

Antihypertensive Medication Patterns in Patients With Hypertension That Is Harder to Control: Insights From the EnligHTN Study

Jesper N. Bech,^{1*} Terry McCormack,² Vivek Bhalla,^{3,4} Naomi R. Ben Dor,⁵⁻⁷ Julian Segura,⁸ Søren Hougaard Christiansen,⁹ Ina T. Andersen,⁹ Clement Erhard,¹⁰ Kirsty M. Rhodes,¹¹ Tom Norris,¹² Esteban Coto,¹³ Joachim Weil¹⁴

Affiliations:

1. University Clinic in Nephrology and Hypertension, Gødstrup Hospital and Aarhus University, Herning, Denmark
2. Institute of Clinical and Applied Health Research, Hull York Medical School, Hull, United Kingdom
3. Stanford Hypertension Center, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
4. Division of Nephrology, Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA
5. Tau-AZ Beam, Ramat Aviv, Tel Aviv, Israel
6. Nephrology and Hypertension Center, Beilinson Hospital, Petah Tikva, Israel
7. Meuhedet Health Services, Tel Aviv, Israel
8. Hypertension Unit, Department of Nephrology, Hospital Universitario 12 de Octubre, Madrid, Spain
9. Department of Clinical Epidemiology, Aarhus University and Aarhus University Hospital, Aarhus N, Denmark

10. BioPharmaceuticals Medical Evidence Real World Data Science, AstraZeneca,
Cambridge, United Kingdom
11. BioPharmaceuticals Medical Evidence Statistics, AstraZeneca, Cambridge, United
Kingdom
12. Cardiovascular, Renal and Metabolism Evidence Strategy, BioPharmaceuticals Medical,
AstraZeneca, Gothenburg, Sweden
13. Cardiovascular, Renal and Metabolism, BioPharmaceuticals Medical, AstraZeneca,
Gaithersburg, MD, USA
14. Medizinische Klinik II, Sana Kliniken Lübeck GmbH, Lübeck, Germany

*Corresponding author

Corresponding author e-mail address: Jesper.noergaard.bech@goedstrup.rm.dk

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Supplementary Methods

Data Sources

The original data sources for each country included in this analysis were: IQVIA Ambulatory electronic medical records (EMR)-US linked with IQVIA PharMetrics® Plus Closed Health Plan claims (United States); Clinical Practice Research Datalink Aurum database linked to Hospital Episode Statistics and Office for National Statistics (United Kingdom); IQVIA™ Disease Analyzer database (Germany); Meuhedet Health Services database (Israel); Teletrón longitudinal EMR database (Spain); Danish Civil Registration System, Danish National Patient Registry, Danish National Prescription Registry, Register of Laboratory Results for Research, and EMR based in the Central Denmark Region (Denmark).

Additional Eligibility Criteria

Only a hospital hypertension diagnosis code was accepted for patients from Denmark; for all other countries, hospital and non-hospital hypertension diagnosis codes were accepted. The prescription of the third antihypertensive had to have been after the hypertension diagnosis; however, the two antihypertensive drug regimens could have been initiated either before or after the hypertension diagnosis. Patients could have initiated antihypertensive treatment prior to a hypertension diagnosis due to related comorbidities such as chronic kidney disease or heart failure. Patients from Denmark could have also received antihypertensive treatment before a hospital hypertension diagnosis was received, since hypertension is primarily managed by general practitioners. A stable regimen of two drugs was defined as ≥ 2 fills/prescriptions/dispensations of the same two drugs and remaining on the same two drugs once the third antihypertensive class was added to the regimen.

Diagnostic, Laboratory, and Medication Codes

Comorbidities during the baseline period were defined using either International Classification of Disease (versions 9 and 10) or Read diagnosis codes. Laboratory data values that were dated closest to index (including ≤ 14 days after index for all countries except Denmark) were extracted for analyses. Laboratory values were based on either Logical Observation Identifier Names and Codes, Systematized Nomenclature of Medicine – Clinical Terms or Read Codes, or Nomenclature for Properties and Units codes. Anatomical Therapeutic Chemical Classification System, National Drug Code Directory medication codes, and Clinical Practice Research Datalink product codes were used for coding of medications (available on request).

Prescription Overlap and Grace Period

If a prescription was refilled prior to the last day of available supply and the overlap was $\leq 25\%$, the supply of the refill was pushed to start at the end of the available supply; however, if the overlap was $>25\%$ then the longest prescription's start and end date was used. If a patient did not refill their prescription before the end of their available supply (allowing a 30-day grace period between refills), the dose was considered zero from after the last day of available supply (i.e., without a grace period) until end of follow-up.

Medication Dose Classification

A global dose schema was created across the countries in order to standardize actual antihypertensive medication doses prescribed to patients. Input on prescribed doses was received from clinical experts practicing in each of the included countries and combined into a single schema, which categorized doses into 'low/usual/maximum (max)' (see **Table 1**). If discrepancies were observed between countries, the majority categorization was used.

Dose and Discontinuation Plots

Using the aforementioned global schema, a 365-day dose matrix was created with 365 columns (one for each day of follow up), and rows equal to the number of patients included (see example matrix shown below). For each day of treatment, each patient was defined as being on a 'low/usual/max' dose in accordance with the global schema. Using this matrix, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated for each type of antihypertensive medication class included in this analysis.

ID	Drug (class agent)	Day				
		1	2	3	...	365
ID_1	ACEi – captopril	low	low	low	low	max
ID_2	ACEi – enalapril	low	low	low	low	discontinued
ID_3	MRA – spironolactone	low	low	low	low	NA
ID_N	CCB – nifedipine	usual	usual	usual	usual	max

Supplementary Tables

Table S1. Common antihypertensives received as part of stable two-drug regimen at baseline in patients with harder-to-control hypertension by country and third antihypertensive class

Common antihypertensives as part of stable regimen at baseline	US					
	ACEi (n = 398)	ARB (n = 550)	CCB (n = 1269)	BB (n = 1550)	Diuretics (n = 1555)	MRA (n = 318)
Monotherapies, n (%)						
ACEi	0 (0.0)	71 (12.9)	277 (21.8)	353 (22.8)	518 (33.3)	70 (22.0)
ARB	36 (9.0)	0 (0.0)	336 (26.5)	393 (25.4)	577 (37.1)	98 (30.8)
CCB	165 (41.5)	221 (40.2)	0 (0.0)	439 (28.3)	638 (41.0)	54 (17.0)
BB	227 (57.0)	334 (60.7)	423 (33.3)	0 (0.0)	909 (58.5)	171 (53.8)
Diuretics	207 (52.0)	263 (47.8)	327 (25.8)	523 (33.7)	0 (0.0)	127 (39.9)
MRA	26 (6.5)	46 (8.4)	24 (1.9)	99 (6.4)	77 (5.0)	0 (0.0)
Combination therapies ^a , n (%)						
ACEi with CCB	0 (0.0)	2 (0.4)	0 (0.0)	52 (3.4)	64 (4.1)	3 (0.9)
ACEi with thiazide diuretic	NA	NA	NA	NA	NA	NA
ACEi with diuretic	0 (0.0)	18 (3.3)	204 (16.1)	215 (13.9)	0 (0.0)	26 (8.2)
ACEi with other medication classes	NA	NA	NA	NA	NA	NA

ARB with CCB	1 (0.3)	0 (0.0)	0 (0.0)	26 (1.7)	20 (1.3)	1 (0.3)
ARB with thiazide diuretic	NA	NA	NA	NA	NA	NA
ARB with diuretic	13 (3.3)	0 (0.0)	301 (23.7)	274 (17.7)	0 (0.0)	18 (5.7)
BB with CCB	NA	NA	NA	NA	NA	NA
BB with diuretic	20 (5.0)	21 (3.8)	21 (1.7)	0 (0.0)	0 (0.0)	3 (0.9)
BB with thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with non-thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with other medication classes	NA	NA	NA	NA	NA	NA
MRA with diuretic	1 (0.3)	4 (0.7)	4 (0.3)	2 (0.1)	0 (0.0)	0 (0.0)
Potassium-sparing diuretic with thiazide diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with loop diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with other diuretic	NA	NA	NA	NA	NA	NA

Common antihypertensives as part of stable regimen at baseline	UK					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(n = 2876)	(n = 1871)	(n = 4575)	(n = 3930)	(n = 9100)	(n = 630)
Monotherapies, n (%)						
ACEi	NA	1176 (62.9)	3083 (67.4)	2553 (65.0)	5798 (63.7)	339 (53.8)

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ARB	123 (4.3)	NA	1173 (25.6)	933 (23.7)	1919 (21.1)	104 (16.5)
CCB	2416 (84.0)	1438 (76.9)	NA	3095 (78.8)	6980 (76.7)	169 (26.8)
BB	1375 (47.8)	492 (26.3)	2656 (58.1)	NA	2440 (26.8)	379 (60.2)
Diuretics	1290 (44.9)	415 (22.2)	1505 (32.9)	861 (21.9)	453 (5.0)	222 (35.2)
MRA	42 (1.5)	20 (1.1)	52 (1.1)	73 (1.9)	98 (1.1)	NA
Combination therapies ^a , <i>n</i> (%)						
ACEi with CCB	NA	NA	NA	NA	4 (0.0)	NA
ACEi with thiazide diuretic	NA	1 (0.1)	28 (0.6)	3 (0.1)	1 (0.0)	NA
ACEi with diuretic	NA	NA	NA	NA	NA	NA
ACEi with other medication classes	NA	NA	NA	NA	NA	NA
ARB with CCB	2 (0.1)	NA	NA	6 (0.2)	5 (0.1)	NA
ARB with thiazide diuretic	2 (0.1)	NA	81 (1.8)	23 (0.6)	12 (0.1)	NA
ARB with diuretic	NA	NA	NA	NA	NA	NA
BB with CCB	2 (0.1)	NA	NA	NA	1 (0.0)	NA
BB with diuretic	NA	NA	NA	NA	NA	NA
BB with thiazide diuretic	NA	NA	NA	NA	1 (0.0)	NA
BB with non-thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with other medication classes	NA	NA	NA	NA	NA	NA

MRA with diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with thiazide diuretic	4 (0.1)	NA	9 (0.2)	1 (0.0)	3 (0.0)	NA
Potassium-sparing diuretic with loop diuretic	7 (0.2)	NA	15 (0.3)	1 (0.0)	2 (0.0)	NA
Potassium-sparing diuretic with other diuretic	NA	NA	NA	NA	NA	NA

