

Supplemental Material

Data S1.

SUPPLEMENTAL METHODS

The propensity score was estimated using gradient boosted classification and regression trees (CART) to determine the probability of being prescribed a RAAS inhibitor or not. Briefly, a CART partitions the feature space into disjoint regions and assigns a constant value in these regions. While highly interpretable, a single CART has poor predictive performance. With gradient boosting, several single trees are combined by sequentially adding CARTs to predict the (pseudo) residuals from the former CARTs, creating an ensemble with a superior predictive performance.¹³⁸ Indeed, gradient boosted CARTs have many desirable properties as they handle missing covariate values, interactions and non-linear associations without the need for prior model specification. The influence of each additional CART is controlled via a shrinkage parameter and the optimal number of CARTs to include was determined by the average standardized mean differences (SMD) between the study groups. For each iteration, the SMD was calculated for every variable and averaged. The number of CARTs was then selected where the average SMD was minimized. Recommendations were followed for tuning the hyperparameters, allowing for the assessment of up to four-way interactions with the shrinkage parameter set to 0.0005.¹³⁹ Each CART was fitted in a random subsample of 50% and 50,000 iterations were run.

Table S1. Variables chosen to represent concepts in The Summary of Product Characteristics for key drugs in the studied drug classes.

	ATC codes	ICD codes	Procedure codes	Other
ACE inhibitors, ARBs and similar	C09			
Digoxin	C01A			
Drugs used in diabetes	A10			
NSAIDs	M01A			
Drugs affecting the immune system	L03, L04			
Corticosteroids	H02AB			
CYP3A4-inhibiting drugs	J05AE03, J01FA09, S01AA01, J02AB, J02AC, V03AX03, C01BD01, J01MA02, L04AD, L04AA10, L01C			
CYP3A4-inducing drugs	L02BB, N03AB02, N03AF01, N03AF02, N03AX11, J04AB02, J04AB04			
Angioedema		T78.3, D84.1		
Diabetes mellitus		E10-E14		
Renal disease		N17-N19		
Hepatic disease		K70-K77, B18		
Psychiatric disease		F20-F29, F32-F34, F41		
	ATC codes	ICD codes	Procedure codes	Other

Neuropsychiatric disease	<i>F40, F42, F50, F60, F61, F84.0, F84.1, F84.5, F90</i>	
Neoplasms	<i>C00-D48</i>	
Autoimmune disease	K900, E271, L80, D51	
Obesity	E65, E66	
Heart valve disease	I05, I06, I07, I08, I09.1, I34, I35, I36, I37, I38, I39, Q23.0, Q23.1, Q23.2, Q23.3, Z95.2, Z95.3, Z95.4	FG, FJE, FJF, FK, FM
Hypertrophic cardiomyopathy	I42.1, I42.2	
Age		From SCB: 2020-01 minus (birth year, birth month)
Sex		From SCB
Ethnicity (own country of birth, parents' country of birth)		From SCB: FodGrEg4, FodGrFar4, FodGrMor4
Socioeconomic status (SEI, marital status, highest education)		From SCB LISA 2018: ESeG_J16, Civil, Sun2000niva_old

ACE denotes angiotensin-converting enzyme; ARBs, angiotensin II type-I receptor blockers; NSAID, nonsteroidal anti-inflammatory drug; SCB, Statistics Sweden; SEI, socio-economic index.

Table S2. Baseline characteristics of persons using an angiotensin converting enzyme inhibitor.

