

Supplemental material

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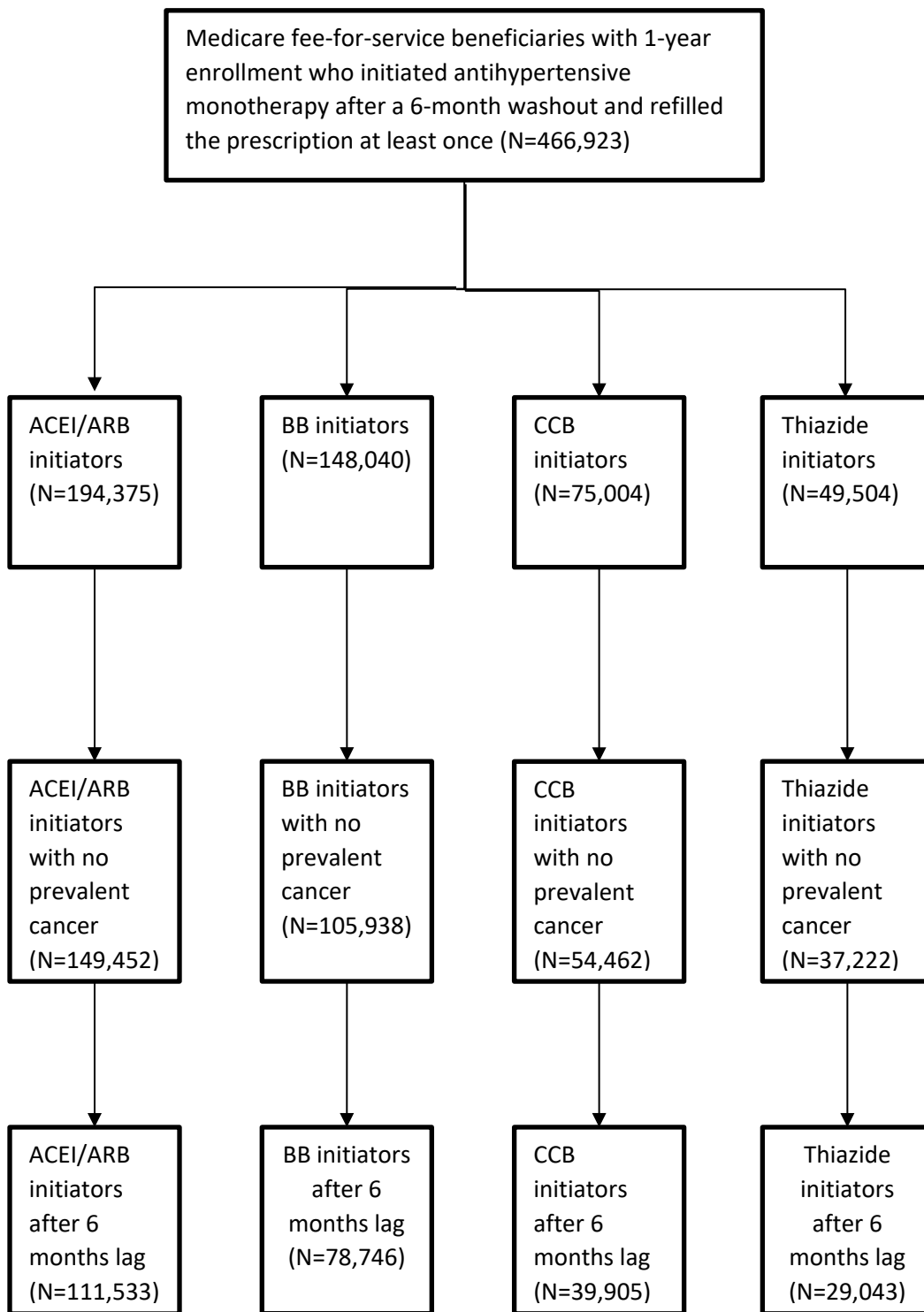
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Figure legends:

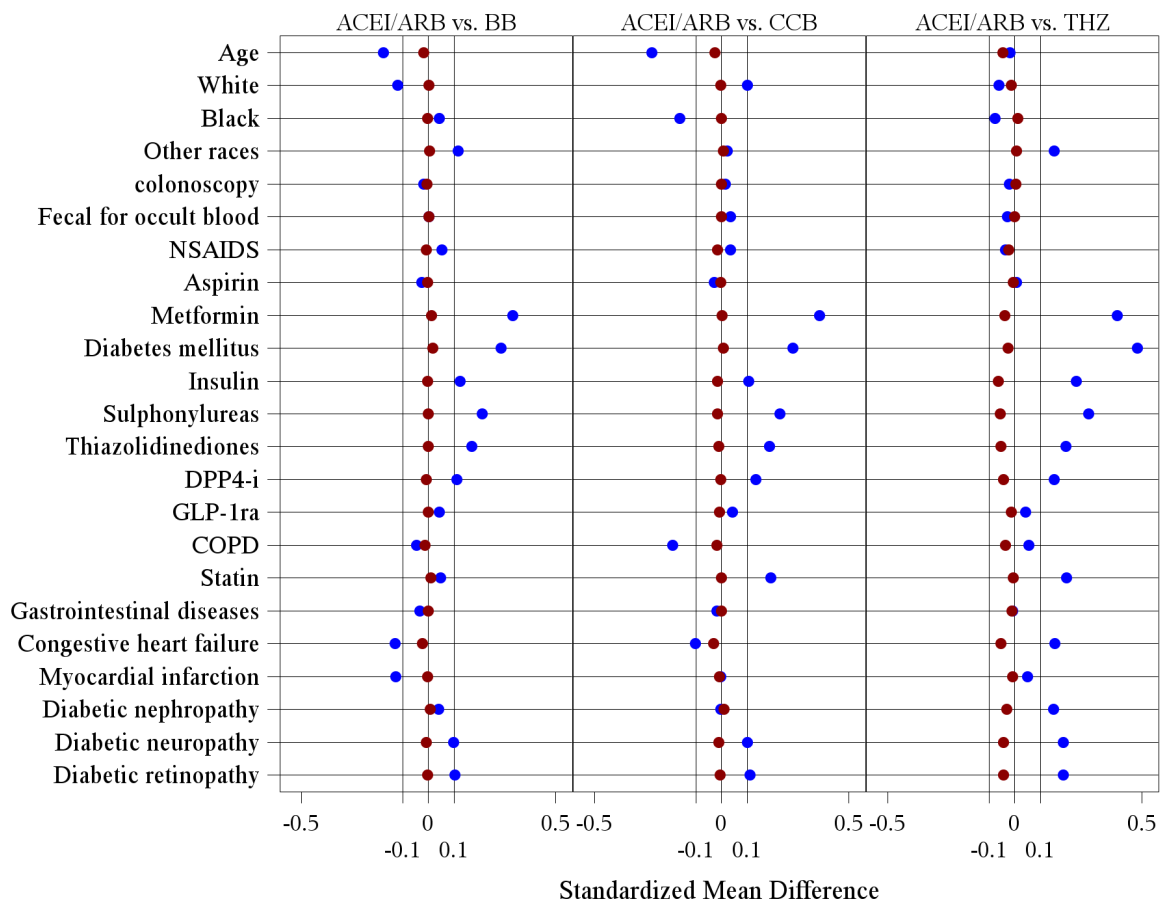
eFigure 1. Flowchart of the study population for angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), thiazide diuretics (THZ), calcium channel blockers (CCB), beta blockers (BB)

eFigure 2. Standardized mean differences (covariate balance) between ACEI/ARB versus other anti-hypertensive agents among Medicare beneficiaries

eFigure 1.



eFigure 2.



ACEI – Angiotensin converting enzyme inhibitors, ARB – Angiotensin receptor blockers, THZ – Thiazide diuretics, CCB – Calcium channel blockers, BB – Beta blockers, NSAIDs – Non-steroidal anti-inflammatory drugs, DPP4-i – Dipeptidyl peptidase-4 inhibitors, GLP-1ra – Glucagon like peptide-1 receptor agonists, COPD – Chronic obstructive pulmonary disease

eTable 1. Codes used to identify prevalent cancer at baseline

<p>ICD-9-CM diagnostic codes^a:</p> <p>140·0–208·92 (except 173·X), 209·00–209·36, 209·70-209·79, 230·X, 231·X, 233·X, 234·X, 235·X, 236·X, 237·0-237·1, 237·3, 237·5-237·6, 237·7, 237·9, 238·4, 238·6, 238·7 (all but 238·78), 239·6, 239·7, 273·2, 273·3, 277·89, 288·4, 795·06, 795·16, 796·76, V10·X, V87·41, V66·1, V66·2, V67·1, V67·2, V71·1</p>
<p>HCPCS codes^b:</p> <p>G8371, G8372, G8377, J9999, G0355, G0356, G8376, G8377, G8380, G8381, G8464, G8465, G8518, G8519, G8520, G9050-G9054, G9063-G9067, G9069-G9117, G9131-G9133, G9118-G9130, G9134-G9139, G9714-G9715, G9726, G0256, G0261</p>
<p>CPT^c:</p> <p>49220, 3271F, 3272F, 3273F, 3274F, 3300F – 3318F, 3321F, 3370F, 3372F, 3374F, 3376F, 3378F, 3380F, 3382F, 3384F, 3386F, 3388F, 3390F, 4163F, 4164F, 4180F, 4201F</p>

^a ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification

^b HCPCS Healthcare Common Procedure Coding System

^c CPT Current Procedural Terminology

eTable 2. Codes used to define any incident cancer during follow up

<p>Any Cancer ICD-9-CM diagnostic codes^a:</p> <p>140·0–208·92 (except 173·X), 209·00 – 209·36, 209·70-209·79,</p> <p>233·0, 236·0, 237·0-237·1, 237·5-237·6, 237·72, 237·9, 238·4, 238·6, 238·7X (all but 238·78),</p> <p>239·6, 239·7, 273·2, 273·3, 277·89, 288·4, 795·06, 795·16, 796·76</p>

^a ICD-9-CM International Classification of Disease, Ninth Revision, Clinical Modification

eTable 3. ICD-9-CM codes used to identify colorectal cancer outcomes

ICD-9-CM codes
153.xx, 154.0, 154.1, 154.2, 230.3, 230.4

eTable 4. Distribution of baseline characteristics among angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers versus beta blocker initiators from Medicare Current Beneficiary Survey 2006-2011^a