Common antihypertensives as part of stable regimen at baseline	Germany					
	ACEi (n = 2648)	ARB (n = 2432)	CCB (n = 9952)	BB (n = 7617)	Diuretics (n = 7892)	MRA (n = 1384)
Monotherapies, n (%)						
ACEi	0 (0.0)	400 (16.4)	3546 (35.6)	2150 (28.2)	3724 (47.2)	512 (37.0)
ARB	100 (3.8)	0 (0.0)	2150 (21.6)	1229 (16.1)	2249 (28.5)	256 (18.5)
CCB	1029 (38.9)	980 (40.3)	0 (0.0)	2191 (28.8)	2972 (37.7)	222 (16.0)
BB	1673 (63.2)	1433 (58.9)	4792 (48.2)	0 (0.0)	4225 (53.5)	795 (57.4)
Diuretics	1100 (41.5)	765 (31.5)	1218 (12.2)	1363 (17.9)	0 (0.0)	518 (37.4)
MRA	160 (6.0)	122 (5.0)	77 (0.8)	253 (3.3)	226 (2.9)	0 (0.0)
Combination therapies ^a , n (%)						
ACEi with CCB	0 (0.0)	35 (1.4)	0 (0.0)	481 (6.3)	399 (5.1)	30 (2.2)
ACEi with thiazide diuretic	NA	NA	NA	NA	NA	NA

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ACEi with diuretic	0 (0.0)	104 (4.3)	1799 (18.1)	1533 (20.1)	0 (0.0)	63 (4.6)
ACEi with other medication classes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
ARB with CCB	15 (0.6)	0 (0.0)	0 (0.0)	453 (5.9)	399 (5.1)	26 (1.9)
ARB with thiazide diuretic	NA	NA	NA	NA	NA	NA
ARB with diuretic	37 (1.4)	0 (0.0)	1802 (18.1)	1335 (17.5)	0 (0.0)	71 (5.1)
BB with CCB	19 (0.7)	11 (0.5)	0 (0.0)	0 (0.0)	26 (0.3)	0 (0.0)
BB with diuretic	NA	NA	NA	NA	NA	NA
BB with thiazide diuretic	336 (12.7)	269 (11.1)	269 (2.7)	0 (0.0)	200 (2.5)	11 (0.8)
BB with non-thiazide diuretic	17 (0.6)	8 (0.3)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
BB with other medication classes	1 (0)	1 (0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
MRA with diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with thiazide diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with loop diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with other diuretic	74 (2.8)	56 (2.3)	26 (0.3)	82 (1.1)	0 (0.0)	6 (0.4)

Spain

Common antihypertensives as part of stable regimen at baseline	ACEi (n = 81)	ARB (n = 38)	CCB (n = 482)	BB (n = 299)	Diuretics (n = 226)	MRA (n = 27)
Monotherapies, n (%)						
ACEi	0 (0.0)	6 (15.8)	56 (11.6)	48 (16.1)	74 (32.7)	6 (22.2)
ARB	8 (9.9)	0 (0.0)	42 (8.7)	30 (10.0)	54 (23.9)	5 (18.5)
CCB	16 (19.8)	5 (13.2)	0 (0.0)	19 (6.4)	58 (25.7)	2 (7.4)
BB	42 (51.9)	19 (50.0)	47 (9.8)	0 (0.0)	93 (41.2)	16 (59.3)
Diuretics	30 (37.0)	9 (23.7)	29 (6.0)	47 (15.7)	0 (0.0)	10 (37.0)
MRA	5 (6.2)	3 (7.9)	3 (0.6)	9 (3.0)	19 (8.4)	0 (0.0)
Combination therapies ^a , n (%)						
ACEi with CCB	0 (0.0)	2 (5.3)	0 (0.0)	21 (7.0)	36 (15.9)	1 (3.7)
ACEi with thiazide diuretic	NA	NA	NA	NA	NA	NA
ACEi with diuretic	0 (0.0)	1 (2.6)	167 (34.7)	68 (22.7)	0 (0.0)	0 (0.0)
ACEi with other medication classes	NA	NA	NA	NA	NA	NA
ARB with CCB	2 (2.5)	0 (0.0)	0 (0.0)	28 (9.4)	10 (4.4)	2 (7.4)
ARB with thiazide diuretic	NA	NA	NA	NA	NA	NA
ARB with diuretic	9 (11.1)	0 (0.0)	212 (44.0)	98 (32.8)	0 (0.0)	2 (7.4)
BB with CCB	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)
BB with diuretic	4 (4.9)	7 (18.4)	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)

BB with thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with non-thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with other medication classes	NA	NA	NA	NA	NA	NA
MRA with diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with thiazide diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with loop diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with other diuretic	NA	NA	NA	NA	NA	NA

Common antihypertensives as part of stable regimen at baseline	Israel					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(n = 86)	(n = 40)	(n = 167)	(n = 235)	(n = 158)	(n = 35)

Monotherapies, n (%)

ACEi	0 (0.0)	10 (25.0)	33 (19.8)	32 (13.6)	38 (24.1)	17 (48.6)
ARB	10 (11.6)	0 (0.0)	22 (13.2)	15 (6.4)	26 (16.5)	9 (25.7)
CCB	21 (24.4)	16 (40.0)	0 (0.0)	31 (13.2)	25 (15.8)	2 (5.7)
BB	43 (50.0)	27 (67.5)	45 (26.9)	0 (0.0)	51 (32.3)	26 (74.3)
Diuretics	7 (8.1)	1 (2.5)	1 (0.6)	5 (2.1)	0 (0.0)	1 (2.9)
MRA	4 (4.7)	4 (10.0)	3 (1.8)	2 (0.9)	7 (4.4)	0 (0.0)

Combination therapies^a, *n* (%)

ACEi with CCB	0 (0.0)	1 (2.5)	0 (0.0)	19 (8.1)	18 (11.4)	0 (0.0)
ACEi with thiazide diuretic	NA	NA	NA	NA	NA	NA
ACEi with diuretic	0 (0.0)	4 (10.0)	52 (31.1)	41 (17.4)	0 (0.0)	0 (0.0)
ACEi with other medication classes	NA	NA	NA	NA	NA	NA
ARB with CCB	26 (30.2)	0 (0.0)	0 (0.0)	76 (32.3)	57 (36.1)	6 (17.1)
ARB with thiazide diuretic	NA	NA	NA	NA	NA	NA
ARB with diuretic	10 (11.6)	0 (0.0)	53 (31.7)	46 (19.6)	0 (0.0)	1 (2.9)
BB with CCB	NA	NA	NA	NA	NA	NA
BB with diuretic	NA	NA	NA	NA	NA	NA
BB with thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with non-thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with other medication classes	NA	NA	NA	NA	NA	NA
MRA with diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with thiazide diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with loop diuretic	NA	NA	NA	NA	NA	NA

Potassium-sparing diuretic with
other diuretic

0 (0.0)

0 (0.0)

0 (0.0)

0 (0.0)

0 (0.0)

0 (0.0)

Common antihypertensives as part of stable regimen at baseline	Denmark ^b					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(n = 60)	(n = 160)	(n = 500)	(n = 465)	(n = 485)	(n = 410)
Monotherapies, n (%)						
ACEi	5 (8)	35 (22)	135 (27)	125 (27)	145 (30)	115 (28)
ARB	10 (17)	5 (3)	215 (43)	230 (49)	295 (61)	185 (45)
CCB	40 (67)	100 (63)	5 (1)	270 (58)	365 (75)	175 (43)
BB	35 (58)	85 (53)	230 (46)	5 (1)	135 (28)	155 (38)
Diuretics	35 (58)	75 (47)	150 (30)	130 (28)	5 (1)	130 (32)
MRA	5 (8)	10 (6)	10 (2)	15 (3)	10 (2)	5 (1)
Combination therapies ^a , n (%)						
ACEi with CCB	NA	NA	NA	NA	NA	NA
ACEi with thiazide diuretic	NA	NA	NA	NA	NA	NA
ACEi with diuretic	5 (8)	5 (3)	30 (6)	25 (5)	5 (1)	5 (1)
ACEi with other medication classes	NA	NA	NA	NA	NA	NA
ARB with CCB	NA	NA	NA	NA	NA	NA
ARB with thiazide diuretic	NA	NA	NA	NA	NA	NA

ARB with diuretic	5 (8)	5 (3)	85 (17)	50 (11)	5 (1)	25 (6)
BB with CCB	NA	NA	NA	NA	NA	NA
BB with diuretic	NA	NA	NA	NA	NA	NA
BB with thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with non-thiazide diuretic	NA	NA	NA	NA	NA	NA
BB with other medication classes	NA	NA	NA	NA	NA	NA
MRA with diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with thiazide diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with loop diuretic	NA	NA	NA	NA	NA	NA
Potassium-sparing diuretic with other diuretic	NA	NA	NA	NA	NA	NA

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor antagonists, *NA* not applicable, *UK* United Kingdom, *US* United States

^aCombination therapies that are available vary between countries; therefore, combinations that are not prescribed to patients within a certain country are denoted with NA

^bData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S2. Dose category of third medication at index in patients with harder-to-control hypertension by country and third antihypertensive class

Dose category of third antihypertensive class at index at class level, <i>n</i> (%)	US					
	ACEi (<i>n</i> = 398)	ARB (<i>n</i> = 550)	CCB (<i>n</i> = 1269)	BB (<i>n</i> = 1550)	Diuretics (<i>n</i> = 1488)	MRA (<i>n</i> = 317)
Max dose	93 (23.4)	144 (26.2)	279 (22.0)	238 (15.4)	458 (30.8)	47 (14.8)
Usual dose	198 (49.7)	42 (7.6)	30 (2.4)	429 (27.7)	132 (8.9)	222 (70.0)
Low dose	107 (26.9)	291 (52.9)	958 (75.5)	883 (57.0)	898 (60.3)	48 (15.1)
Missing dose	0 (0.0)	73 (13.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)

Dose category of third antihypertensive class at index at class level, <i>n</i> (%)	UK					
	ACEi (<i>n</i> = 2876)	ARB (<i>n</i> = 1871)	CCB (<i>n</i> = 4575)	BB (<i>n</i> = 3930)	Diuretics (<i>n</i> = 9100)	MRA (<i>n</i> = 630)
Max dose	280 (9.7)	211 (11.3)	626 (13.7)	150 (3.8)	2821 (31.0)	25 (4.0)
Usual dose	404 (14.0)	90 (4.8)	123 (2.7)	260 (6.6)	395 (4.3)	405 (64.3)
Low dose	2192 (76.2)	1570 (83.9)	3826 (83.6)	3520 (89.6)	5884 (64.7)	200 (31.7)
Missing dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Dose category of third antihypertensive class at index at class level, <i>n</i> (%)	Germany					
	ACEi (<i>n</i> = 2648)	ARB (<i>n</i> = 2432)	CCB (<i>n</i> = 9947)	BB (<i>n</i> = 7617)	Diuretics (<i>n</i> = 7866)	MRA (<i>n</i> = 1384)

