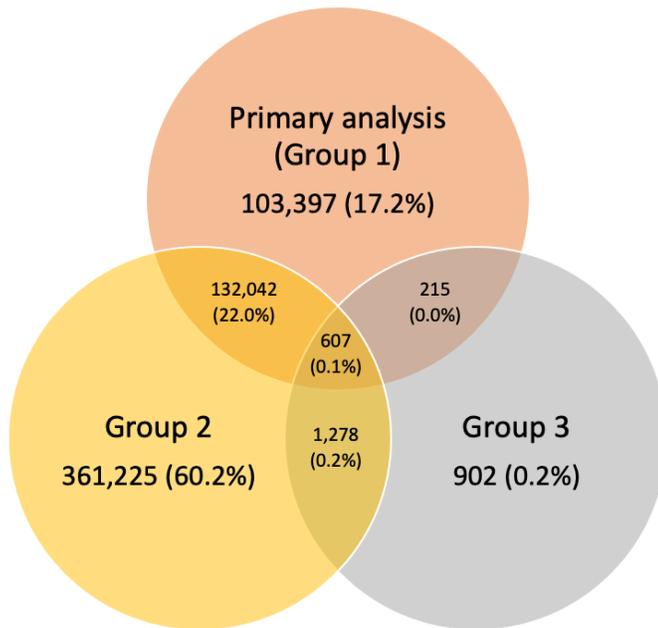


eFigure 1. Eczematous dermatitis group overlap



Notes: ^aGroup 1 was used for the primary analysis and includes codes used in validation study, group 2 includes non-specific eczema codes, and group 3 includes drug-induced dermatitis codes

eTable 1. Read codes used to define eczematous dermatitis groups

READ Code ^a	Description
Group 1: Primary analysis - codes used in validation study	
M12z100	Eczema NOS
M111.00	Atopic dermatitis/eczema
M112.00	Infantile eczema
M113.00	Flexural eczema
M114.00	Allergic (intrinsic) eczema
Group 2: Additional eczema codes not used in validation study	
1D14.00	C/O: a rash
R021z00	[D]Rash and other nonspecific skin eruption NOS
M12z000	Dermatitis NOS
R021.00	[D]Rash and other nonspecific skin eruption
1D15.00	C/O: itching
2227.00	O/E - rash present
2227.11	O/E - allergic rash
M18z.12	Itch
A57z.11	Non specific viral rash
2227.12	O/E - itchy rash
2I14.00	O/E - a rash
M1...11	Dermatitis/dermatoses
M119.00	Discoid eczema
M12z111	Discoid eczema
H330.00	Extrinsic (atopic) asthma
2FU..00	O/E - erythematous rash
M11z.00	Atopic dermatitis NOS
2FO..00	O/E - discoid rash
Myu2200	[X]Exacerbation of eczema
M1y0.00	Nummular dermatitis
M117.00	Neurodermatitis - atopic
Myu2.00	[X]Dermatitis and eczema
M115.00	Besnier's prurigo
Group 3: Drug-induced dermatitis codes	
M130.00	Ingestion dermatitis due to drugs
Myu2800	[X]Dermatitis due to other substances taken internally
M130200	Drug-induced erythroderma
M12A100	Drug photoallergic response
M12A000	Drug phototoxic response
M130.11	Drug induced rash

^aCodes including "eczema, dermatitis, atopic, rash, itch, dermatology, dermatologist, and biopsy with skin, punch, and/or shave"