	Unweighted			Weighted		
	ACE inhibitor (N=47998)	CCB or TZD (N=48418)	SMD	ACE inhibitor (N=164053.3)	CCB or TZD (N=161185.2)	SMD
Female, N (%)	22083 (46.0)	25899 (53.5)	0.150	81684.7 (49.8)	81177.1 (50.4)	0.011
Age in years, median [IQR]	62.0 [53.0-71.0]	65.0 [56.0-74.0]	0.232	63.0 [54.0-72.0]	64.0 [55.0-72.0]	0.028
Yearly income in SEK, median [IQR]	384120 [243840-522360]	339120 [213600-489720]	0.136	377915 [237120-521520]	374640 [235920-516515]	0.027
Education, N (%)			0.053			0.011
Elementary school	9618 (20.2)	10738 (22.4)		32054.0 (19.7)	31899.6 (19.9)	
High school	23119 (48.6)	22677 (47.2)		78406.5 (48.1)	77422.9 (48.4)	
Academic	14389 (30.2)	14141 (29.5)		50731.5 (31.1)	49168.7 (30.7)	
Postgraduate	474 (1.0)	452 (0.9)		1687.9 (1.0)	1572.5 (1.0)	
Marital Status, N (%)			0.123			0.010
Unmarried	11153 (23.3)	9840 (20.3)		35619.8 (21.7)	34583.8 (21.5)	
Married	26108 (54.4)	25755 (53.3)		89915.5 (54.9)	88364.6 (54.9)	
Divorced	7336 (15.3)	7974 (16.5)		25542.7 (15.6)	25583.9 (15.9)	
Widow	3352 (7.0)	4790 (9.9)		12820.2 (7.8)	12498.6 (7.8)	
Region of birth, N (%)			0.042			0.010
Africa	504 (1.1)	624 (1.3)		1554.9 (0.9)	1579.3 (1.0)	
Asia	1919 (4.0)	2059 (4.3)		6072.1 (3.7)	6138.4 (3.8)	
Nordic countries	1820 (3.8)	1593 (3.3)		5658.7 (3.4)	5658.1 (3.5)	
North America	119 (0.2)	135 (0.3)		388.7 (0.2)	395.8 (0.2)	
Rest of Europe	2595 (5.4)	2429 (5.0)		7727.0 (4.7)	7493.9 (4.6)	
South America	269 (0.6)	221 (0.5)		845.1 (0.5)	791.4 (0.5)	
Sweden	40975 (85.4)	41141 (85.0)		139055.2 (86.3)	141841.4 (86.5)	
Medical history, N (%)						
Angioedema	64 (0.1)	194 (0.4)	0.052	350.5 (0.2)	388.9 (0.2)	0.006
Diabetes mellitus	657 (1.4)	448 (0.9)	0.042	1789.0 (1.1)	1868.0 (1.2)	0.006
Renal disease	698 (1.5)	491 (1.0)	0.040	1827.9 (1.1)	1415.9 (0.9)	0.024
Hepatic disease	528 (1.1)	552 (1.1)	0.004	1684.6 (1.0)	1685.3 (1.0)	0.002
Psychiatric disease	3316 (6.8)	2844 (5.9)	0.038	9759.6 (5.9)	9853.1 (6.1)	0.007

	Unweighted			Weighted		
	ACE inhibitor	CCB or TZD	SMD	ACE inhibitor	CCB or TZD	SMD
Medical history, N (%)						

Neuropsychiatric disease	937 (2.0)	911 (1.9)	0.005	2872.5 (1.8)	2884.8 (1.8)	0.003
Neoplasms	2699 (5.6)	3041 (6.3)	0.028	9796.4 (6.0)	9748.5 (6.0)	0.003
Autoimmune disease	296 (0.6)	304 (0.6)	0.001	1027.9 (0.6)	1093.7 (0.7)	0.006
Obesity	1311 (2.7)	1075 (2.2)	0.033	4124.1 (2.5)	4248.1 (2.6)	0.008
Heart valve disease	472 (1.0)	423 (0.9)	0.011	1650.1 (1.0)	1320.3 (0.8)	0.020
Hypertrophic cardiomyopathy	10 (0.0)	8 (0.0)	0.003	32.4 (0.0)	36.5 (0.0)	0.002
Pharmacotherapy, N (%)						
Antidiabetic drugs	853 (1.8)	540 (1.1)	0.055	2334.3 (1.4)	2387.0 (1.5)	0.005
NSAID	31269 (65.1)	32456 (67.0)	0.040	109853.1 (67.0)	109069.3 (67.7)	0.015
Immune system- affecting drugs	821 (1.7)	837 (1.7)	0.001	2730.6 (1.7)	2693.8 (1.7)	0.001
Previous ACE inhibitor/ARB	34888 (72.7)	13988 (28.9)	0.974	98581.5 (60.1)	95444.3 (59.2)	0.018