Max dose	751 (28.4)	607 (25.0)	2451 (24.6)	1040 (13.7)	3874 (49.1)	34 (2.5)
Usual dose	1254 (47.4)	805 (33.1)	199 (2.0)	1372 (18.0)	553 (7.0)	1208 (87.3)
Low dose	643 (24.3)	1020 (41.9)	7297 (73.3)	5205 (68.3)	3439 (43.6)	142 (10.3)
Missing dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Dose category of third antihypertensive class at index at class level, <i>n</i> (%)	Spain					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(<i>n</i> = 81)	(<i>n</i> = 38)	(<i>n</i> = 482)	(<i>n</i> = 299)	(<i>n</i> = 226)	(<i>n</i> = 27)
Max dose	24 (29.6)	5 (13.2)	129 (26.8)	39 (13.0)	76 (33.6)	0 (0.0)
Usual dose	17 (21.0)	10 (26.3)	34 (7.1)	35 (11.7)	20 (8.9)	18 (66.7)
Low dose	40 (49.4)	23 (60.5)	319 (66.2)	225 (75.3)	130 (57.5)	9 (33.3)
Missing dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Dose category of third antihypertensive class at index at class level, <i>n</i> (%)	Israel					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(<i>n</i> = 86)	(<i>n</i> = 40)	(<i>n</i> = 167)	(<i>n</i> = 235)	(<i>n</i> = 158)	(<i>n</i> = 35)
Max dose	3 (3.5)	3 (7.5)	38 (22.8)	9 (3.8)	93 (58.9)	6 (17.1)
Usual dose	60 (69.8)	19 (47.5)	128 (76.6)	27 (11.5)	65 (41.1)	29 (82.9)
Low dose	23 (26.7)	18 (45.0)	0 (0.0)	199 (84.7)	0 (0.0)	0 (0.0)
Missing dose	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Denmark ^a						
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Dose category of third antihypertensive class at index at class level, <i>n</i> (%)	ACEi (<i>n</i> = 65)	ARB (<i>n</i> = 170)	CCB (<i>n</i> = 500)	BB (<i>n</i> = 465)	Diuretics (<i>n</i> = 485)	MRA (<i>n</i> = 410)
Max dose	5 (8)	20 (13)	45 (9)	30 (6)	5 (1)	5 (1)
Usual dose	25 (42)	5 (3)	5 (1)	20 (4)	10 (2)	355 (87)
Low dose	35 (58)	145 (91)	450 (90)	415 (89)	470 (97)	50 (12)
Missing dose	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor antagonists, *UK* United Kingdom, *US* United States

Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Differences in drug cohort total numbers versus other tables are due to missing dose data, or in the case of Denmark, a result of rounding procedures taken to ensure General Data Protection Regulation compliance

^aData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S3. Clinical characteristics at baseline by country and third antihypertensive class in patients who were excluded from the study due to discontinuation of one of the two pre-index date stable regimen drugs before discontinuation of the third drug

Characteristics at baseline	US					
	ACEi (n = 717)	ARB (n = 1571)	CCB (n = 1903)	BB (n = 1767)	Diuretics (n = 1368)	MRA (n = 323)
Demographics						
Age, mean (SD), years	57.0 (12.0)	57.5 (11.3)	57.6 (11.3)	57.9 (12.3)	59.8 (12.2)	56.7 (13.5)
Male sex, n (%)	368 (51.3)	777 (49.5)	999 (52.5)	907 (51.3)	721 (52.7)	115 (35.6)
Female sex, n (%)	349 (48.7)	794 (50.5)	904 (47.5)	860 (48.7)	647 (47.3)	208 (64.4)
BMI (kg/m ²), mean (SD)	33.0 (7.7)	32.5 (7.1)	32.6 (7.4)	32.9 (7.5)	33.1 (7.7)	33.5 (8.2)
Physiological measurements						
SBP (mmHg), mean (SD)	136.5 (18.5)	135.9 (17.6)	138.8 (18.9)	133.6 (17.4)	136.1 (18.4)	130.6 (18.2)
DBP (mmHg), mean (SD)	81.7 (11.3)	81.8 (11.1)	83.4 (11.8)	80.4 (10.9)	80.6 (11.7)	79.5 (12.0)
BP missing, n (%)	91 (12.7)	156 (9.9)	204 (10.7)	191 (10.8)	164 (12.0)	33 (10.2)
Below country-specific BP goal ^a , n (%)	142 (19.8)	324 (20.6)	326 (17.1)	425 (24.1)	307 (22.4)	91 (28.2)
eGFR (mL/min/1.73 m ²), mean (SD)	79.7 (22.6)	80.5 (19.9)	77.7 (22.2)	77.2 (23.4)	75.2 (22.9)	78.7 (21.5)
Comorbidities of interest, n (%)						
Heart failure	87 (12.1)	170 (10.8)	120 (6.3)	250 (14.1)	261 (19.1)	107 (33.1)
Chronic kidney disease	141 (19.7)	304 (19.4)	388 (20.4)	431 (24.4)	355 (26.0)	78 (24.1)

Myocardial infarction	68 (9.5)	141 (9.0)	134 (7.0)	173 (9.8)	143 (10.5)	42 (13.0)
Stroke – ischemic	26 (3.6)	56 (3.6)	68 (3.6)	54 (3.1)	70 (5.1)	8 (2.5)
Stroke – hemorrhagic	43 (6.0)	83 (5.3)	95 (5.0)	93 (5.3)	98 (7.2)	12 (3.7)
Type 2 diabetes	223 (31.1)	384 (24.4)	538 (28.3)	577 (32.7)	475 (34.7)	100 (31.0)
Hyperkalemia	27 (3.8)	42 (2.7)	61 (3.2)	55 (3.1)	58 (4.2)	12 (3.7)
Hypokalemia	45 (6.3)	78 (5.0)	93 (4.9)	99 (5.6)	74 (5.4)	45 (13.9)
Secondary hyperaldosteronism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)

Characteristics at baseline	UK					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(n = 4954)	(n = 7196)	(n = 5780)	(n = 4024)	(n = 8111)	(n = 618)

Demographics

Age, mean (SD), years	64.5 (13.1)	61.1 (12.7)	62.0 (13.7)	61.8 (14.6)	62.3 (14.5)	66.0 (15.0)
Male sex, <i>n</i> (%)	2421 (48.9)	3275 (45.5)	2997 (51.9)	2050 (50.9)	4062 (50.1)	361 (58.4)
Female sex, <i>n</i> (%)	2533 (51.1)	3921 (54.5)	2783 (48.1)	1974 (49.1)	4049 (49.9)	257 (41.6)
BMI (kg/m ²), mean (SD)	30.6 (7.0)	30.6 (6.5)	30.5 (6.5)	30.2 (6.6)	31.6 (7.3)	30.4 (7.7)

Physiological measurements

SBP (mmHg), mean (SD)	146.8 (18.4)	143.4 (16.8)	152.1 (19.8)	142.0 (19.1)	146.5 (18.0)	137.5 (20.9)
DBP (mmHg), mean (SD)	84.3 (12.4)	84.0 (11.3)	87.7 (13.1)	83.7 (12.6)	85.0 (12.6)	80.1 (13.5)
BP missing, <i>n</i> (%)	139 (2.8)	191 (2.7)	186 (3.2)	158 (3.9)	247 (3.0)	33 (5.3)

Below country-specific BP goal ^a , <i>n</i> (%)	1688 (34.1)	3051 (42.4)	1426 (24.7)	1825 (45.4)	2708 (33.4)	324 (52.4)
eGFR (mL/min/1.73 m ²), mean (SD)	82.1 (19.3)	86.3 (17.7)	83.4 (20.7)	84.0 (20.9)	83.6 (20.2)	78.7 (21.4)
Comorbidities of interest, <i>n</i> (%)						
Heart failure	311 (6.3)	169 (2.3)	240 (4.2)	363 (9.0)	477 (5.9)	252 (40.8)
Chronic kidney disease	2555 (51.6)	3726 (51.8)	3251 (56.2)	2155 (53.6)	4445 (54.8)	392 (63.4)
Myocardial infarction	153 (3.1)	269 (3.7)	471 (8.1)	327 (8.1)	212 (2.6)	67 (10.8)
Stroke – ischemic	186 (3.8)	222 (3.1)	182 (3.1)	143 (3.6)	304 (3.7)	38 (6.1)
Stroke – hemorrhagic	108 (2.2)	127 (1.8)	102 (1.8)	111 (2.8)	196 (2.4)	28 (4.5)
Type 2 diabetes	700 (14.1)	1002 (13.9)	1221 (21.1)	759 (18.9)	1390 (17.1)	122 (19.7)
Hyperkalemia	66 (1.3)	54 (0.8)	92 (1.6)	68 (1.7)	127 (1.6)	8 (1.3)
Hypokalemia	113 (2.3)	91 (1.3)	88 (1.5)	68 (1.7)	116 (1.4)	59 (9.5)
Secondary hyperaldosteronism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Characteristics at baseline	Germany					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(<i>n</i> = 3156)	(<i>n</i> = 5651)	(<i>n</i> = 9168)	(<i>n</i> = 8855)	(<i>n</i> = 7404)	(<i>n</i> = 1509)

Demographics

Age, mean (SD), years	71.9 (12.7)	67.0 (12.9)	68.4 (12.7)	69.4 (13.2)	71.2 (13.3)	72.0 (12.7)
Male sex, <i>n</i> (%)	1602 (50.8)	2754 (48.7)	4620 (50.4)	4660 (52.6)	3741 (50.5)	842 (55.8)
Female sex, <i>n</i> (%)	1554 (49.2)	2897 (51.3)	4548 (49.6)	4195 (47.4)	3663 (49.5)	667 (44.2)