eTable 2. Participant characteristics by antihypertensive drug class

Characteristic	Alpha Blockers N = 88,579 (5.86%)	Angiotensin- Converting Enzyme Inhibitors N = 302,887 (22.58%)	Angiotensin Receptor Blockers N = 114,634 (7.61%)	Beta Blockers N = 196,576 (15.60%)	Calcium Channel Blockers N = 256,706 (19.32%)	Diuretics N = 311,631 (26.86%)
Sex						
Female	37,042 (41.82)	159,386 (52.62)	68,158 (59.46)	106,255 (54.05)	143,785 (56.01)	172,195 (55.26)
Male	51,537 (58.18)	143,501 (47.38)	46,476 (40.54)	90,321 (45.95)	112,921 (43.99)	139,436 (44.74)
Townsend score						
1 (least deprived)	22,567 (25.48)	76,470 (25.25)	31,338 (27.34)	50,869 (25.88)	66,115 (25.76)	76,178 (24.44)
2	20,914 (23.61)	70,996 (23.44)	27,666 (24.13)	47,143 (23.98)	60,845 (23.7)	73,114 (23.46)
3	18,551 (20.94)	63,580 (20.99)	23,801 (20.76)	41,393 (21.06)	53,916 (21.00)	65,829 (21.12)
4	15,952 (18.01)	55,554 (18.34)	19,531 (17.04)	34,779 (17.69)	45,851 (17.86)	58,009 (18.61)
5 (most deprived)	10,595 (11.96)	36,287 (11.98)	12,298 (10.73)	22,392 (11.39)	29,979 (11.68)	38,501 (12.35)
Hypertension						
Yes	74,731 (84.37)	240,236 (79.32)	101,866 (88.86)	137,011 (69.70)	221,128 (86.14)	214,960 (68.98)
No	13,848 (15.63)	62,651 (20.68)	12,768 (11.14)	59,565 (30.30)	35,578 (13.86)	96,671 (31.02)
Chronic kidney disease						
Yes	31,184 (35.20)	95,341 (31.48)	42,572 (37.14)	56,691 (28.84)	70,777 (27.57)	79,077 (25.38)
No	57,395 (64.80)	207,546 (68.52)	72,062 (62.86)	139,885 (71.16)	185,929 (72.43)	232,554 (74.62)
Flu vaccination						
Yes	3,638 (4.11)	10,861 (3.59)	3,983 (3.47)	6,212 (3.16)	8,284 (3.23)	11,665 (3.74)
No	84,941 (95.89)	292,026 (96.41)	110,651 (96.53)	190,364 (96.84)	248,422 (96.77)	299,966 (96.26)
General practice visits						
0	17,126 (19.33)	64,997 (21.46)	20,694 (18.05)	47,188 (24.00)	56,112 (21.86)	77,133 (24.75)
1-5	40,111 (45.28)	141,770 (46.81)	51,086 (44.56)	92,273 (46.94)	119,169 (46.42)	146,574 (47.03)
6+	31,342 (35.38)	96,120 (31.73)	42,854 (37.38)	57,115 (29.05)	81,425 (31.72)	87,924 (28.21)
Age at start-of-follow-up (yrs)						
Mean (SD)	67.07 (7.01)	67.08 (7.49)	66.32 (6.84)	67.02 (7.24)	66.72 (7.20)	68.52 (8.10)
Median (IQR)	65.50 (11.58)	65.00 (12.13)	64.50 (10.51)	65.50 (11.50)	64.50 (11.50)	66.64 (13.01)
Duration of follow-up (yrs)						
Mean (SD)	11.29 (4.71)	10.82 (4.77)	11.23 (4.62)	11.12 (4.82)	10.91 (4.80)	10.58 (4.96)
Median (IQR)	11.54 (7.62)	11.00 (7.39)	11.53 (7.21)	11.52 (7.56)	11.04 (7.35)	10.69 (7.96)

eTable 3a. Sensitivity Analysis 1: Cox proportional hazard ratios for eczematous dermatitis by antihypertensive drug class, additionally adjusted for time-updated hypertension