Unweighted and weighted characteristics of the study groups included in the secondary analysis, comprised of all Swedish residents using an angiotensin converting enzyme inhibitor in monotherapy, compared to those using a calcium channel blocker or thiazide diuretic in monotherapy; as of January 1st 2020. ACE denotes angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SEK, Swedish Kronor (currency of Sweden: 8.5 SEK = 1.0 USD); SMD, standardized mean difference; TZD, thiazide diuretic.

Table S3. Baseline characteristics of persons using an angiotensin II type-I receptor blocker.

	Unweighted			Weighted		
	ARB (N=68239)	CCB or TZD (N=48418)	SMD	ARB (N=164293.3)	CCB or TZD (N=161185.2)	SMD
Female, N (%)	34245 (50.2)	25899 (53.5)	0.066	82107.3 (50.0)	81177.1 (50.4)	0.008
Age in years, median [IQR]	63.0 [54.0-71.0]	65.0 [56.0-74.0]	0.205	63.0 [54.0-72.0]	64.0 [55.0-72.0]	0.030
Yearly income in SEK, median [IQR]	398640 [253080-541320]	339120 [213600-489720]	0.202	378000 [237480-521280]	374640 [235920-516515]	0.029
Education, N (%)			0.143			0.019
Elementary school	11562 (17.0)	10738 (22.4)		31777.6 (19.5)	31899.6 (19.9)	
High school	32762 (48.3)	22677 (47.2)		78422.5 (48.1)	77422.9 (48.4)	
Academic	22684 (33.4)	14141 (29.5)		51148.9 (31.4)	49168.7 (30.7)	
Postgraduate	833 (1.2)	452 (0.9)		1765.2 (1.1)	1572.5 (1.0)	
Marital Status, N (%)			0.123			0.010
Unmarried	14680 (21.5)	9840 (20.3)		35561.6 (21.7)	34583.8 (21.5)	
Married	38507 (56.5)	25755 (53.3)		90156.4 (54.9)	88364.6 (54.9)	
Divorced	10337 (15.2)	7974 (16.5)		25512.2 (15.5)	25583.9 (15.9)	
Widow	4651 (6.8)	4790 (9.9)		12898.9 (7.9)	12498.6 (7.8)	
Region of birth, N (%)			0.101			0.011
Africa	461 (0.7)	624 (1.3)		1509.2 (0.9)	1579.3 (1.0)	
Asia	2183 (3.2)	2059 (4.3)		6081.4 (3.7)	6138.4 (3.8)	
Nordic countries	2347 (3.4)	1593 (3.3)		5709.3 (3.5)	5658.1 (3.5)	
North America	141 (0.2)	135 (0.3)		391.6 (0.2)	395.8 (0.2)	
Rest of Europe	2783 (4.1)	2429 (5.0)		7711.9 (4.7)	7493.9 (4.6)	
South America	320 (0.5)	221 (0.5)		799.0 (0.5)	791.4 (0.5)	
Sweden	59997 (87.9)	41141 (85.0)		142070.0 (86.5)	141841.4 (86.5)	
Medical history, N (%)						
Angioedema	139 (0.2)	194 (0.4)	0.036	395.7 (0.2)	388.9 (0.2)	<0.001
Diabetes mellitus	662 (1.0)	448 (0.9)	0.005	1727.9 (1.1)	1868.0 (1.2)	0.010
Renal disease	662 (1.0)	491 (1.0)	0.004	1845.1 (1.1)	1415.9 (0.9)	0.025
Hepatic disease	616 (0.9)	552 (1.1)	0.024	1621.0 (1.0)	1685.3 (1.0)	0.006
Psychiatric disease	3783 (5.5)	2844 (5.9)	0.054	9810.3 (6.0)	9853.1 (6.1)	0.006