EnligHTN Medication Patterns

Supplementary Material

BMI (kg/m ²), mean (SD)	29.6 (6.5)	29.4 (5.8)	30.0 (6.1)	30.1 (6.0)	30.1 (6.0)	29.7 (6.4)
Physiological measurements						
SBP (mmHg), mean (SD)	140.2 (20.9)	145.1 (22.1)	150.8 (24.5)	140.7 (22.0)	143.3 (22.2)	138.0 (22.2)
DBP (mmHg), mean (SD)	81.4 (11.5)	83.9 (12.0)	85.8 (13.2)	82.1 (12.5)	82.6 (12.5)	79.7 (12.7)
BP missing, <i>n</i> (%)	2553 (80.9)	4478 (79.2)	7256 (79.1)	7126 (80.5)	5955 (80.4)	1200 (79.5)
Below country-specific BP goal ^a , <i>n</i> (%)	251 (8.0)	405 (7.2)	515 (5.6)	729 (8.2)	549 (7.4)	150 (9.9)
eGFR (mL/min/1.73 m ²), mean (SD)	71.6 (20.9)	77.8 (20.0)	76.6 (21.0)	73.5 (22.0)	73.9 (23.1)	69.8 (22.0)
Comorbidities of interest, <i>n</i> (%)						
Heart failure	479 (15.2)	422 (7.5)	528 (5.8)	970 (11.0)	1109 (15.0)	512 (33.9)
Chronic kidney disease	474 (15.0)	710 (12.6)	1211 (13.2)	1252 (14.1)	1102 (14.9)	290 (19.2)
Myocardial infarction	140 (4.4)	168 (3.0)	194 (2.1)	298 (3.4)	182 (2.5)	83 (5.5)
Stroke – ischemic	80 (2.5)	106 (1.9)	180 (2.0)	181 (2.0)	169 (2.3)	40 (2.7)
Stroke – hemorrhagic	26 (0.8)	22 (0.4)	51 (0.6)	36 (0.4)	30 (0.4)	5 (0.3)
Type 2 diabetes	587 (18.6)	789 (14.0)	1430 (15.6)	1593 (18.0)	1302 (17.6)	314 (20.8)
Hyperkalemia	11 (0.3)	8 (0.1)	34 (0.4)	22 (0.2)	35 (0.5)	6 (0.4)
Hypokalemia	43 (1.4)	36 (0.6)	63 (0.7)	85 (1.0)	59 (0.8)	50 (3.3)
Secondary hyperaldosteronism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Characteristics at baseline	Spain					
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	ACEi (n = 30)	ARB (n = 27)	CCB (n = 139)	BB (n = 106)	Diuretics (n = 92)	MRA (n = 14)
Demographics						
Age, mean (SD), years	71.3 (12.3)	65.7 (13.8)	61.5 (12.2)	66.6 (13.1)	67.6 (13.2)	66.1 (15.3)
Male sex, n (%)	21 (70.0)	13 (48.1)	93 (66.9)	65 (61.3)	52 (56.5)	10 (71.4)
Female sex, n (%)	9 (30.0)	14 (51.9)	46 (33.1)	41 (38.7)	40 (43.5)	4 (28.6)
BMI (kg/m ²), mean (SD)	27.5 (4.3)	31.3 (5.9)	30.4 (5.7)	29.5 (6.3)	30.0 (6.5)	27.6 (3.3)
Physiological measurements						
SBP (mmHg), mean (SD)	144.1 (24.3)	146.6 (22.0)	149.1 (22.6)	137.3 (19.6)	141.8 (22.5)	142.5 (19.8)
DBP (mmHg), mean (SD)	80.8 (13.6)	87.2 (15.4)	89.2 (12.3)	82.2 (13.0)	80.5 (13.4)	78.4 (12.5)
BP missing, n (%)	3 (10.0)	1 (3.7)	5 (3.6)	6 (5.7)	1 (1.1)	0 (0.0)
Below country-specific BP goal ^a , n (%)	11 (36.7)	9 (33.3)	34 (24.5)	50 (47.2)	39 (42.4)	5 (35.7)
eGFR (mL/min/1.73 m ²), mean (SD)	75.9 (25.3)	73.7 (23.5)	84.5 (17.0)	79.5 (18.9)	75.6 (22.3)	79 (24.8)
Comorbidities of interest, n (%)						
Heart failure	4 (13.3)	1 (3.7)	4 (2.9)	15 (14.1)	13 (14.1)	4 (28.6)
Chronic kidney disease	13 (43.3)	9 (33.3)	40 (28.8)	27 (25.5)	25 (27.2)	4 (28.57)
Myocardial infarction	4 (13.3)	1 (3.7)	5 (3.6)	8 (7.5)	12 (13.0)	1 (7.1)
Stroke – ischemic	0 (0.0)	0 (0.0)	3 (2.2)	3 (2.8)	6 (6.5)	0 (0.0)
Stroke – hemorrhagic	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.9)	0 (0.0)	0 (0.0)

Type 2 diabetes	5 (16.7)	4 (14.8)	27 (19.4)	19 (17.9)	20 (21.7)	0 (0.0)
Hyperkalemia	1 (3.3)	0 (0.0)	2 (1.4)	2 (1.9)	0 (0.0)	0 (0.0)
Hypokalemia	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Secondary hyperaldosteronism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Characteristics at baseline	Israel					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(n = 16)	(n = 73)	(n = 55)	(n = 75)	(n = 29)	(n = 20)

Demographics

Age, mean (SD), years	67.5 (12.9)	65.4 (11.8)	59.6 (13.6)	61.8 (11.9)	61.5 (18.8)	59.5 (11.8)
Male sex, <i>n</i> (%)	2 (12.5)	34 (46.6)	22 (40.0)	41 (54.7)	14 (48.3)	5 (25.0)
Female sex, <i>n</i> (%)	14 (87.5)	39 (53.4)	33 (60.0)	34 (45.3)	15 (51.7)	15 (75.0)
BMI (kg/m ²), mean (SD)	28.5 (4.2)	28.4 (4.1)	28.2 (5.1)	28.9 (5.0)	29.5 (3.6)	30.1 (4.3)

Physiological measurements

SBP (mmHg), mean (SD)	135.2 (21.8)	134.8 (21.9)	140.2 (20.0)	134.7 (19.5)	137.7 (23.4)	128.9 (18.4)
DBP (mmHg), mean (SD)	77.3 (8.8)	77.93 (12.5)	80.9 (13.3)	78.50 (11.8)	80.5 (15.7)	75.9 (11.6)
BP missing, <i>n</i> (%)	NA	NA	NA	NA	NA	NA
Below country-specific BP goal ^a , <i>n</i> (%)	7 (43.8)	40 (55.6)	22 (41.5)	34 (45.9)	12 (44.4)	13 (72.2)
eGFR (mL/min/1.73 m ²), mean (SD)	81.3 (19.4)	80.7 (17.2)	83.2 (18.6)	82.7 (20.9)	78.9 (24.3)	85.4 (19.7)

Comorbidities of interest, *n* (%)

Heart failure	3 (18.8)	7 (9.6)	1 (1.8)	10 (13.3)	1 (3.4)	5 (25.0)
Chronic kidney disease	11 (68.8)	46 (63.0)	27 (49.1)	44 (58.7)	16 (55.2)	7 (35.0)
Myocardial infarction	2 (12.5)	13 (17.8)	5 (9.1)	7 (9.3)	1 (3.4)	4 (20.0)
Stroke – ischemic	NA	NA	NA	NA	NA	NA
Stroke – hemorrhagic	NA	NA	NA	NA	NA	NA
Type 2 diabetes	8 (50.0)	17 (23.3)	9 (16.4)	29 (38.7)	6 (20.7)	9 (45.0)
Hyperkalemia	0 (0.0)	0 (0.0)	1 (1.8)	2 (2.7)	1 (3.4)	0 (0.0)
Hypokalemia	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.0)
Secondary hyperaldosteronism	NA	NA	NA	NA	NA	NA

Characteristics at baseline	Denmark ^b					
	ACEi	ARB	CCB	BB	Diuretics	MRA
	(n = 105)	(n = 375)	(n = 490)	(n = 525)	(n = 455)	(n = 405)

Demographics

Age, mean (SD), years	68 (16)	67 (13)	67 (12)	68 (13)	63 (14)	64 (14)
Male sex, <i>n</i> (%)	55 (52)	190 (51)	245 (50)	295 (56)	295 (65)	195 (48)
Female sex, <i>n</i> (%)	50 (48)	185 (49)	245 (50)	230 (44)	160 (35)	210 (52)
BMI (kg/m ²), mean (SD)	28 (6)	28 (5)	28 (6)	29 (9)	29 (13)	29 (6)

Physiological measurements

SBP (mmHg), mean (SD)	146 (24)	149 (23)	155 (23)	145 (23)	148 (22)	149 (25)
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DBP (mmHg), mean (SD)	84 (14)	84 (13)	112 (478)	85 (14)	85 (16)	86 (16)
BP missing, <i>n</i> (%)	35 (33)	135 (36)	150 (31)	105 (20)	165 (36)	110 (27)
Below country-specific BP goal ^a , <i>n</i> (%)	30 (40)	80 (33)	80 (24)	160 (38)	95 (33)	105 (36)
eGFR (mL/min/1.73 m ²), mean (SD)	75 (23)	78 (21)	79 (21)	77 (21)	83 (21)	80 (20)
Comorbidities of interest, <i>n</i> (%)						
Heart failure	15 (14)	25 (7)	15 (3)	45 (9)	15 (3)	50 (12)
Chronic kidney disease	80 (76)	270 (72)	365 (74)	395 (75)	295 (65)	300 (74)
Myocardial infarction	10 (10)	25 (7)	45 (9)	60 (11)	35 (8)	40 (10)
Stroke – ischemic	10 (10)	25 (7)	40 (8)	45 (9)	50 (11)	30 (7)
Stroke – hemorrhagic	5 (5)	10 (3)	20 (4)	10 (2)	5 (1)	5 (1)
Type 2 diabetes	15 (14)	70 (19)	100 (20)	105 (20)	65 (14)	105 (26)
Hyperkalemia	5 (5)	5 (1)	5 (1)	5 (1)	5 (1)	5 (1)
Hypokalemia	30 (29)	50 (13)	100 (20)	85 (16)	40 (9)	120 (30)
Secondary hyperaldosteronism	5 (5)	15 (4)	10 (2)	5 (1)	15 (3)	15 (4)

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *BMI* body mass index, *BP* blood pressure, *CCB* calcium channel blocker, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *MRA* mineralocorticoid receptor antagonists, *NA* not available, *SBP* systolic blood pressure, *SD* standard deviation, *UK* United Kingdom, *US* United States

^aBP targets were 130/80 mmHg for US patients, and 140/90 mmHg for all other patients

^bData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S4. Clinical characteristics at baseline in patients from Denmark with harder-to-control hypertension by third antihypertensive class (100-day grace period)

Characteristics at baseline	Denmark ^b					
	ACEi (n = 95)	ARB (n = 225)	CCB (n = 710)	BB (n = 620)	Diuretics (n = 680)	MRA (n = 445)
Demographics						
Age, mean (SD), years	72 (14)	70 (12)	69 (12)	68 (13)	65 (14)	66 (14)
Male sex, n (%)	45 (47)	105 (47)	365 (51)	355 (57)	430 (63)	230 (52)
Female sex, n (%)	50 (53)	120 (53)	345 (49)	265 (43)	250 (37)	215 (48)
BMI (kg/m ²), mean (SD)	28 (9)	28 (5)	30 (12)	29 (13)	29 (11)	30 (34)
Physiological measurements						
SBP (mmHg), mean (SD)	146 (23)	151 (23)	156 (24)	147 (23)	150 (24)	148 (24)
DBP (mmHg), mean (SD)	81 (15)	84 (14)	86 (15)	84 (13)	86 (16)	84 (15)
BP missing, n (%)	30 (32)	90 (40)	240 (34)	160 (26)	260 (38)	130 (29)
Below country-specific BP goal ^a , n (%)	25 (38)	40 (30)	105 (22)	175 (38)	120 (29)	100 (31)
eGFR (mL/min/1.73 m ²), mean (SD)	73 (22)	72 (23)	77 (20)	79 (20)	82 (19)	78 (21)
Comorbidities of interest, n (%)						
Heart failure	20 (21)	15 (7)	40 (6)	30 (5)	20 (3)	90 (20)

Chronic kidney disease	75 (79)	185 (82)	550 (77)	460 (74)	465 (68)	335 (75)
Myocardial infarction	15 (16)	20 (9)	65 (9)	50 (8)	45 (7)	35 (8)
Stroke – ischemic	15 (16)	25 (11)	75 (11)	55 (9)	90 (13)	30 (7)
Stroke – hemorrhagic	5 (5)	5 (2)	20 (3)	15 (2)	10 (1)	5 (1)
Type 2 diabetes	25 (26)	45 (20)	160 (23)	125 (20)	130 (19)	130 (29)
Hyperkalemia	5 (6)	5 (2)	10 (1)	5 (1)	5 (1)	5 (1)
Hypokalemia	25 (28)	30 (14)	130 (18)	95 (15)	55 (8)	100 (22)
Secondary hyperaldosteronism	5 (5)	10 (4)	15 (2)	10 (2)	20 (3)	10 (2)