	HR (95%CI) ^a	Primary Analysis Results (for comparison) HR (95%CI)
Any antihypertensive	1.29 (1.26, 1.32)	1.29 (1.26, 1.31)
By antihypertensive class ^b		
Alpha Blockers	1.08 (1.05, 1.11)	1.08 (1.05, 1.11)
Angiotensin-Converting Enzyme Inhibitors	1.02 (1.00, 1.05)	1.02 (1.00, 1.04)
Angiotensin Receptor Blockers	1.13 (1.10, 1.15)	1.12 (1.09, 1.15)
Beta Blockers	1.05 (1.02, 1.07)	1.04 (1.02, 1.06)
Calcium Channel Blockers	1.17 (1.15, 1.19)	1.16 (1.14, 1.18)
Diuretics	1.23 (1.20, 1.25)	1.21 (1.19, 1.24)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, chronic kidney disease, and time-varying hypertension.

^bAdditionally adjusted for remaining five antihypertensive drug classes

eTable 3b. Sensitivity Analysis 2: Cox proportional hazard ratios for eczematous dermatitis by antihypertensive drug class stratified by hypertension

Antihypertensive Drug Class	Hypertension HR (95%CI)	No hypertension HR (95%CI)
Any antihypertensive ^a	1.21 (1.17, 1.25)	1.30 (1.26, 1.34)
By antihypertensive class ^b		
Alpha Blockers	1.05 (1.02, 1.08)	1.33 (1.24, 1.42)
Angiotensin-Converting Enzyme Inhibitors	1.01 (0.99, 1.04)	1.03 (0.98, 1.07)
Angiotensin Receptor Blockers	1.13 (1.10, 1.16)	1.16 (1.07, 1.27)
Beta Blockers	1.01 (0.98, 1.03)	1.12 (1.07, 1.16)
Calcium Channel Blockers	1.16 (1.14, 1.19)	1.16 (1.10, 1.22)
Diuretics	1.17 (1.14, 1.20)	1.30 (1.25, 1.34)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease.

^bAdditionally adjusted for remaining five antihypertensive drug classes

eTable 3c. Sensitivity Analysis 3: Cox proportional hazard ratios for eczematous dermatitis by antihypertensive drug class among participants who only received one type of antihypertensive^{a,b}

Antihypertensive Drug Class	HR (95%CI) N=140,955	
	Calcium Channel Blockers	Ref
Alpha Blockers	1.16 (1.06, 1.26)	1.26 (1.15, 1.38)
Angiotensin-Converting Enzyme Inhibitors	0.92 (0.86, 0.98)	Ref
Angiotensin Receptor Blockers	0.83 (0.68, 1.02)	0.91 (0.74, 1.11)
Beta Blockers	1.01 (0.95, 1.08)	1.11 (1.04, 1.18)
Diuretics	1.12 (1.06, 1.18)	1.22 (1.15, 1.30)

Note: Results from the same model are presented in two ways. The first column shows calcium channel blockers as a reference group because they are the first line treatment recommended for hypertension in adults over age 55 by the UK National Institute for Clinical Excellence. The second column shows angiotensin-converting enzyme inhibitors as the reference group because they had the smallest effect size in primary analysis. ^aAdjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease.

^bExclusion criteria was implemented for all drugs at the same time

eTable 3d. Sensitivity Analysis 4: Cox proportional hazard ratios for eczematous dermatitis by antihypertensive drug class allowing participants to accrue unexposed patient time if they do not receive a subsequent prescription for the drug of interest within 3 months

Antihypertensive Drug Class	HR (95%CI)
Any antihypertensive	N/A ^a
By antihypertensive class ^b	
Alpha Blockers	1.06 (1.02, 1.10)
Angiotensin-Converting Enzyme Inhibitors	1.01 (0.99, 1.03)
Angiotensin Receptor Blockers	1.11 (1.08, 1.14)
Beta Blockers	0.98 (0.95, 1.00)
Calcium Channel Blockers	1.16 (1.14, 1.19)
Diuretics	1.16 (1.14, 1.18)

^aResults for any antihypertensive could not be calculated in cases when multiple classes had the same start date.