	Unweighted			Weighted		
	ARB	CCB or TZD	SMD	ARB	CCB or TZD	SMD

Medical history, N (%)						
Neuropsychiatric disease	1053 (1.5)	911 (1.9)	0.026	2852.2 (1.7)	2884.8 (1.8)	0.004
Neoplasms	4113 (6.0)	3041 (6.3)	0.011	9838.5 (6.0)	9748.5 (6.0)	0.003
Autoimmune disease	452 (0.7)	304 (0.6)	0.004	1075.1 (0.7)	1093.7 (0.7)	0.003
Obesity	1758 (2.6)	1075 (2.2)	0.023	4091.8 (2.5)	4248.1 (2.6)	0.009
Heart valve disease	703 (1.0)	423 (0.9)	0.016	1597.1 (1.0)	1320.3 (0.8)	0.016
Hypertrophic cardiomyopathy	16 (0.0)	8 (0.0)	0.005	36.5 (0.0)	36.5 (0.0)	<0.001
Pharmacotherapy, N (%)						
Antidiabetic drugs	946 (1.4)	540 (1.1)	0.024	2363.6 (1.4)	2387.0 (1.5)	0.004
NSAID	46869 (68.7)	32456 (67.0)	0.035	110303.8 (67.1)	109069.3 (67.7)	0.011
Immune system- affecting drugs	1080 (1.6)	837 (1.7)	0.011	2677.9 (1.6)	2693.8 (1.7)	0.003
Previous ACE inhibitor/ARB	49826 (73.0)	13988 (28.9)	0.984	98700.6 (60.1)	95444.3 (59.2)	0.018

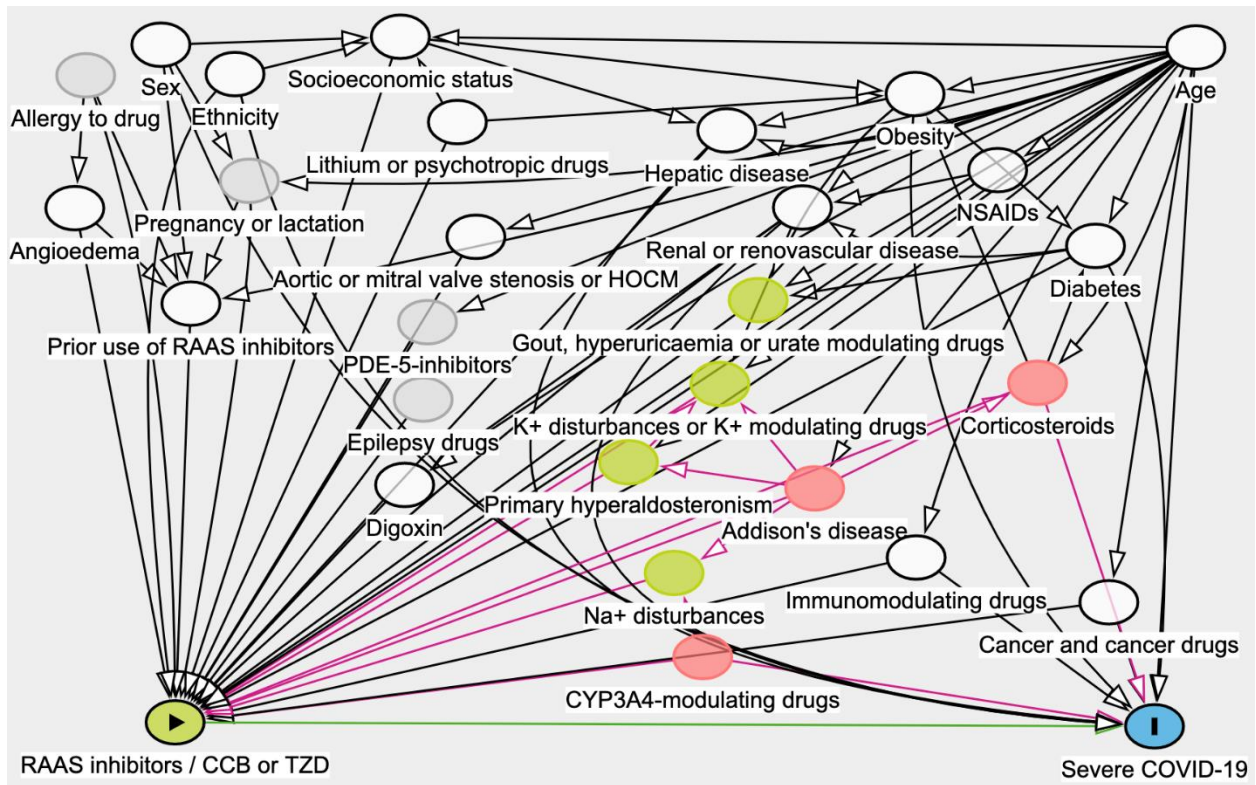
Unweighted and weighted characteristics of the study groups included in the secondary analysis, comprised of all Swedish residents using an angiotensin II type-I receptor blocker in monotherapy, compared to those using a calcium channel blocker or thiazide diuretic in monotherapy; as of January 1st 2020. ACE denotes angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker; CCB, calcium channel blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug; SEK, Swedish Kronor (currency of Sweden: 8.5 SEK = 1.0 USD); SMD, standardized mean difference; TZD, thiazide diuretic.