ACEi angiotensin-converting enzyme inhibitors, ARB angiotensin-II receptor blocker, BB beta blocker, BMI body mass index, BP blood pressure; CCB calcium channel blocker, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, MRA mineralocorticoid receptor antagonists, NA not available, SBP systolic blood pressure, SD standard deviation

^aBP target was 140/90 mmHg

^bData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S5. Discontinuation of and adherence to third medication up to 24 months from index in patients from Denmark with harder-to-control hypertension by third antihypertensive class (100-day grace period)

	Denmark ^e					
	ACEi (<i>n</i> = 95)	ARB (<i>n</i> = 225)	CCB (<i>n</i> = 710)	BB (<i>n</i> = 620)	Diuretics (<i>n</i> = 680)	MRA (<i>n</i> = 445)
Persistence^a						
Discontinuation of third medication class up to 12 months ^b , %	46	39	35	43	42	48
Discontinuation of third medication class up to 24 months ^b , %	65	51	46	53	56	65
Time to discontinuation (years), median (25 th percentile, 75 th percentile)	1.4 (0.3, ∞)	1.8 (0.3, 5.7)	2.6 (0.6, 6.1)	1.6 (0.3, 6.2)	1.6 (0.3, 4.4)	1.1 (0.3, 3.2)
Discontinuation rate ^c (95% CI), person-years	0.5 (0.3–0.6)	0.4 (0.3–0.4)	0.3 (0.3–0.3)	0.4 (0.3–0.4)	0.4 (0.4–0.5)	0.5 (0.4–0.6)
Adherence^d						
At 6 months						
PDC, median (25 th percentile, 75 th percentile), %	100 (85, 100)	100 (87, 100)	100 (98, 100)	100 (61, 100)	100 (89, 100)	100 (57, 100)
PDC > 80%, <i>n</i> (%)	70 (74)	175 (78)	575 (81)	445 (72)	530 (78)	315 (71)

PDC > 50%, <i>n</i> (%)	90 (95)	220 (98)	685 (96)	580 (94)	675 (99)	435 (98)
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At 12 months

PDC, median (25 th percentile, 75 th percentile), %	100 (60, 100)	100 (66, 100)	100 (82, 100)	100 (55, 100)	100 (67, 100)	99 (55, 100)
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PDC > 80%, <i>n</i> (%)	65 (68)	165 (73)	545 (77)	410 (66)	495 (73)	295 (66)
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PDC > 50%, <i>n</i> (%)	75 (79)	180 (80)	600 (85)	485 (78)	555 (82)	355 (80)
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At 24 months

PDC, median (25 th percentile, 75 th percentile), %	100 (47, 100)	100 (58, 100)	100 (66, 100)	99 (41, 100)	99 (55, 100)	94 (55, 100)
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PDC > 80%, <i>n</i> (%)	65 (68)	160 (71)	505 (71)	390 (63)	465 (68)	265 (60)
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PDC > 50%, <i>n</i> (%)	70 (74)	175 (78)	570 (80)	440 (71)	525 (77)	340 (76)
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ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *CI* confidence interval, *MRA* mineralocorticoid receptor antagonists, *PDC* proportion of days covered

^aA one-pill-per-day dosage regimen was assumed for all third antihypertensive medications. If a prescription was refilled prior to the last day of available supply and the overlap was $\leq 25\%$, the supply of the refill was pushed to start at the end of the available supply; however, if the overlap was $> 25\%$ then the longest prescription's start and end date was used. If a new prescription at a different dose was collected, it was assumed that there was a switch in dose and the new dose was started at the date of collection. If a patient did not refill their prescription before the end of their available supply (allowing a 100-day grace period between refills), the dose was considered zero from after the last day of available supply (i.e., without a grace period) until end of follow-up

^bTime-to-event (i.e., discontinuation) was estimated with the Kaplan–Meier method; individuals without discontinuation (including those who were lost to follow-up, reached the end of observation without discontinuation, or who died) were right-censored at their last observed date

^cThe numerator was the number of patients with discontinuation (i.e., not number of discontinuation events), and the denominator was the patient-years at risk for (i.e., time to discontinuation or end of follow-up, whichever comes first)

^dAdherence was defined as the PDC during a fixed period, at 6, 12, and 24 months, starting from index date to end of follow-up. For individual drug classes,

'Covered' denoted the availability of the prescribed one-pill-per-day dose and was tracked using an array of days' supply for each fill. Each day in the denominator had a maximum of 1 day's supply, which prevented the PDC exceeding 100% if there were any prescription overlaps

^eData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S6. Blood pressure control at 12 and 24 months from index in patients from Denmark with harder-to-control hypertension by third antihypertensive class (100-day grace period)

	Denmark ^d					
	ACEi (n = 95)	ARB (n = 225)	CCB (n = 710)	BB (n = 620)	Diuretics (n = 680)	MRA (n = 445)
BP at 12 months						
Missing BP measurement at index or follow-up, n (%)	75 (79)	190 (84)	600 (85)	515 (83)	610 (90)	370 (83)
SBP (mmHg), median (25 th percentile, 75 th percentile)	NA	138 (127, 153)	140 (128, 152)	146 (133, 161)	140 (130, 155)	136 (123, 149)
DBP (mmHg), median (25 th percentile, 75 th percentile)	NA	75 (71, 84)	79 (72, 86)	81 (72, 88)	81 (75, 86)	77 (70, 84)
Time of 12-month BP measurement (years), median (25 th percentile, 75 th percentile)	NA	1.00 (0.92, 1.00)	1.00 (0.92, 1.08)	1.00 (0.83, 1.08)	1.00 (0.83, 1.08)	1.00 (0.92, 1.08)
Change in SBP from index to 12 months ^a (mmHg), median (25 th percentile, 75 th percentile)	NA	-8 (-18, 5)	-13 (-34, 1)	4 (-14, 17)	-12 (-31, 1)	-9 (-25, 11)

Change in DBP from index to 12

months^a (mmHg), median (25thpercentile, 75th percentile)

NA

−7 (−13, 4)

−6 (−17, 4)

−2 (−11, 6)

−7 (−15, 1)

−4 (−14, 6)

BP below goal^b, *n* (%)

10 (50)

25 (71)

65 (59)

45 (43)

45 (64)

50 (67)

BP at 24 months

Missing BP measurement at index or

follow-up, *n* (%)

NA

205 (91)

640 (90)

560 (90)

640 (94)

400 (90)

SBP (mmHg), median (25th percentile,75th percentile)

NA

NA

139 (129, 154)

140 (125, 158)

136 (124, 154)

141 (128, 156)

DBP (mmHg), median (25th percentile,75th percentile)

NA

NA

79 (71, 85)

78 (70, 87)

81 (72, 90)

78 (70, 93)

Time of 24-month BP measurement

(years), median (25th percentile, 75th

percentile)

NA

NA

2.00 (1.83,
2.08)2.00 (1.83,
2.08)2.00 (1.83,
2.08)2.00 (1.92,
2.08)

Change in SBP from index to 24

months^c (mmHg), median (25thpercentile, 75th percentile)

NA

NA

−14 (−36, 1)

−5 (−21, 11)

−11 (−32, 6)

−1 (−17, 8)

Change in DBP from index to 24

months^c (mmHg), median (25th

percentile, 75th percentile)

NA

NA

–6 (–20, 3)

–5 (–15, 5)

–4 (–12, 4)

–3 (–12, 6)

BP below goal^b, *n* (%)

NA

15 (75)

45 (64)

35 (58)

30 (75)

30 (67)

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *BP* blood pressure, *CCB* calcium channel blocker, *DBP* diastolic blood pressure, *mmHg* millimeters of mercury, *MRA* mineralocorticoid receptor antagonists, *SBP* systolic blood pressure

^aFor BP measurement at 12 months, measurements from 9 to < 15 months were used. If multiple BP measurements were available in the 9 to < 15-month period, the mean of BP measurement was used and the time of BP measurement set to the midpoint of the interval. Change in BP presented as 12-month BP measurement – index BP measurement

^bBP target was 140/90 mmHg

^cFor BP measurements at 24 months, measurements from 21 to < 27 months were used. If multiple BP measurements were available in the 21 to < 27-month period, the mean of BP measurement was used and the time of BP measurement set to the midpoint of the interval. Change in BP presented as 24-month BP measurement – index BP measurement

^dData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S7. Common antihypertensives received as part of stable two-drug regimen at baseline in patients from Denmark with harder-to-control hypertension by third antihypertensive class (100-day grace period)

Common antihypertensives as part of stable regimen at baseline	Denmark ^a					
	ACEi (n = 95)	ARB (n = 225)	CCB (n = 710)	BB (n = 620)	Diuretics (n = 680)	MRA (n = 445)
Monotherapies, n (%)						
ACEi	5 (5)	40 (18)	240 (34)	195 (31)	195 (29)	115 (26)
ARB	15 (16)	5 (2)	430 (61)	375 (60)	435 (64)	255 (57)
CCB	60 (63)	145 (64)	5 (1)	375 (60)	525 (77)	220 (49)
BB	55 (58)	125 (56)	325 (46)	5 (1)	170 (25)	150 (34)
Diuretics	50 (53)	110 (49)	375 (53)	260 (42)	5 (1)	145 (33)
MRA	5 (5)	10 (4)	10 (1)	15 (2)	5 (1)	5 (1)
Combination therapies, n (%)						
ACEi with diuretic	5 (5)	5 (2)	40 (6)	30 (5)	5 (1)	5 (1)
ARB with diuretic	5 (5)	5 (2)	110 (15)	60 (10)	5 (1)	20 (4)

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor antagonists

^aData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

Table S8. Dose category of third medication at index in patients from Denmark with harder-to-control hypertension by third antihypertensive class (100-day grace period)

Dose category at index at class level, <i>n</i> (%)	Denmark ^a					
	ACEi (<i>n</i> = 95)	ARB (<i>n</i> = 230)	CCB (<i>n</i> = 710)	BB (<i>n</i> = 625)	Diuretics (<i>n</i> = 685)	MRA (<i>n</i> = 450)
Max dose	5 (5)	25 (11)	60 (8)	35 (6)	5 (1)	5 (1)
Usual dose	35 (37)	5 (2)	5 (1)	25 (4)	15 (2)	385 (87)
Low dose	55 (58)	200 (87)	645 (91)	565 (90)	665 (97)	60 (13)
Missing dose	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