	Before weighting ^b		After weighting ^b		Absolute standardized mean difference ^c	
	ACEI/ARB (N=285, %)	Beta blocker (N=288, %)	ACEI/ARB (%)	Beta blocker (%)		
Age						
	66-70	29	23	29	29	0.003
	71-75	19	21	19	21	0.03
	76-80	21	19	21	19	0.05
	81-85	16	21	16	19	0.08
	85+	15	16	15	12	0.06
Sex						
	Male	44	39	44	44	0.01
Race						
	White	85	89	85	87	0.03
	Black	7.7	6.3	7.7	6.6	0.04
	Others	7.0	5.2	7.0	6.9	0.003
Cardiovascular diseases		7.4	8.0	7.4	6.8	0.02
COPD		14	9.0	14	16	0.05
Gastrointestinal diseases		<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.005
No. of office visits						
	0	62	62	62	60	0.05
	1 to 3	19	19	19	19	0.006
	>3	19	19	19	21	0.05
No. of hospital admissions		11	21	11	10	0.03
Colonoscopy + FOBT		<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.005
Statins		31	32	31	30	0.02
NSAIDS ^d		13	17	13	14	0.006
Aspirin ^d		<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.03
Smoking						
	Never	44	46	44	43	0.03
	Former	10	8.2	10	10	0.03
	Current	46	45	46	47	0.02
Body mass index						
	<25	39	43	39	42	0.08
	25-30	43	40	43	39	0.07

	>30	18	17	18	19	0.02
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ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, BB – beta blockers, COPD – chronic obstructive pulmonary diseases, FOBT – fecal for occult blood, NSAID – Non-steroidal anti-inflammatory drugs

^a Baseline was defined as a 12-month period before the first prescription date during which covariates were assessed (6 months for comedications). Drug initiators were identified after a 6-month drug-free period.

^b Propensity score weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB). Covariates in the propensity score estimation included all the variables in this eTable except smoking and body mass index. The intent of the eTable is to show that potential confounders such as smoking and body mass index are balanced between our exposure groups (therefore less chance of confounding) even though they are unmeasured in the main cohorts.

^c Absolute standardized mean difference was obtained by finding the absolute difference between the proportions in each comparison group divided by the standard deviation, and it is a measure of the balance of covariate distributions after propensity score weighting.

^d NSAIDs and Aspirin use might not be captured well in the claims data since most of these agents are available over the counter.

^e No cell size <11 is reported according to the data user agreement with the Center for Medicare and Medicaid Services

eTable 5. Distribution of baseline characteristics among angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers versus calcium channel blocker initiators, from Medicare Current Beneficiary Survey 2006-2011^a

		Before weighting ^b		After weighting ^b		Absolute standardized mean difference ^c
		ACEI/ARB (N=419, %)	CCB (N=146, %)	ACEI/ARB (%)	CCB (%)	
Age (Mean, SD)		76.9 (7.4)	80.3 (8.2)	76.9 (7.4)	77.1 (8.4)	0.03
Sex						
	Male	46	50	46	50	0.08
Race						
	White	83	77	83	83	0.008
	Black	8.3	9.6	8.3	<11 ^e	0.04
	Others	8.4	13	8.4	9.7	0.05
Diabetes mellitus		21	15	21	27	0.09
	Insulin	6.2	<11 ^e	6.2	<11 ^e	0.07
	Oral anti-hyperglycemic drugs	16	<11 ^e	16	14	0.06
	Diabetes complications	5.0	<11 ^e	5.0	<11 ^e	0.06
	Cardiovascular diseases	11	14	11	12	0.04
	COPD	15	17	15	13	0.08
	Gastrointestinal diseases	<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.09
No. of office visits						
	0	60	62	61	62	0.03
	1 to 3	19	16	19	16	0.08
	>3	21	22	20	22	0.03
No. of hospital admissions		14	26	14	15	0.05
	Colonoscopy + FOBT	4.8	<11 ^e	4.8	<11 ^e	0.04
	Statins	35	26	35	37	0.04
	NSAIDS ^d	14	13	14	14	0.02
	Aspirin ^d	1.7	<11 ^e	1.7	<11 ^e	0.02
Smoking						
	Never	44	40	44	40	0.07
	Former	11	12	11	12	0.05
	Current	45	48	45	48	0.06
Body mass index						
	<25	35	40	35	36	0.002
	25-30	43	43	43	41	0.04
	>30	22	17	22	23	0.008

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, CCB – calcium channel blockers, COPD – chronic obstructive pulmonary diseases, FOBT – fecal for occult blood, NSAID – Non-steroidal anti-inflammatory drugs

^a Baseline was defined as a 12-month period before the first prescription date during which covariates were assessed (6 months for comedications). Drug initiators were identified after a 6-month drug-free period.

^b Propensity score weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB). Covariates in the propensity score estimation included all the variables in this eTable except smoking and body mass index. The intent of the eTable is to show that potential confounders such as smoking and body mass index are balanced between our exposure groups (therefore less chance of confounding) even though they are unmeasured in the main cohorts.

^c Absolute standardized mean difference was obtained by finding the absolute difference between the proportions in each comparison group divided by the standard deviation, and it is a measure of the balance of covariate distributions after propensity score weighting.

^d NSAIDs and Aspirin use might not be captured well in the claims data since most of these agents are available over the counter.

^e No cell size <11 is reported according to the data user agreement with the Center for Medicare and Medicaid Services

eTable 6. Distribution of baseline characteristics among angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers versus thiazide initiators from Medicare Current Beneficiary Survey 2006-2011^a