Table S4. Unadjusted and adjusted associations of RAAS inhibitor use with COVID-19 outcomes.

Outcome	Rate of outcome with RAAS inhibitor use <i>versus</i> use of a CCB or TZD (HR and 95% CI)			
	Intention to treat		As treated	
	Unadjusted	Adjusted	Unadjusted	Adjusted
RAAS inhibitor (n=115684)				
Hospitalization with COVID-19	0.92 (0.70-1.21)	0.92 (0.71-1.22)	0.89 (0.67-1.19)	0.89 (0.66-1.20)
Death with COVID-19	1.17 (0.66-2.10)	1.22 (0.68-2.19)	1.17 (0.65-2.10)	1.22 (0.69-2.31)
Hospitalization or death with COVID-19 combined	0.96 (0.74-1.25)	0.97 (0.74-1.27)	0.91 (0.70-1.19)	0.95 (0.71-1.26)
ACE inhibitor (n=47998)				
Hospitalization with COVID-19	0.89 (0.64-1.22)	0.89 (0.64-1.23)	0.84 (0.60-1.18)	0.85 (0.60-1.19)
Death with COVID-19	1.04 (0.52-2.01)	0.97 (0.48-1.93)	0.97 (0.48-1.97)	0.94 (0.46-1.92)
Hospitalization or death with COVID-19 combined	0.94 (0.69-1.27)	0.95 (0.69-1.29)	0.89 (0.65-1.23)	0.91 (0.65-1.26)
ARB (n=68239)				
Hospitalization with COVID-19	0.93 (0.69-1.26)	0.94 (0.70-1.27)	0.92 (0.67-1.26)	0.93 (0.67-1.27)
Death with COVID-19	1.28 (0.64-2.59)	1.25 (0.63-2.49)	1.35 (0.67-2.73)	1.68 (0.69-2.77)
Hospitalization or death with COVID-19 combined	0.97 (0.73-1.31)	0.99 (0.73-1.32)	0.96 (0.71-1.30)	0.98 (0.72-1.33)

