SUPPLEMENTAL MATERIAL

Supplemental Methods

Data Sources and Study design

The study aimed to compare whether renin-angiotensin system inhibitor (RASI)-only or calcium channel blocker (CCB)-only was clinically more beneficial as initial antihypertensive therapy from the LIFE Study database comprising 14 municipality-level sources of claims data between 2016 and 2020. The time to treatment failure (TTF) was compared between RASI-only (n=707) and CCB-only (n=1,096) groups. To accurately assess whether RASI or CCB is more effective as a primary antihypertensive drug, patients receiving other antihypertensives were excluded (total, n=426; beta-blocker, n=190; alpha-blocker, n=95; thiazide, n=57; and mineralocorticoid-receptor antagonists, n=149; including duplication). In addition, patients taking both RASI and CCB were excluded (n=151). A total of 1,330 patients were eligible for the second evaluation **(Supplemental Figure 1)**. Antihypertensive drugs were defined as those summarized in **Supplemental Table 1**. The diagnostic criteria for hypertension were determined as registration of hypertension and administration of antihypertensive drugs. The date of diagnosis was determined as the first day of administration of antihypertensive drugs. As an indicator for clinical

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outcomes, TTF, defined as the time between the first and last administration of VSP inhibitors, was used. Medical history was extracted according to the Elixhauser Comorbidity Index. **(18)**

Statistical analysis

Statistical analysis was performed using the same protocol described in the main paper. The without-RASI group for the primary endpoint and the CCB-only for the secondary endpoint were set as references; the hazard ratio (HR) was described with a 95% confidence interval (CI). $P < 0.05$ was considered statistically significant for all other statistical analyses. Statistical analyses were performed using Python, version 3.8.5 (Python Software Foundation, Beaverton, Oregon, USA).

Supplemental Results

Patient characteristics

The LIFE Study database comprised 1,588,335 patients. In this study, 4,004 patients fulfilled the inclusion criteria. After excluding patients who received only one cycle of VSP inhibitors (n=426) and those who were not diagnosed with hypertension before or during VSP inhibitor therapy (n=1,196), a total of 2,380 patients with

hypertension were eligible. Among them, 1,954 patients treated with RASI and CCB were selected. After exclusion of patients treated with both RASI and CCB, a total of 1,803 patients were eligible: RASI-only (n=707) and CCB-only (n=1,096). The study design is shown in **Supplemental Figure 1**. Patient characteristics and primary cancer lesions with associated VSP inhibitors are described in **Supplemental Tables 2 and 3**.

RASI-only vs. CCB-only for hypertension in patients treated with VSP inhibitors

Median TTFs were 171 [63–396] days in the RASI-only group and 168 [69–389] days in the CCB-only group, and no significant difference was detected between groups (*P*=0.584, log-rank test; **Supplemental Figure 2**). In addition, there was no significant gap between groups using the unadjusted, adjusted Cox proportional hazard model, and inverse probability of treatment weighting (IPTW) model **(Supplemental Table 4)**. Other propensity models were also unable to detect the clinical effects of RASIs.

Even in the patients who received VSP inhibitor treatment for more than 4 weeks, no significant difference in TTF was demonstrated between RASI-only and CCB-only groups: HR 0.93 [0.84–1.03] (*P*=0.143) in the adjusted model with HR 0.92 [0.82–1.03] (*P*=0.131) in the IPTW model **(Supplemental Table 4)**. Similar results were

obtained in models restricted to the patients newly diagnosed with hypertension after VSP inhibitor administration. Besides, no subgroup revealed a significant favourable clinical impact of RASI-only treatment **(Supplemental Table 5)**.

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Supplemental Table 1. Definition of Antihypertensive drugs

Renin-angiotensin system inhibitors
Angiotensin-converting enzyme inhibitors
Alacepril
benazepril hydrochloride
Captopril
Cilazapril hydrate
Delapril hydrochloride
Enalapril maleate
Imidapril hydrochloride
Lisinopril hydrate
Temocapril hydrochloride
Trandolapril
Perindopril erbumine
Quinapril hydrochloride
Angiotensin-II receptor blockers
Azilsartan
candesartan cilexetil
Irbesartan
Telmisartan
losartan potassium
Olmesartan medoxomil
Valsartan
Calcium channel blockers
Amlodipine besylate
Aranidipine
Barnidipine hydrochloride
Benidipine hydrochloride
Cilnidipine
Efonidipine hydrochloride ethanolate
Felodipine
Manidipine hydrochloride
Nicardipine hydrochloride
Nifedipine
Nisoldipine
Nitrendipine
Nilvadipine
Alpha blockers
Bunazosin hydrochloride
Doxazosin mesylate
Prazosin hydrochloride
Terazosin hydrochloride hydrate
Urapidil

Beta blockers*
Acebutolol hydrochloride
Amosulalol hydrochloride
Arotinolol hydrochloride
Atenolol
Betaxolol hydrochloride
Bevantolol hydrochloride
Bisoprolol fumarate
Carteolol hydrochloride
Carvedilol
Nipradilol
Pindolol
Propranolol hydrochloride
Mineralocorticoid receptor antagonists
Eplerenone
Spironolactone
Triamterene
Thiazide
Benzylhydrochlorothiazide
Hydrochlorothiazide
Indapamide
Mefruside
Trichlormethiazide
Tripamide