	Before weighting ^b		After weighting ^b		Absolute standardized mean difference ^c	
	ACEI/ARB (N=285, %)	THZ (N=124, %)	ACEI/ARB (%)	THZ (%)		
Age						
	66-70	29	25	29	27	0.03
	71-75	19	26	19	19	0.02
	76-80	21	15	21	19	0.04
	81-85	16	18	16	18	0.06
	85+	15	16	15	17	0.04
Sex						
	Male	44	36	44	43	0.03
Race						
	White	85	88	85	86	0.01
	Black	7.7	<11 ^e	7.7	<11 ^e	0.02
	Others	7.0	<11 ^e	7.0	<11 ^e	0.03
Cardiovascular diseases		7.4	<11 ^e	7.4	7.6	0.009
COPD		14	11	14	12	0.08
Gastrointestinal diseases		<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.04
No. of office visits						
	0	62	64	62	67	0.09
	1 to 3	19	20	19	18	0.02
	>3	19	16	19	15	0.1
No. of hospital admissions		11	<11 ^e	11	<11 ^e	0.07
Colonoscopy + FOBT		<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.001
Statins		31	23	31	29	0.05
NSAIDS ^d		13	18	13	14	0.03
Aspirin ^d		<11 ^e	<11 ^e	<11 ^e	<11 ^e	0.005
Smoking						
	Never	44	42	44	42	0.01
	Former	10	<11 ^e	10	<11 ^e	0.1
	Current	46	52	46	51	0.1
Body mass index						
	<25	39	36	39	34	0.1
	25-30	43	42	43	43	0.04
	>30	18	22	18	23	0.1

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – thiazide diuretics, COPD – chronic obstructive pulmonary diseases, FOBT – fecal for occult blood, NSAID – Non-steroidal anti-inflammatory drugs

^a Baseline was defined as a 12-month period before the first prescription date during which covariates were assessed (6 months for comedications). Drug initiators were identified after a 6-month drug-free period.

^b Propensity score weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB). Covariates in the propensity score estimation include all the variables in this eTable except smoking and body mass index. The intent of the eTable is to show that potential confounders such as smoking and body mass index are balanced between our exposure groups (therefore less chance of confounding) even though they are unmeasured in the main cohorts.

^c Absolute standardized mean difference was obtained by finding the absolute difference between the proportions in each comparison group divided by the standard deviation, and it is a measure of the balance of covariate distributions after propensity score weighting.

^d NSAIDs and Aspirin use might not be captured well in the claims data since most of these agents are available over the counter.

^e No cell size <11 is reported according to the data user agreement with the Center for Medicare and Medicaid Services

eTable 7. Cumulative risks of colorectal cancer at 1, 3 and 5 years of follow up among antihypertensive initiators from Medicare^a

Drugs Comparison	Duration of follow up	Drugs	Cumulative risks (per 1,000)	RD per 1,000 (95% CI)	
Intention-to-treat analyses with 6 months lag					
ACEI/ARB vs. BB	1 year	ACEI/ARB	1.8	-0.63 (-1.2, -0.08)	
		BB	2.5		
	3 years	ACEI/ARB	6.1		-0.28 (-1.3, 0.78)
		BB	6.4		
	5 years	ACEI/ARB	10		1.4 (-0.27, 2.9)
		BB	8.9		
ACEI/ARB vs. CCB	1 year	ACEI/ARB	1.8	0.08 (-0.51, 0.66)	
		CCB	1.8		
	3 years	ACEI/ARB	6.2		1.2 (0.07, 2.3)
		CCB	4.9		
	5 years	ACEI/ARB	10		1.7 (0.35, 3.8)
		CCB	8.5		
ACEI/ARB vs. THZ	1 year	ACEI/ARB	1.8	-0.20 (-1.10, 0.71)	
		THZ	2.0		
	3 years	ACEI/ARB	6.2		0.53 (-1.0, 2.1)
		THZ	5.6		
	5 years	ACEI/ARB	10		0.35 (-2.5, 3.2)
		THZ	9.8		
As treated analyses with 6 months lag					
ACEI/ARB vs. BB	1 year	ACEI/ARB	1.9	-0.43 (-1.1, 0.20)	
		BB	2.3		
	3 years	ACEI/ARB	7.2		1.6 (-0.25, 3.4)
		BB	5.6		

	5 years	ACEI/ARB	11	3.6 (0.52, 6.6)
		BB	6.7	
ACEI/ARB vs. CCB	1 year	ACEI/ARB	1.8	0.0018 (-0.75, 0.76)
		CCB	1.8	
	3 years	ACEI/ARB	7.1	1.6 (-0.45, 3.7)
		CCB	5.5	
	5 years	ACEI/ARB	11	0.86 (-4.3, 5.9)
		CCB	10	
ACEI/ARB vs. THZ	1 year	ACEI/ARB	1.8	-1.0 (-2.8, 0.74)
		THZ	2.9	
	3 years	ACEI/ARB	7.5	0.41 (-3.1, 3.9)
		THZ	7.1	
	5 years	ACEI/ARB	12	0.12 (-6.5, 6.7)
		THZ	11	

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, RD – risk differences, CI – confidence intervals

eTable 8. Time varying incidence of colorectal cancer among antihypertensive initiators over the duration of follow up according to intention-to-treat analyses with no lag^a