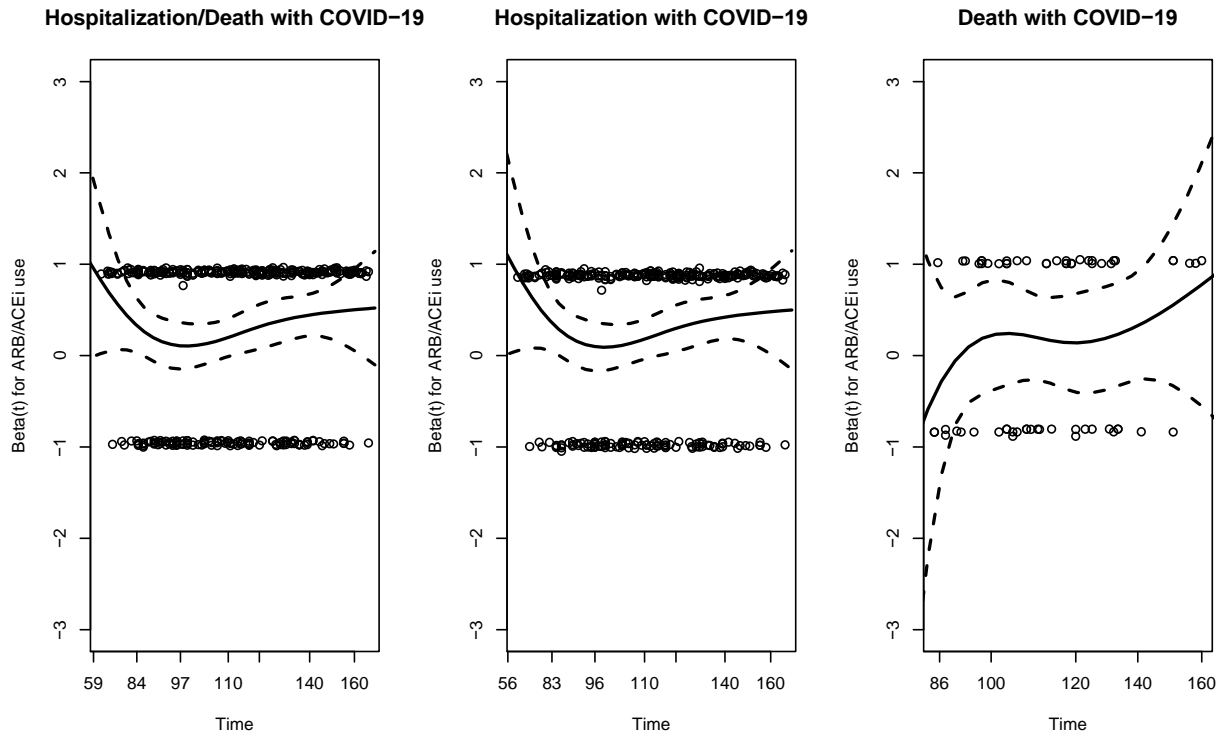
Swedish residents on antihypertensive monotherapy with RAAS inhibitor were compared to those on monotherapy with either a calcium channel blocker or thiazide diuretic, in both an intention to treat and an as treated model. In addition to assessing the associations of each RAAS inhibitor combined, the associations of ACE inhibitor and ARB use were also assessed independently of each other. RAAS denotes renin-angiotensin aldosterone system; CCB, calcium channel blocker; TZD, thiazide diuretic; HR, Cox proportional hazard ratio; CI, confidence interval; COVID-19, coronavirus disease 2019; ACE, angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker.

Figure S1. Causal assumptions.



The directed acyclic graphs approach used to identify the bias-minimized models investigating the total effects in this study. CCB denotes calcium channel blockers; COVID-19, coronavirus disease 2019; HOCM, hypertrophic obstructive cardiomyopathy; NSAIDs, non-steroidal anti-inflammatory drugs; PDE-5-inhibitors, phosphodiesterase type 5 inhibitors; RAAS, renin-angiotensin aldosterone system; TZD, thiazide diuretic.

Figure S2. Proportionality of the hazards.



Raw (circles) and spline smoothed (solid lines) scaled Schoenfeld residuals for RAAS inhibitor use and hospitalization or death with COVID-19 (left panel), for hospitalization with COVID-19 (middle panel), and death with COVID-19 (right panel), ± 2 standard errors (broken lines). Although the test indicates non-proportional hazards, the smoothed association between the scaled Schoenfeld residuals reveals little. ACE denotes angiotensin converting enzyme; ARB, angiotensin II type-I receptor blocker; COVID-19, coronavirus disease 2019; RAAS denotes renin-angiotensin aldosterone system.