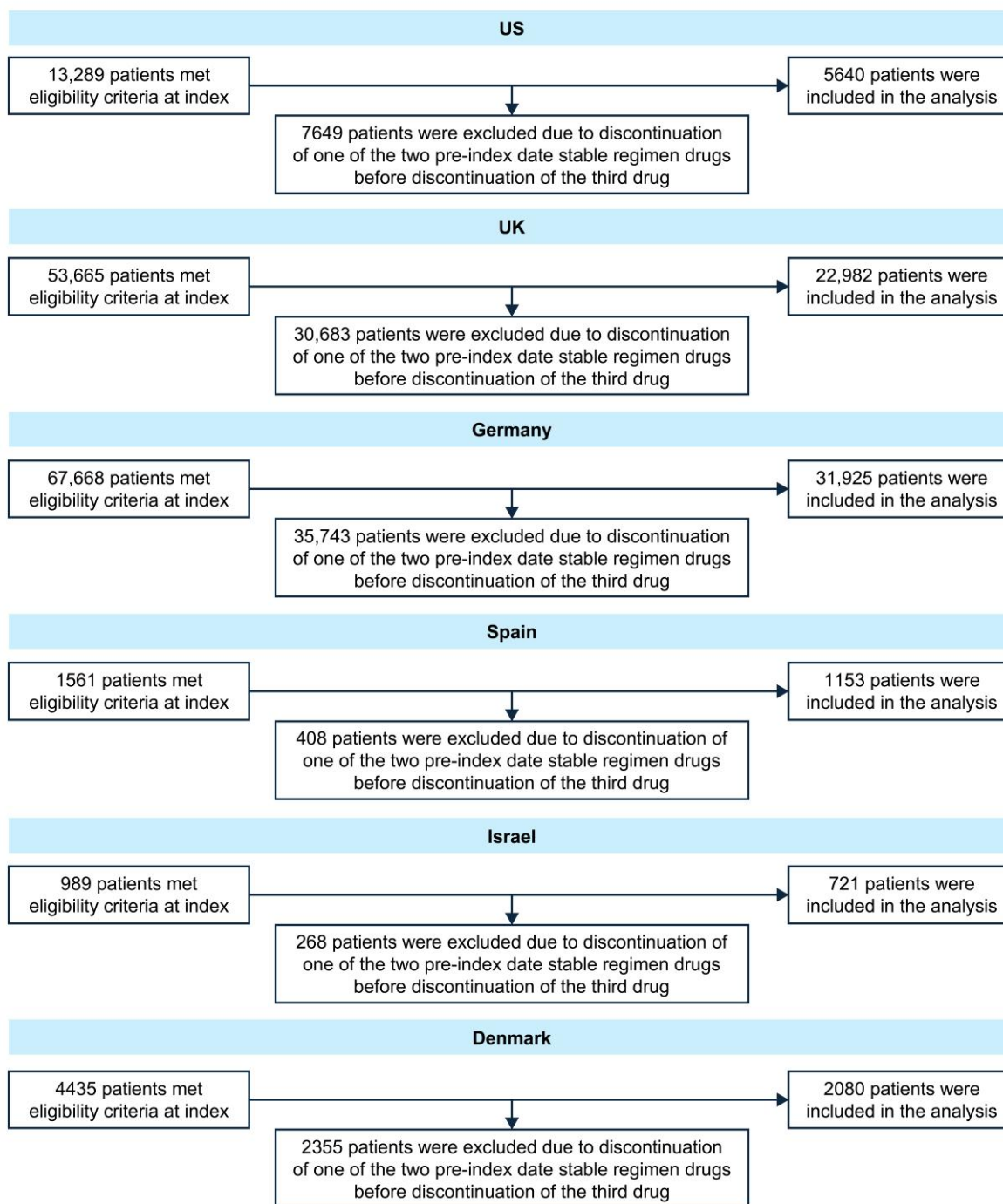
ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor antagonists

Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Differences in drug cohort total numbers versus other tables are due to the result of rounding procedures taken to ensure General Data Protection Regulation compliance

^aData of continuous variables for patients in Denmark were reported at 0 decimal places, and the number of patients was rounded to the nearest five due to General Data Protection Regulation constraints

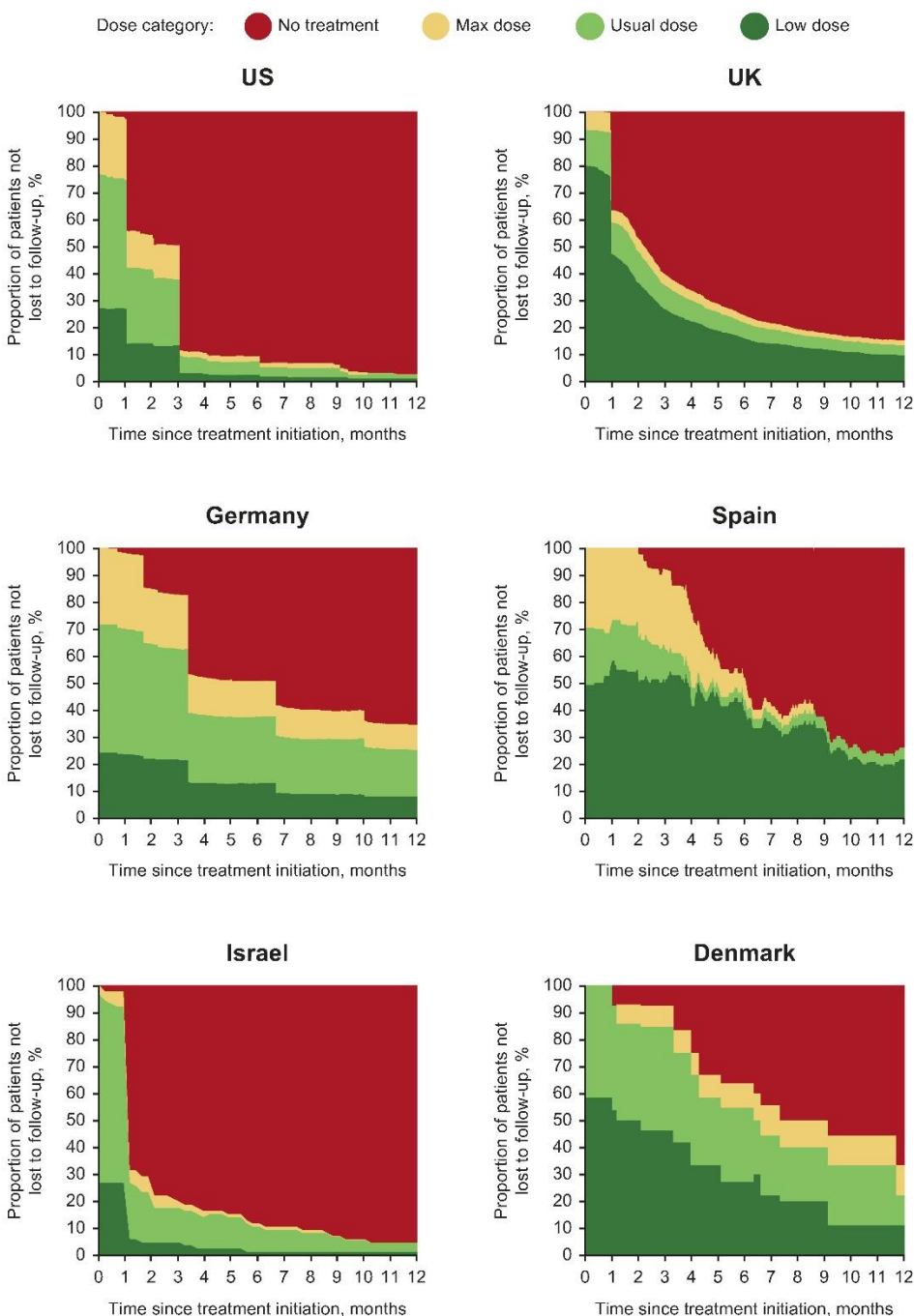
Supplementary Figures

Fig. S1 Patient selection and attrition across countries



UK United Kingdom, US United States

Fig. S2 Dose category and discontinuation of angiotensin-converting enzyme inhibitors as a third treatment from index to 12 months in patients with harder-to-control hypertension

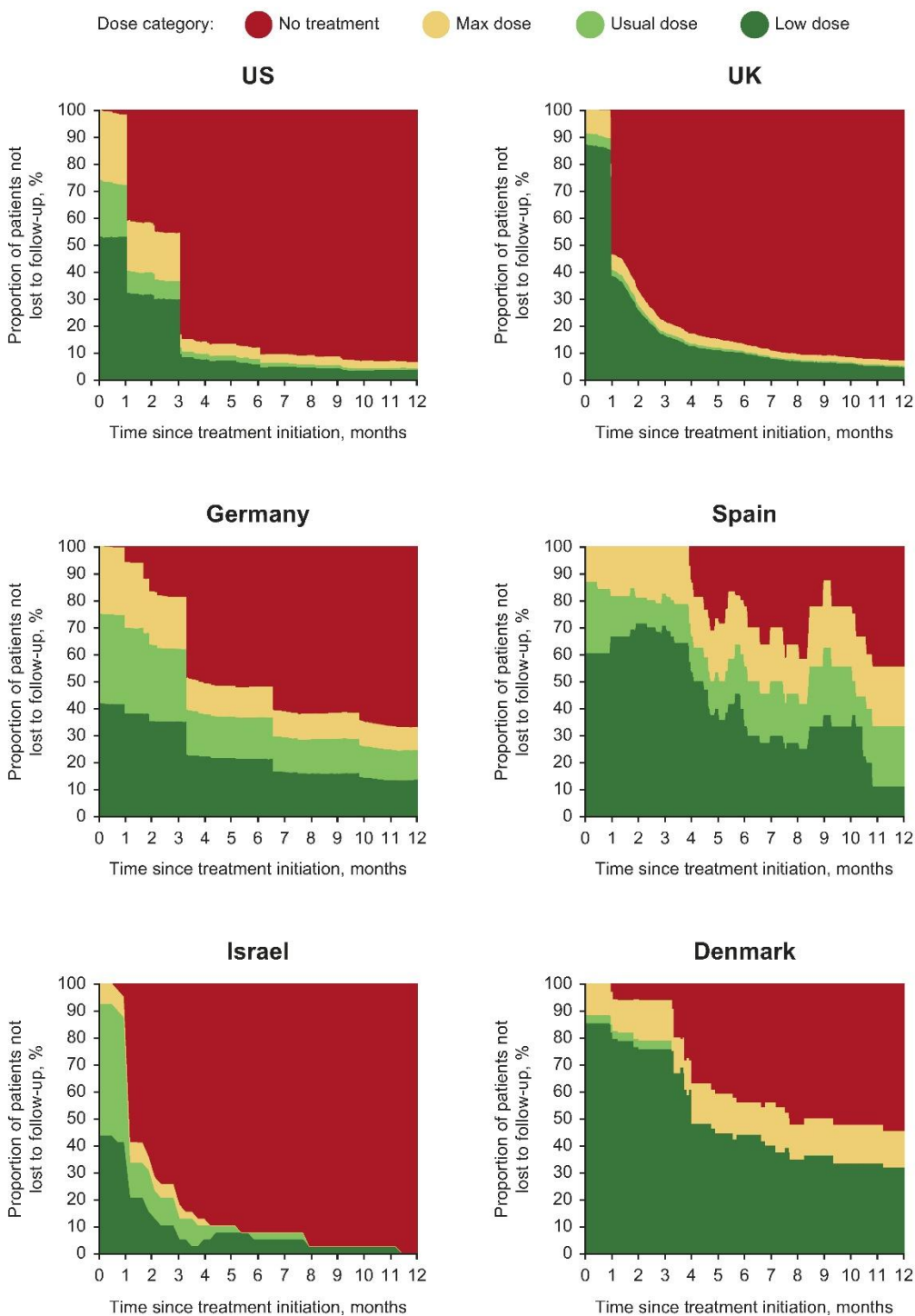


Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of angiotensin-converting enzyme inhibitors, or who switch to no treatment (red), from index to 12 months.

Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are

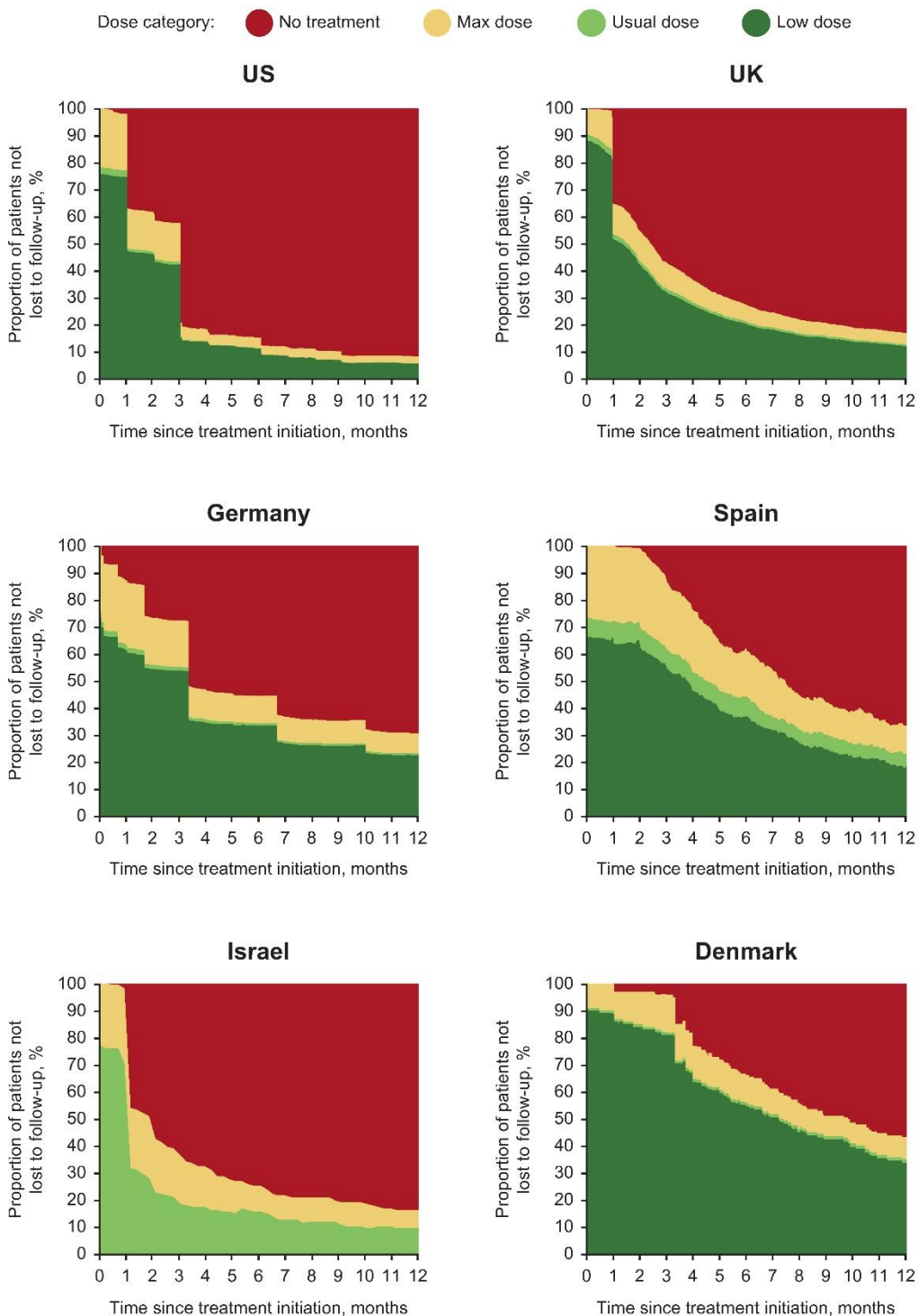
representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *UK* United Kingdom, *US* United States

Fig. S3 Dose category and discontinuation of angiotensin-II receptor blockers as a third treatment from index to 12 months in patients with harder-to-control hypertension



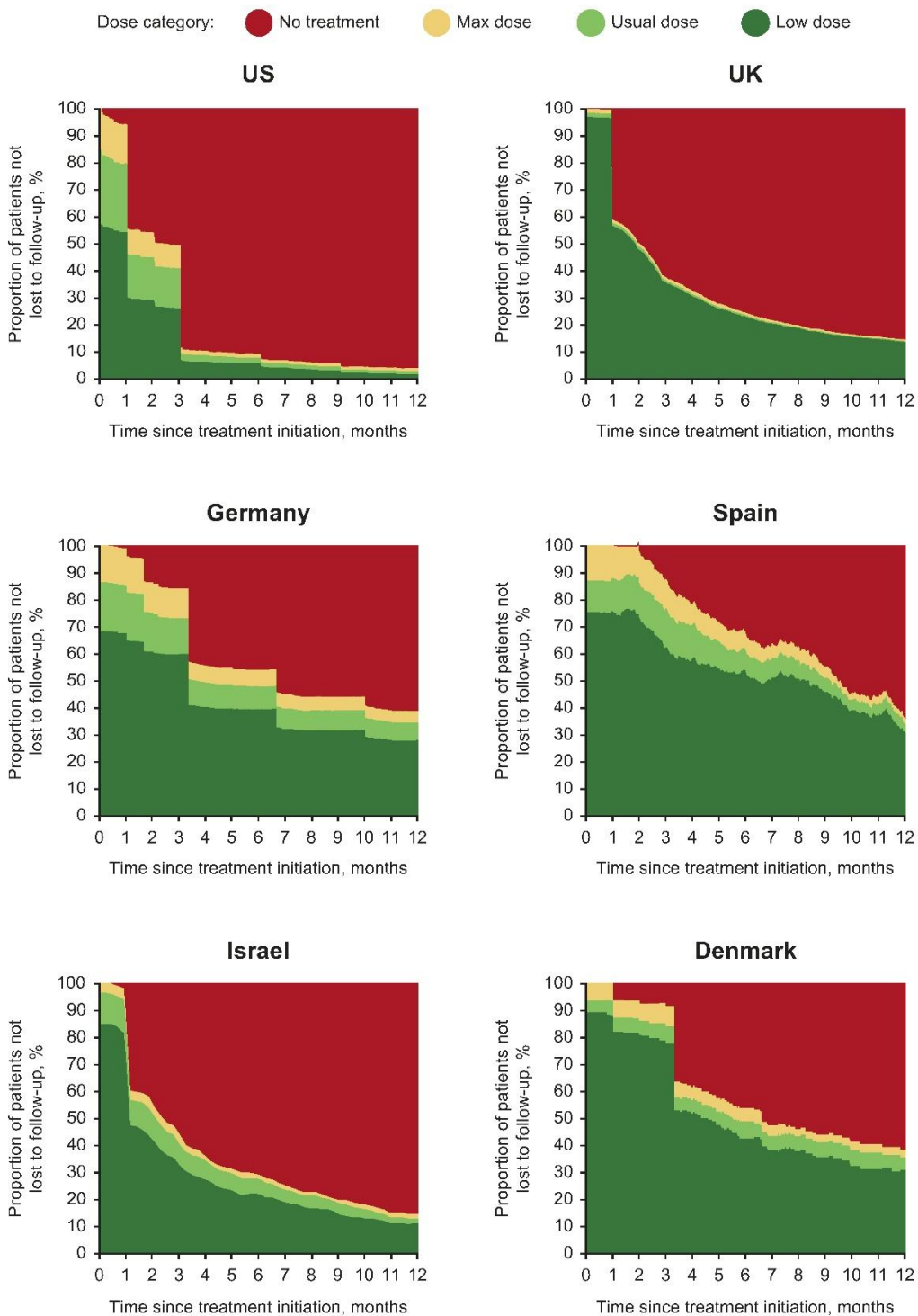
Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of angiotensin-II receptor blockers, or who switch to no treatment (red), from index to 12 months. Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *UK* United Kingdom, *US* United States

Fig. S4 Dose category and discontinuation of calcium channel blockers as a third treatment from index to 12 months in patients with harder-to-control hypertension



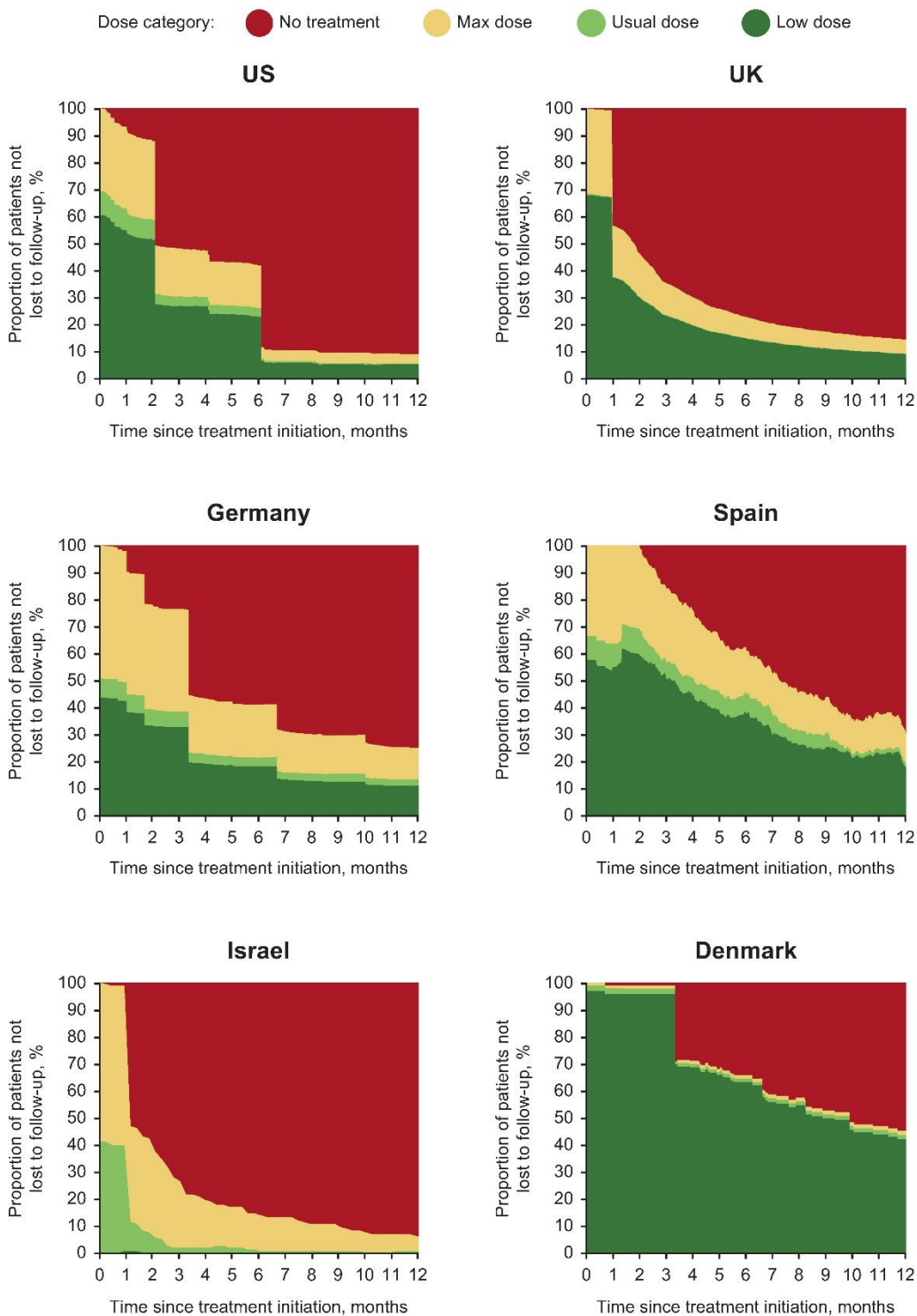
Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of calcium channel blockers, or who switch to no treatment (red), from index to 12 months. Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *UK* United Kingdom, *US* United States