Duration of follow up	No. of events ^b	Total sample size ^b	Incidence rates (95% CI) ^c	Weighted HR (95% CI) ^d
0 to 6 months^e				
ACEI/ARB	139	128,340	2.4 (2.0-2.8)	0.8 (0.6, 1.1)
BB	119	91,399	2.9 (2.3-3.6)	1.0
ACEI/ARB	139	128,340	2.4 (2.0-2.8)	0.8 (0.6, 1.2)
CCB	60	46,932	2.8 (2.1-3.7)	1.0
ACEI/ARB	138	128,320	2.3 (2.0, 2.8)	1.2 (0.8, 1.9)
THZ	29	33,427	1.9 (1.2, 2.9)	1.0
6 to 12 months^e				
ACEI/ARB	98	111,584	1.9 (1.5-2.3)	0.8 (0.6, 1.2)
BB	83	78,676	2.3 (1.7-3.0)	1.0
ACEI/ARB	98	111,584	1.9 (1.5-2.3)	1.0 (0.6, 1.7)
CCB	34	40,125	1.8 (1.2-2.9)	1.0
ACEI/ARB	96	111,708	1.8 (1.5, 2.3)	1.3 (0.8, 2.1)
THZ	19	29,434	1.4 (0.9, 2.2)	1.0
12 to 24 months^e				
ACEI/ARB	160	95,377	1.9 (1.7-2.3)	0.8 (0.7, 1.1)
BB	132	66,977	2.3 (1.9-2.8)	1.0
ACEI/ARB	160	95,377	1.9 (1.7-2.3)	1.2 (0.9, 1.7)
CCB	46	33,736	1.6 (1.2-2.2)	1.0
ACEI/ARB	157	95,555	1.9 (1.6, 2.2)	0.9 (0.6, 1.5)
THZ	44	25,700	2.0 (1.3, 3.0)	1.0
24 to 36 months^e				
ACEI/ARB	118	69,693	2.0 (1.7-2.4)	1.0 (0.8, 1.4)
BB	78	48,622	1.9 (1.5-2.5)	1.0

ACEI/ARB	118	69,693	2.0 (1.7-2.4)	1.1 (0.8, 1.7)
CCB	35	24,067	1.8 (1.3-2.5)	1.0
ACEI/ARB	117	70,001	2.0 (1.7, 2.4)	0.9 (0.6, 1.4)
THZ	37	19,482	2.3 (1.5, 3.4)	1.0
36 months onwards^e				
ACEI/ARB	157	48,378	2.2 (1.8-2.5)	1.4 (1.0, 1.8)
BB	81	33,679	1.6 (1.3-2.0)	1.0
ACEI/ARB	157	48,378	2.2 (1.8-2.5)	1.3 (0.9, 1.8)
CCB	40	16,379	1.7 (1.2-2.2)	1.0
ACEI/ARB	156	48,675	2.1 (1.8, 2.5)	1.1 (0.7, 1.7)
THZ	41	13,893	2.0 (1.3, 3.0)	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – thiazide diuretics, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a Intention-to-treat (intention to treat, ITT) analysis is based on follow up until the end of study/enrollment, death, other incident cancer outcomes, whatever comes earlier.

^b No. of events and sample size were weighted by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the ACEI/ARB cohort.

^c Incidence rates are per 1,000 population.

^d Weighted hazard ratios were adjusted for baseline covariates in eTable 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

^e No lag period was assumed for these analyses. Follow up started from the second prescription date and ended on the date of treatment changes or death or gap in enrollment.

eTable 9. Time varying incidence of colorectal cancer among antihypertensive initiators over the duration of treatment according to as treated analyses with no lag period^a

Duration of treatment	No. of events ^b	Total sample size ^b	Incidence rates (95% CI) ^c	Weighted HR (95% CI) ^d
0 to 6 months^e				
ACEI/ARB	109	128,335	2.2 (1.8, 2.7)	0.8 (0.6, 1.0)
BB	98	91,394	2.9 (2.3, 3.7)	1.0
ACEI/ARB	110	128,335	2.2 (1.8, 2.7)	0.8 (0.5, 1.1)
CCB	51	46,932	2.9 (2.1, 4.0)	1.0
ACEI/ARB	110	128,335	2.2 (1.8, 2.7)	1.2 (0.7, 2.0)
THZ	23	33,555	1.9 (1.1, 3.3)	1.0
6 to 12 months^e				
ACEI/ARB	48	71,121	1.7 (1.3, 2.3)	0.8 (0.5, 1.2)
BB	41	47,160	2.3 (1.5, 3.4)	1.0
ACEI/ARB	47	72,371	1.7 (1.2, 2.2)	1.1 (0.6, 1.9)
CCB	15	25,176	1.5 (0.9, 2.6)	1.0
ACEI/ARB	48	71,688	1.7 (1.3, 2.3)	1.8 (0.8, 3.9)
THZ	<11 ^f	16,624	1.0 (0.5, 2.1)	1.0
12 to 24 months^e				
ACEI/ARB	56	42,781	1.9 (1.4, 2.4)	1.1 (0.7, 1.6)
BB	34	27,880	1.8 (1.3, 2.5)	1.0
ACEI/ARB	60	43,958	1.9 (1.5, 2.5)	1.1 (0.6, 1.9)
CCB	19	15,233	1.8 (1.1, 3.0)	1.0
ACEI/ARB	59	43,157	1.9 (1.5, 2.5)	0.6 (0.3, 1.3)
THZ	22	9,685	3.4 (1.5, 7.6)	1.0
24 months onwards^e				
ACEI/ARB	53	20,423	2.0 (1.5, 2.6)	1.5 (0.9, 2.5)
BB	22	13,175	1.3 (0.8, 2.0)	1.0

ACEI/ARB	55	21,256	2.0 (1.5, 2.5)	0.9 (0.6, 1.5)
CCB	21	7,301	2.2 (1.4, 3.3)	1.0
ACEI/ARB	61	20,656	2.3 (1.8, 2.9)	0.9 (0.4, 2.0)
THZ	14	4,352	2.6 (1.2, 6.0)	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – thiazide diuretics, CCB – calcium channel blockers, BB – beta blockers, HR – hazard ratios, CI – confidence intervals

^a As treated (AT) analysis is based on follow up until the end of study/enrollment, death, other incident cancer outcomes, or switching/discontinuation/ augmentation of drugs, whatever comes earlier.

^b No. of events and sample size were weighted by stabilized standardized morbidity ratio weighting, where every patient was weighted to reflect the covariate distributions in the exposed population.