^bAdditionally adjusted for remaining five antihypertensive drug classes.

eTable 3e. Sensitivity Analysis 5: Cox proportional hazard ratios for eczematous dermatitis by antihypertensive drug class censoring after 3, 9, and 12 months of treatment

Antihypertensive Drug Class	HR (95%CI)
Censor after 3 months	
Any antihypertensive ^a	1.22 (1.14, 1.31)
By antihypertensive class^b	
Alpha Blockers	1.05 (0.93, 1.19)
Angiotensin-Converting Enzyme Inhibitors	0.98 (0.92, 1.06)
Angiotensin Receptor Blockers	1.16 (1.04, 1.29)
Beta Blockers	0.90 (0.82, 0.99)
Calcium Channel Blockers	1.15 (1.07, 1.24)
Diuretics	1.28 (1.20, 1.37)
Censor after 9 months	
Any antihypertensive ^a	1.27 (1.22, 1.32)
By antihypertensive class^b	
Alpha Blockers	1.12 (1.05, 1.20)
Angiotensin-Converting Enzyme Inhibitors	1.07 (1.03, 1.11)
Angiotensin Receptor Blockers	1.18 (1.11, 1.25)
Beta Blockers	1.01 (0.96, 1.07)
Calcium Channel Blockers	1.25 (1.20, 1.31)
Diuretics	1.30 (1.25, 1.36)
Censor after 12 months	
Any antihypertensive ^a	1.28 (1.23, 1.32)
By antihypertensive class^b	
Alpha Blockers	1.13 (1.06, 1.20)
Angiotensin-Converting Enzyme Inhibitors	1.08 (1.04, 1.12)
Angiotensin Receptor Blockers	1.17 (1.11, 1.24)
Beta Blockers	1.04 (0.99, 1.09)
Calcium Channel Blockers	1.27 (1.23, 1.32)
Diuretics	1.31 (1.26, 1.35)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease.

^bAdditionally adjusted for remaining five antihypertensive drug classes.

eTable 4. Descriptive characteristics for different definitions of the outcome

Characteristic	Primary analysis – eczema codes used in validation study (Group 1)		More general eczema codes (Group 2)		Drug-induced dermatitis codes only (Group 3)	
	Eczematous dermatitis N = 105,007 (6.73%)	No eczematous dermatitis N = 1,456,351 (93.27%)	Eczema N = 278,487 (18.87%)	No eczema N = 1,197,231 (81.13%)	Dermatitis N = 2,013 (0.12%)	No dermatitis N = 1,689,100 (99.88%)
Sex						
Female	57,403 (54.67)	788,510 (54.14)	158,474 (56.91)	633,751 (52.93)	1,212 (60.21)	917,406 (54.31)
Male	47,604 (45.33)	667,841 (45.86)	120,013 (43.09)	563,480 (47.07)	801 (39.79)	771,694 (45.69)
Townsend score						
1 (least deprived)	29,536 (28.13)	380,620 (26.14)	75,369 (27.06)	313,062 (26.15)	524 (26.03)	446,724 (26.45)
2	24,910 (23.72)	346,849 (23.82)	66,373 (23.83)	286,649 (23.94)	491 (24.39)	401,754 (23.79)
3	21,226 (20.21)	302,053 (20.74)	57,081 (20.50)	248,939 (20.79)	396 (19.67)	348,567 (20.64)
4	17,818 (16.97)	255,376 (17.54)	47,936 (17.21)	209,287 (17.48)	353 (17.54)	294,488 (17.43)
5 (most deprived)	11,517 (10.97)	171,453 (11.77)	31,728 (11.39)	139,294 (11.63)	249 (12.37)	197,567 (11.70)
Hypertension						
Yes	60,647 (57.76)	646,853 (44.42)	159,270 (57.19)	509,304 (42.54)	1,275 (63.34)	767,165 (45.42)
No	44,360 (42.24)	809,498 (55.58)	119,217 (42.81)	687,927 (57.46)	738 (36.66)	921,935 (54.58)
Age at start-of-follow-up (years)						
Mean (SD)	66.96 (7.63)	67.39 (9.00)	67.05 (7.86)	67.68 (9.15)	67.55 (7.76)	67.26 (8.90)
Median (IQR)	64.50 (11.50)	63.50 (13.09)	64.50 (11.87)	63.50 (13.50)	65.51 (12.50)	63.50 (12.50)
Duration of follow-up (years)						
Mean (SD)	5.59 (4.27)	7.01 (5.16)	9.75 (5.07)	6.45 (4.97)	9.98 (5.23)	6.89 (5.11)
Median (IQR)	4.69 (6.34)	5.95 (8.02)	9.54 (7.99)	5.47 (7.28)	9.78 (8.41)	5.74 (7.99)