Fig. S5 Dose category and discontinuation of beta blockers as a third treatment from index to 12 months in patients with harder-to-control hypertension



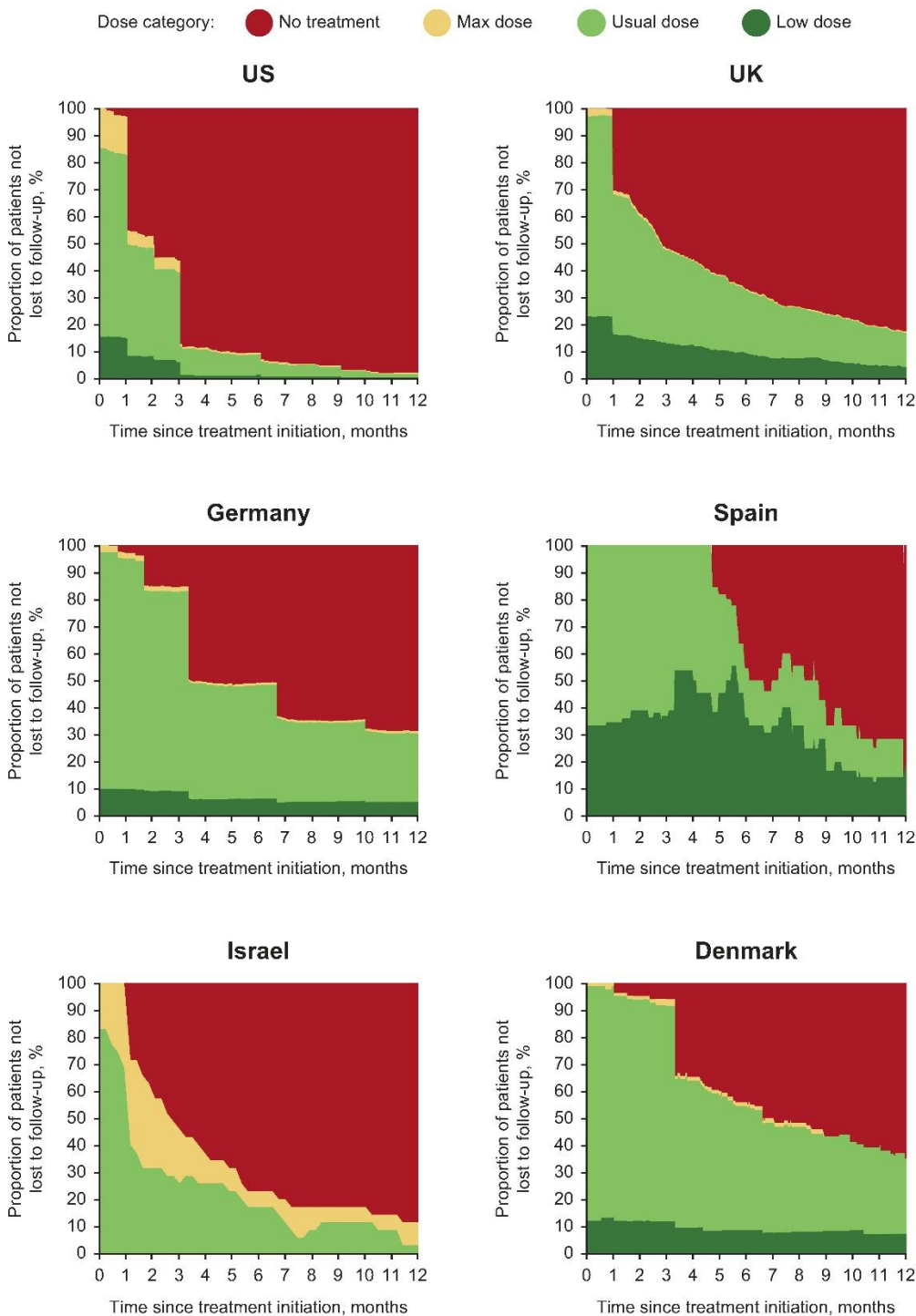
Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of beta blockers, or who switch to no treatment (red), from index to 12 months. Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *UK* United Kingdom, *US* United States

Fig. S6 Dose category and discontinuation of diuretics as a third treatment from index to 12 months in patients with harder-to-control hypertension



Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of diuretics, or who switch to no treatment (red), from index to 12 months. Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *UK* United Kingdom, *US* United States

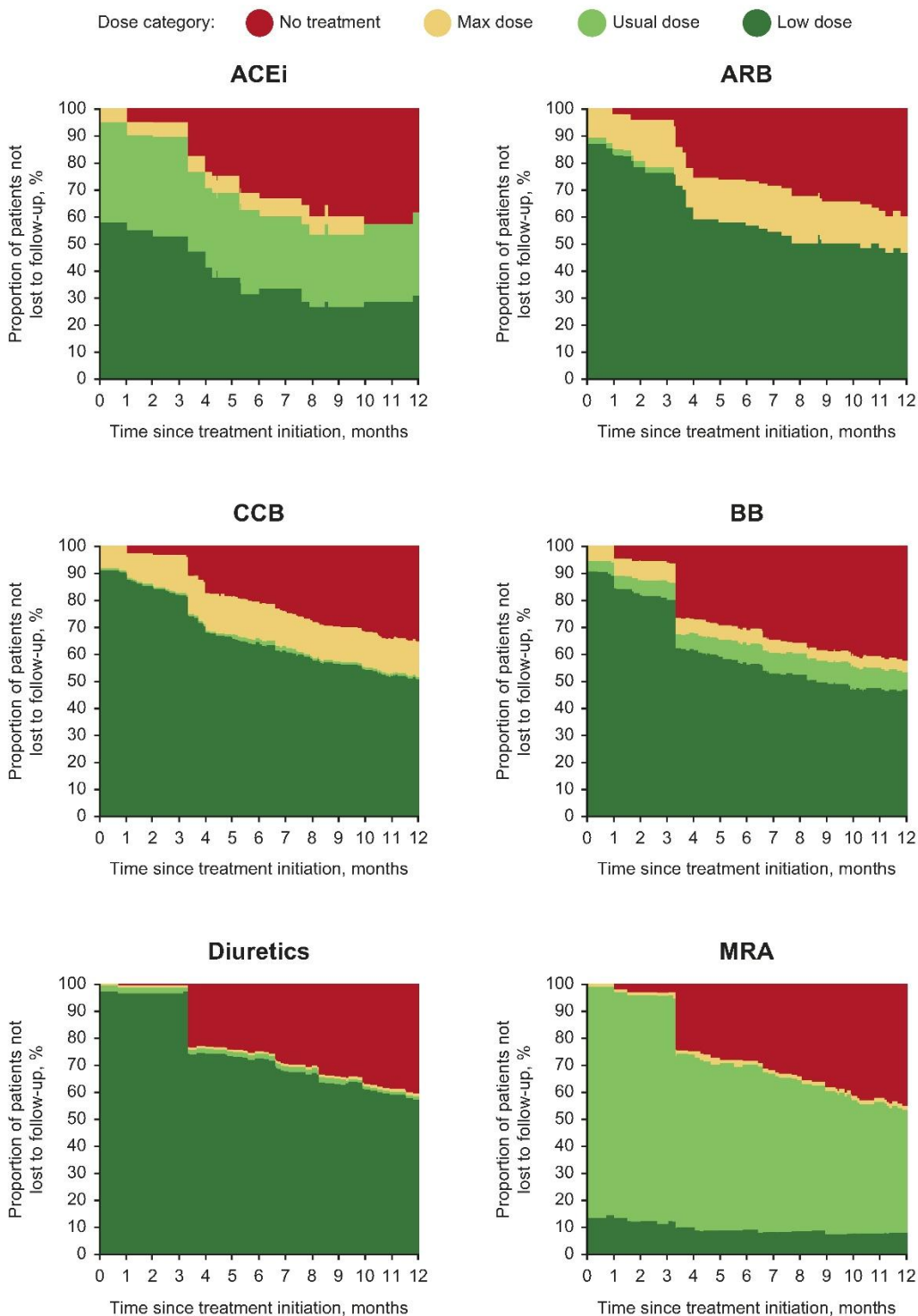
Fig. S7 Dose category and discontinuation of mineralocorticoid receptor antagonists as a third treatment from index to 12 months in patients with harder-to-control hypertension



Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of mineralocorticoid receptor antagonists, or who switch to no treatment (red), from index to 12 months.

Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *UK* United Kingdom, *US* United States.

Fig. S8 Dose category and discontinuation of common drug classes as a third treatment from index to 12 months in patients from Denmark with harder-to-control hypertension (100-day grace period)



Proportion of patients treated with a low dose (dark green), usual dose (light green), or max dose (orange) category of mineralocorticoid receptor antagonists, or who switch to no treatment (red), from index to 12 months.

Categorization of doses into low/usual/max was based on global schema. Low, usual and max categories are representative of the range of medication doses received by patients in this study, which may include both off-label and licensed doses. Input on prescribed doses was received from clinical experts practicing in each of the included countries. If discrepancies were observed between countries, the majority categorization was used. Using a 365-day dose matrix that defined the dose per day per patient in accordance with the global schema, the daily proportion of patients who were on a low/usual/max dose or who had discontinued treatment were calculated. *ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin-II receptor blocker, *BB* beta blocker, *CCB* calcium channel blocker, *MRA* mineralocorticoid receptor antagonists