^c Incidence rates are per 1,000 population.

^d Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting is implemented by stabilized morbidity ratio weighting, where patients were weighted to reflect the covariate distributions in the ACEI/ARB cohort. ACEI/ARB group was given a weight of 1 and each comparator $PS/(1-PS) * (1-prev)/prev$, in which PS is the propensity score and prev is the marginal prevalence (proportion) of ACEI/ARB users in the study population.

^e No lag period was assumed for these analyses. Follow up started from the second prescription date and the follow up time is stratified into these intervals.

^f No cell size <11 is reported according to the data user agreement with the center for Medicare and Medicaid Service

eTable 10. Incidence of colorectal cancer among antihypertensive initiators after excluding diabetes mellitus diagnoses at baseline

Drugs Comparison	No. of events	Total sample size	Follow up years (median, IQR)	Incidence rates ^a	Crude HR (95% CI)	Weighted HR (95% CI) ^b
Intention-to-treat analyses with 6 months lag						
ACEI/ARB	301	67,949	2.2 (1.0, 3.7)	1.8	1.0 (0.8, 1.2)	1.0 (0.9, 1.2)
BB	257	58,468	2.2 (0.9, 3.7)	1.8	1.0	1.0
ACEI/ARB	301	67,949	2.2 (1.0, 3.7)	1.8	0.9 (0.8, 1.1)	1.0 (0.8, 1.3)
CCB	131	29,547	2.0 (0.8, 3.5)	1.9	1.0	1.0
ACEI/ARB	301	67,949	2.2 (1.0, 3.7)	1.8	0.9 (0.8, 1.2)	0.9 (0.7, 1.2)
THZ	115	23,853	2.4 (1.1, 4.0)	1.9	1.0	1.0
As treated analyses with 6 months lag						
ACEI/ARB	121	65,452	0.6 (0.3, 1.4)	1.7	0.9 (0.8, 1.3)	1.0 (0.8, 1.3)
BB	102	56,366	0.6 (0.2, 1.3)	1.7	1.0	1.0
ACEI/ARB	119	67,587	0.6 (0.3, 1.4)	1.7	0.9 (0.6, 1.2)	0.9 (0.7, 1.4)
CCB	58	29,410	0.6 (0.2, 1.3)	1.9	1.0	1.0
ACEI/ARB	121	67,587	0.6 (0.3, 1.4)	1.7	0.9 (0.7, 1.4)	0.9 (0.6, 1.3)
THZ	41	23,702	0.5 (0.2, 1.3)	1.8	1.0	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a Incidence rates are per 1,000 population.

^b Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

eTable 11. Incidence of colorectal cancer among antihypertensive initiators after excluding congestive heart failure and myocardial infarction diagnoses at baseline

Drugs comparison	No. of events	Total sample size	Follow up years (median, IQR)	Incidence rates ^a	Crude HR (95% CI)	Weighted HR (95% CI) ^b
Intention-to-treat analyses with 6 months lag						
ACEI/ARB	444	98,431	2.2 (1.0, 3.7)	1.9	1.0 (0.9, 1.2)	0.9 (0.8, 1.1)
BB	292	65,461	2.2 (1.0, 3.7)	1.9	1.0	1.0
ACEI/ARB	444	98,431	2.2 (1.0, 3.7)	1.9	0.9 (0.8, 1.1)	1.1 (0.9, 1.4)
CCB	153	33,817	2.0 (0.9, 3.5)	2.0	1.0	1.0
ACEI/ARB	444	98,431	2.2 (1.0, 3.7)	1.9	1.0 (0.9, 1.3)	0.9 (0.7, 1.2)
THZ	125	26,992	2.4 (1.1, 4.0)	1.8	1.0	1.0
As treated analyses with 6 months lag						
ACEI/ARB	198	97,883	0.6 (0.3, 1.4)	1.9	1.1 (0.8, 1.3)	1.0 (0.8, 1.3)
BB	119	64,796	0.5 (0.2, 1.3)	1.9	1.0	1.0
ACEI/ARB	196	94,196	0.6 (0.3, 1.4)	1.9	0.9 (0.7, 1.2)	1.1 (0.8, 1.5)
CCB	70	33,651	0.6 (0.2, 1.4)	2.0	1.0	1.0
ACEI/ARB	196	97,883	0.6 (0.3, 1.4)	1.9	1.1 (0.8, 1.5)	0.8 (0.5, 1.2)
THZ	46	26,813	0.5 (0.2, 1.3)	1.8	1.0	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a Incidence rates are per 1,000 population.

^b Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

eTable 12. Incidence of colorectal cancer among angiotensin converting enzyme inhibitors or angiotensin receptor blockers only versus other antihypertensive agents among Medicare beneficiaries