eTable 5. Cox proportional hazard ratios for eczematous dermatitis by antihypertensive drug class with different definitions of the outcome

Antihypertensive Drug Class	More general eczema codes (Group 2) HR (95%CI)	Drug-induced dermatitis codes (Group 3) HR (95%CI)
Any antihypertensive ^a	1.33 (1.31, 1.34)	2.25 (1.96, 2.59)
By antihypertensive class ^b		
Alpha Blockers	1.06 (1.04, 1.08)	1.25 (1.05, 1.47)
Angiotensin-Converting Enzyme Inhibitors	1.07 (1.06, 1.09)	1.18 (1.04, 1.35)
Angiotensin Receptor Blockers	1.11 (1.10, 1.13)	1.26 (1.07, 1.47)
Beta Blockers	1.08 (1.06, 1.09)	1.50 (1.32, 1.71)
Calcium Channel Blockers	1.13 (1.11, 1.14)	1.41 (1.23, 1.61)
Diuretics	1.19 (1.18, 1.21)	1.40 (1.22, 1.61)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease.

^bAdditionally adjusted for remaining five antihypertensive drug classes.

eTable 6. Associations between antihypertensive drugs and a negative control (seborrheic keratosis diagnosis code)

Antihypertensive Drug Class	HR (95%CI)
Any antihypertensive ^a	0.96 (0.94, 0.98)
By antihypertensive class ^b	
Alpha Blockers	1.00 (0.97, 1.04)
Angiotensin-Converting Enzyme Inhibitors	0.90 (0.87, 0.92)
Angiotensin Receptor Blockers	1.11 (1.07, 1.15)
Beta Blockers	1.03 (1.00, 1.06)
Calcium Channel Blockers	0.98 (0.96, 1.01)
Diuretics	0.93 (0.90, 0.95)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease.

^bAdditionally adjusted for remaining five antihypertensive drug classes.

eTable 7. E-values

Antihypertensive Drug Class	E-value
Any antihypertensive	1.90
Alpha Blockers	1.37
Angiotensin-Converting Enzyme Inhibitors	1.16
Angiotensin Receptor Blockers	1.51
Beta Blockers	1.28
Calcium Channel Blockers	1.62
Diuretics	1.76

eTable 8. Relative rate of eczematous dermatitis among those with antihypertensives additionally adjusting for calendar year

	Adjusted HR (95%CI)
Any antihypertensive ^a	1.29 (1.26, 1.31)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, chronic kidney disease, and calendar year

eTable 9. Relative rate of eczematous dermatitis among those with antihypertensives accounting for competing risk of death

	Adjusted Subdistribution HR (95%CI)
Any antihypertensive ^a	1.35 (1.31-1.39)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, and chronic kidney disease

eTable 10. Relative rate of eczematous dermatitis by antihypertensive drug class additionally adjusting for congestive heart failure, varicose veins, and asteatotic eczema

	Adjusted HR (95%CI)
Any antihypertensive ^a	1.29 (1.26, 1.31)
By antihypertensive class ^b	
Alpha Blockers	1.08 (1.05, 1.11)
Angiotensin-Converting Enzyme Inhibitors	1.02 (1.00, 1.04)
Angiotensin Receptor Blockers	1.12 (1.09, 1.15)
Beta Blockers	1.04 (1.02, 1.06)
Calcium Channel Blockers	1.16 (1.14, 1.18)
Diuretics	1.21 (1.19, 1.24)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, chronic kidney disease, congestive heart failure, varicose veins, and asteatotic eczema.

