1			2		15
Total	2	6	228	59	1	38	64	19	417
%	0.48%	1.44%	54.68%	14.15%	0.24%	9.11%	15.35%	4.56%	100%

Supplementary Material 6

Supplementary Material 6: Distribution of sales numbers of ACEi substances in Denmark (1997-2016)

Notes: Pharmaceutical drug sale data is from the MedStat database.²⁹ Numbers represent calculated means for all years

Abbreviations: ACEi, ACE-inhibitor



Supplementary Material 7

Supplementary Material 7: Sales numbers of ACEi substances in Denmark (1997-2016)

Notes: Pharmaceutical drug sale data is from the MedStat database.²⁹ Numbers represent 1000 DDD's

Abbreviations: ACEi, ACE-inhibitor; DDD, defined daily dose

Year	Number of sales (1000 DDD)											
	Capto pril	Enala pril	Lisin opril	Perindo pril	Ramipril	Quin april	Benaze pril	Fosino pril	Trandola pril	Moexi pril	Zofen opril	Total
1996	0	0	0	0	0	0	0	0	0	0	0	0
1997	5596	21241	4398	2.3	8171	869	631	617	2768	37	0	44328
1998	5312	21986	4455	2.45	9521	841	564	676	3915	75	0	47345
1999	4804	22501	4.41	2718	10788	788	505	597	5.4	68	0	42769
2000	4287	23622	4346	3.37	13495	775	446	540	6916	29	0	54456
2001	3843	25116	4386	4329	17933	756	430	505	8224	7	0	65529
2002	3.42	27321	4466	5923	23566	733	400	469	9268	0	0	72146
2003	3083	32115	4545	7067	27974	691	351	436	9911	0	0	86173
2004	2741	39863	4847	8134	30409	625	308	394	9931	0	0	97252
2005	2402	47383	4883	9042	35204	580	268	254	9631	0	0	109647
2006	2139	53908	5056	9792	42414	507	243	156	9132	0	0	123347
2007	1869	58976	5379	10582	48389	476	221	102	8827	0	0	134821
2008	1657	63.87	5.88	13.12	55573	454	193	72	8466	0	0	66415
2009	1446	72887	7233	8377	70355	328	119	43	8162	0	0	168950
2010	1248	79175	8039	2768	84302	119	33	14	7986	0	0	183684
2011	1069	78.26	8184	1988	88.23	67	17	1	7415	0	0	18741
2012	914	77731	8.13	1585	92123	51	1	0	6966	0	0	179371
2013	752	75967	8162	1422	93851	42	0	0	6582	0	0	186778
2014	647	73777	7374	1271	94396	27	0	0	6186	0	1	183679
2015	574	72462	6683	1154	94763	1	0	0	5814	0	0	181451
2016	520	70458	6584	1066	95032	0	0	0	5415	0	0	179075
Total	44903	896489	99020	77218	948259	8730	4730	4876	141515	216	1	2225957
%	2.02%	40.27%	4.45%	3.47%	42.6%	0.39%	0.21%	0.22%	6.36%	0.01%	0%	100%

Supplementary Material 8

Supplementary Material 8: ACEi substances received by cohort patients

Notes: Data are known for 141 of 176 patients

Abbreviations: ACEi, ACE-inhibitor

Pharmaceutical	Cohort 1	Cohort 2	Total (%)
Ramipril	18	6	24 (17.02%)
Enalapril	42	34	76 (53.90%)
Trandolapril	2	4	6 (4.26%)
Lisinopril	13	3	16 (11.35%)
Perindolapril	6	1	7 (4.96%)
Enalapril and hydrochlorothiazide	1	10	11 (7.80%)
Ramipril and perindolapril	1	0	1 (0.71%)
All ACEi's	83	58	141 (100%)

Supplementary Material 9

Supplementary Material 9: Number of Danish individuals receiving an ACEi per 1000 inhabitants each year (1997-2016)

Notes: Pharmaceutical drug sales data from the MedStat database²⁹

Abbreviations: ACEi, ACE-inhibitor