Drugs Comparison	No. of events	Total sample size	Follow up years (median, IQR)	Incidence rates ^a	Crude HR (95% CI)	Weighted HR (95% CI) ^b
Intention-to-treat analyses with 6 months lag						
ACEI vs. other antiHT						
ACEI	402	82,868	2.1 (0.9, 3.6)	2.0	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)
BB	364	78,746	2.1 (0.9, 3.6)	2.0	1.0	1.0
ACEI	402	82,868	2.1 (0.9, 3.6)	2.0	1.0 (0.9, 1.2)	1.2 (0.9, 1.5)
CCB	177	39,905	1.9 (0.8, 3.4)	2.0	1.0	1.0
ACEI	402	82,868	2.1 (0.9, 3.6)	2.0	1.1 (0.9, 1.4)	1.1 (0.8, 1.4)
THZ	138	29,043	2.4 (1.1, 4.0)	1.9	1.0	1.0
ARB vs. other antiHT						
ARB	130	28,665	2.2 (1.0, 3.8)	1.9	0.9 (0.8, 1.2)	0.9 (0.8, 1.2)
BB	364	78,746	2.1 (0.9, 3.6)	2.0	1.0	1.0
ARB	130	28,665	2.2 (1.0, 3.8)	1.9	0.9 (0.7, 1.2)	1.1 (0.9, 1.4)
CCB	177	39,905	1.9 (0.8, 3.4)	2.0	1.0	1.0
ARB	130	28,665	2.2 (1.0, 3.8)	1.9	1.0 (0.8, 1.3)	0.9 (0.7, 1.3)
THZ	138	29,043	2.1 (1.1, 4.0)	1.9	1.0	1.0
As treated analyses with 6 months lag						
ACEI vs. other antiHT						
ACEI	176	94,447	0.6 (0.3, 1.4)	1.8	1.1 (0.9, 1.4)	1.1 (0.8, 1.3)
BB	149	90,912	0.5 (0.2, 1.3)	1.7	1.0	1.0
ACEI	171	94,447	0.6 (0.3, 1.4)	1.7	0.9 (0.8, 1.3)	1.1 (0.8, 1.5)
CCB	81	46,551	0.6 (0.2, 1.3)	1.7	1.0	1.0
ACEI	177	94,447	0.6 (0.3, 1.4)	1.8	1.1 (0.8, 1.5)	0.9 (0.5, 1.3)

THZ	52	32,528	0.5 (0.2, 1.2)	1.7	1.0	1.0
ARB vs. other antiHT						
ARB	50	32,271	0.6 (0.3, 1.3)	1.6	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)
BB	149	90,912	0.5 (0.2, 1.3)	1.7	1.0	1.0
ARB	59	32,271	0.6 (0.3, 1.3)	1.8	1.1 (0.8, 1.5)	1.1 (0.8, 1.6)
CCB	81	46,551	0.6 (0.2, 1.3)	1.7	1.0	1.0
ARB	57	32,271	0.6 (0.3, 1.3)	1.8	1.1 (0.7, 1.6)	0.9 (0.6, 1.5)
THZ	52	32,528	0.6 (0.2, 1.2)	1.7	1.0	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a Incidence rates are per 1,000 population.

^b Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

eTable 13. Incidence of colorectal cancer among antihypertensive initiators after allowing prevalent users of other antihypertensive drug classes^a

Drugs Comparison	No. of events	Total sample size	Follow up years (median, IQR)	Incidence rates ^b	Crude HR (95% CI)	Weighted HR (95% CI) ^c
Intention-to-treat analyses with 6 months lag						
ACEI/ARB	1,457	250,779	2.6 (1.3, 4.3)	201	0.9 (0.9, 1.1)	1.0 (0.9, 1.1)
BB	924	160,867	2.4 (1.2, 4.2)	206	1.0	1.0
ACEI/ARB	1,932	332,584	2.6 (1.3, 4.3)	202	0.9 (0.8, 0.9)	0.9 (0.8, 1.0)
CCB	706	111,696	2.4 (1.2, 4.0)	234	1.0	1.0
ACEI/ARB	2,162	350,003	2.5 (1.2, 4.2)	221	1.0 (0.9, 1.1)	0.9 (0.8, 1.0)
THZ	526	80,691	2.8 (1.4, 4.5)	216	1.0	1.0
As treated analyses with 6 months lag						
ACEI/ARB	570	249,337	0.6 (0.3, 1.5)	202	0.9 (0.9, 1.1)	1.1 (0.9, 1.2)
BB	345	159,987	0.6 (0.3, 1.4)	204	1.0	1.0
ACEI/ARB	798	330,738	0.7 (0.3, 1.5)	209	0.9 (0.8, 1.0)	0.9 (0.8, 1.1)
CCB	296	111,149	0.6 (0.3, 1.5)	237	1.0	1.0
ACEI/ARB	902	348,180	0.6 (0.3, 1.5)	230	1.1 (0.9, 1.2)	0.9 (0.7, 1.1)
THZ	179	80,222	0.6 (0.3, 1.3)	219	1.0	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a New users identified after excluding prevalent users of specific drugs in comparison, i.e., in ACEI/ARB vs. BB pair, prevalent use of CCB and thiazide were allowed.

^b Incidence rates are per 1,000 population.

^c Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

eTable 14. Duration of prevalent use of antihypertensive drug classes by each comparison of ACEI/ARB vs. specific active comparator in Medicare beneficiaries

Drugs comparison	Prevalent drug class	Duration (median days)	Interquartile range (first and third quarters)
ACEI/ARB	CCB	272	51, 618
BB		301	66, 677
ACEI/ARB	Thiazide	90	31, 325
BB		229	55, 497
ACEI/ARB	BB	286	72, 622
CCB		324	111, 694
ACEI/ARB	Thiazide	98	32, 381
CCB		281	83, 596
ACEI/ARB	CCB	279	56, 628
Thiazide		341	116, 711
ACEI/ARB	BB	282	68, 616
Thiazide		302	93, 639

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers

eTable 15. Incidence of colorectal cancer among antihypertensive initiators after varying induction or lag periods, according to intention-to-treat analyses^a