^bAdditionally adjusted for remaining five antihypertensive drug classes

eTable 11. Relative rate of eczematous dermatitis by antihypertensive drug class excluding participants with varicose veins and asteatotic eczema

	N	Adjusted HR (95%CI)
Any antihypertensive ^a	832,095	1.30 (1.27, 1.33)
By antihypertensive class ^b		
Alpha Blockers	1,372,413	1.08 (1.05, 1.12)
Angiotensin-Converting Enzyme Inhibitors	1,215,911	1.02 (1.00, 1.04)
Angiotensin Receptor Blockers	1,367,729	1.13 (1.10, 1.16)
Beta Blockers	1,145,197	1.05 (1.03, 1.07)
Calcium Channel Blockers	1,205,764	1.17 (1.14, 1.20)
Diuretics	1,057,192	1.21 (1.19, 1.24)

^aExclusion criteria was implemented for all drugs at the same time and adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, chronic kidney disease, and congestive heart failure

^bAdditionally adjusted for remaining five antihypertensive drug classes

eTable 12. Relative rate of eczematous dermatitis by individual antihypertensive drugs

	N receiving drug (%)	Adjusted HR (95%CI)
Alpha Blockers		
Doxazosin	69887 (4.57)	0.87 (0.83, 0.91)
Alfuzosin	14460 (0.93)	1.27 (1.19, 1.36)
Indoramin	5772 (0.37)	1.24 (1.14, 1.35)
Beta Blockers		
Atenolol	124521 (9.04)	1.00 (0.97, 1.02)
Bisoprolol	96439 (6.31)	1.05 (1.01, 1.09)
Propranolol	28119 (1.88)	1.15 (1.10, 1.21)
Metoprolol	11032 (0.71)	1.10 (1.02, 1.18)
Sotalol	11567 (0.74)	1.14 (1.06, 1.22)
Carvedilol	5767 (0.37)	1.12 (1.00, 1.25)
Nebivolol	6146 (0.39)	1.06 (0.96, 1.18)
Calcium Channel Blockers		
Dihydropyridine		
Amlodipine	195328 (13.36)	1.05 (1.03, 1.08)
Nifedipine	39773 (2.68)	1.05 (1.02, 1.09)
Felodipine	56927 (3.70)	1.03 (0.99, 1.06)
Lercanidiprine	16909 (1.09)	1.03 (0.96, 1.10)
Lacidipine	5537 (0.36)	1.05 (0.95, 1.15)
Non-dihydropyridine		
Diltiazem	40791 (2.68)	1.08 (1.04, 1.12)
Verapamil	10879 (0.70)	1.04 (0.96, 1.11)
Diuretics		
Thiazide		
Bendrofluazide	211722 (15.76)	0.99 (0.96, 1.01)
Indapamide	27772 (1.8)	0.96 (0.91, 1.01)
Loop		
Furosemide	212020 (14.6)	1.19 (1.16, 1.22)
Bumetanide	26599 (1.72)	1.19 (1.13, 1.26)
Potassium-sparing		
Spirolactone	40645 (2.62)	1.17 (1.12, 1.23)
Amiloride	8055 (0.52)	1.15 (1.05, 1.26)

^aExclusion criteria was implemented for all drugs at the same time. Models adjusted for age at start of follow-up, sex, general practice, socioeconomic status, number of general practice visits one year prior to start of follow-up, influenza vaccination one year prior to start of follow-up, chronic kidney disease, and all antihypertensive drug classes