Drugs Comparison	No. of events	Total sample size	Follow up years (median, IQR)	Incidence rates ^b	Crude HR (95% CI)	Weighted HR (95% CI) ^c
Intention-to-treat analyses						
No lag						
ACEI	672	128,340	2.2 (1.0, 3.9)	2.1	1.0 (0.9, 1.1)	0.9 (0.8, 1.1)
BB	480	92,914	2.1 (0.9, 3.8)	2.1	1.0	1.0
ACEI	672	128,340	2.2 (1.0, 3.9)	2.1	1.0 (0.9, 1.1)	1.1 (0.9, 1.3)
CCB	246	47,266	2.0 (0.8, 3.6)	2.2	1.0	1.0
ACEI	672	128,340	2.2 (1.0, 3.9)	2.1	1.1 (0.9, 1.3)	1.1 (0.9, 1.3)
THZ	169	32,922	2.5 (1.1, 4.2)	1.9	1.0	1.0
1-year lag						
ARB	435	95,287	2.0 (0.9, 3.5)	2.0	1.0 (0.9, 1.2)	1.0 (0.9, 1.2)
BB	286	66,795	2.0 (0.9, 3.4)	1.9	1.0	1.0
ARB	435	95,287	2.0 (0.9, 3.5)	2.0	1.0 (0.8, 1.2)	1.2 (0.9, 1.5)
CCB	144	33,211	1.9 (0.8, 3.2)	2.1	1.0	1.0
ARB	435	95,287	2.0 (0.9, 3.5)	2.0	1.1 (0.9, 1.3)	1.0 (0.7, 1.3)
THZ	116	25,314	2.2 (1.1, 3.7)	1.9	1.0	1.0
2-year lag						
ARB	274	69,651	1.8 (0.8, 2.9)	2.1	1.3 (1.0, 1.5)	1.2 (0.9, 1.5)
BB	150	48,107	1.7 (0.8, 2.9)	1.7	1.0	1.0
ARB	274	69,651	1.8 (0.8, 2.9)	2.1	1.0 (0.8, 1.2)	1.2 (0.9, 1.6)
CCB	90	23,235	1.6 (0.8, 2.8)	2.1	1.0	1.0
ARB	274	69,651	1.8 (0.8, 2.9)	2.1	1.0 (0.8, 1.4)	1.0 (0.7, 1.3)
THZ	74	19,282	1.9 (0.9, 3.0)	1.9	1.0	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a New users were identified after excluding prevalent users of specific drugs in comparison, i.e., in ACEI/ARB vs. BB pair, prevalent use of CCB and thiazide were allowed.

^b Incidence rates are per 1,000 population.

^c Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

eTable 16. Incidence of colorectal cancer among antihypertensive initiators after varying induction or lag periods, according to as treated analyses^a

Drugs Comparison	No. of events	Total sample size	Follow up years (median, IQR)	Incidence rates ^b	Crude HR (95% CI)	Weighted HR (95% CI) ^c
As treated analyses						
No lag						
ACEI	266	128,335	0.6 (0.3, 1.4)	2.0	0.9 (0.8, 1.1)	0.9 (0.7, 1.1)
BB	192	92,119	0.5 (0.2, 1.3)	2.1	1.0	1.0
ACEI	272	128,335	0.6 (0.3, 1.4)	2.0	0.8 (0.6, 1.0)	0.9 (0.7, 1.1)
CCB	122	47,266	0.6 (0.2, 1.3)	2.5	1.0	1.0
ACEI	278	128,335	0.6 (0.3, 1.4)	2.1	1.1 (0.9, 1.5)	1.0 (0.6, 1.4)
THZ	57	32,921	0.5 (0.2, 1.2)	1.8	1.0	1.0
1-year lag						
ARB	197	94,210	0.6 (0.3, 1.3)	2.1	1.0 (0.8, 1.3)	1.0 (0.8, 1.3)
BB	129	66,012	0.5 (0.2, 1.3)	2.1	1.0	1.0
ARB	199	94,210	0.6 (0.3, 1.4)	2.1	1.0 (0.7, 1.3)	1.2 (0.9, 1.5)
CCB	69	32,830	0.6 (0.2, 1.3)	2.1	1.0	1.0
ARB	205	94,210	0.6 (0.3, 1.3)	2.2	1.0 (0.7, 1.3)	0.8 (0.5, 1.2)
THZ	52	24,997	0.5 (0.2, 1.2)	2.2	1.0	1.0
2-year lag						
ARB	131	68,055	0.6 (0.3, 1.2)	2.1	1.2 (0.9, 1.5)	1.1 (0.8, 1.5)
BB	75	47,016	0.5 (0.2, 1.1)	1.8	1.0	1.0
ARB	137	68,055	0.6 (0.3, 1.3)	2.2	1.0 (0.7, 1.5)	1.4 (0.9, 2.0)
CCB	43	22,681	0.5 (0.2, 1.3)	2.1	1.0	1.0
ARB	136	68,055	0.6 (0.3, 1.2)	2.2	1.0 (0.7, 1.5)	1.0 (0.6, 1.6)
THZ	34	18,832	0.5 (0.2, 1.1)	2.1	1.0	1.0

ACEI – Angiotensin Converting Enzyme Inhibitors, ARB – Angiotensin Receptor Blockers, THZ – Thiazide diuretics, CCB – Calcium Channel Blockers, BB – Beta Blockers, HR – hazard ratios, CI – confidence intervals, IQR – interquartile range

^a New users were identified after excluding prevalent users of specific drugs in comparison, i.e., in ACEI/ARB vs. BB pair, prevalent use of CCB and thiazide were allowed.

^b Incidence rates are per 1,000 population.

^c Weighted hazard ratios were adjusted for baseline covariates in Table 1. Weighting was implemented by standardized morbidity ratio weighting, where every patient was weighted to reflect covariate distributions in the exposed population (ACEI/ARB).