* Including alpha and beta blockers

Supplemental Table 2. Patient characteristics of RAS-only and CCB-only groups

	Total (n = 1,803)	RASI-only (n = 707)	CCB-only (n = 1,096)	*P* value
Age	74 [68–78]	74 [68–78]	74 [68–78]	0.959
Age				0.357
< 50 years old	24 (1.3%)	6 (0.8%)	18 (1.6%)	
50-70 years old	527 (29.2%)	208 (29.4%)	319 (29.1%)	
≥ 70years old	1,252 (69.4%)	493 (69.7%)	759 (69.3%)	
Male	1,087 (60.2%)	435 (61.5%)	652 (59.5%)	0.388
Timing of hypertension onset				0.170
Pre-existing	1,330 (73.8%)	509 (72.0%)	821 (74.9%)	
New-onset	473 (26.2%)	198 (28.0%)	275 (25.1%)	
Cancer site				0.212
Colorectal	793 (44.0%)	292 (41.3%)	501 (45.7%)	
Stomach	259 (14.4%)	113 (16.0%)	146 (13.3%)	
Liver	432 (24.0%)	171 (24.2%)	261 (23.8%)	
Lung	319 (17.7%)	131 (18.5%)	188 (17.2%)	
VSP Inhibitors				0.187
Ramucirumab	358 (19.9%)	149 (21.1%)	209 (19.1%)	
Bevacizumab	1,162 (64.4%)	453 (64.1%)	709 (64.7%)	
Lenvatinib	136 (7.5%)	58 (8.2%)	78 (7.1%)	
Sorafenib	147 (8.2%)	47 (6.6%)	100 (9.1%)	
Past medical history				
Chronic pulmonary disease	766 (42.5%)	297 (42.0%)	469 (42.8%)	0.742
Psychoses	222 (12.3%)	89 (12.6%)	133 (12.1%)	0.775
CHF	488 (27.1%)	193 (27.3%)	295 (26.9%)	0.858
Valvular disease	232 (12.9%)	96 (13.6%)	136 (12.4%)	0.469
Cardiac arrhythmias	323 (17.9%)	121 (17.1%)	202 (18.4%)	0.477
Depression	295 (16.4%)	119 (16.8%)	176 (16.1%)	0.665
Diabetes	514 (28.5%)	209 (29.6%)	305 (27.8%)	0.426
Renal failure	180 (10.0%)	72 (10.2%)	108 (9.9%)	0.820
Peripheral vascular disorders	281 (15.6%)	122 (17.3%)	159 (14.5%)	0.116
Hypothyroidism	173 (9.6%)	66 (9.3%)	107 (9.8%)	0.763
Liver disease	975 (54.1%)	386 (54.6%)	589 (53.7%)	0.722

CCB: Calcium channel blocker, CHF: congestive heart failure, RASI: renin-angiotensin system inhibitors, VSP: vascular endothelial growth factor signalling pathway

Supplemental Table 3. Combination of primary cancer lesions and VSP inhibitors

		With-RASI vs. Without-RASI					RASI-only vs. CCB-only				
		Primary cancer site				Total	Primary cancer site				Total
		Colorectal	Gastric	Liver	Lung		Colorectal	Gastric	Liver	Lung	
Type of VSP inhibitors	Ramucirumab	38	353	19	74	484	29	259	12	58	358
	Bevacizumab	966	0	174	341	1,481	764	0	137	261	1,162
	Lenvatinib	0	0	197	0	197	0	0	136	0	136
	Sorafenib	0	0	218	0	218	0	0	147	0	147
	Total	1,004	353	608	415	2,380	793	259	432	319	1,803

CRC: colorectal cancer, HCC: Hepatocellular carcinoma, RCC: Renal cell carcinoma, VSP: vascular endothelial growth factor signalling pathway

Supplemental Table 4. TTF analyses between RASI-only and CCB-only groups

Analysis Models	Sample size		HR [95% CI]	*P* value
	RASI-only	CCB-only		
All patients				
Unadjusted analysis	707	1,096	0.97 [0.89–1.07]	0.580
Multivariate analysis*	707	1,096	0.95 [0.86–1.05]	0.289
Propensity score-adjusted model				
IPTW	707	1,086	0.94 [0.85–1.05]	0.265
Regression adjustment	707	1,086	0.94 [0.85–1.04]	0.260
Matching 1:1	697	697	0.96 [0.85–1.07]	0.437
Stratification	707	1,086	0.94 [0.85–1.04]	0.250
Within–propensity score quintile				
1 (Lowest propensity score)	119	240	0.96 [0.76–1.22]	0.731
2	130	228	0.87 [0.68–1.10]	0.241
3	145	214	1.08 [0.86–1.35]	0.527
4	143	215	1.00 [0.80–1.27]	0.968
5 (Highest propensity score)	170	189	0.82 [0.65–1.03]	0.088
Patients who were treated for > 4 weeks with VSP inhibitor administrated				
Unadjusted analysis	642	1,012	0.95 [0.86–1.05]	0.358
Multivariate analysis*	642	1,012	0.93 [0.84–1.03]	0.143
Propensity score-adjusted model (IPTW)	642	1,005	0.92 [0.82–1.03]	0.131
Patients with *de-novo* hypertension after VSP inhibitor administration				
Unadjusted analysis	198	275	0.99 [0.83–1.19]	0.942
Multivariate analysis*	198	275	0.93 [0.77–1.12]	0.428
Propensity score-adjusted model (IPTW)	197	265	0.87 [0.71–1.07]	0.188

CCB: Calcium channel blocker, IPTW: Inverse probability of treatment weighting, RASI: renin-angiotensin system inhibitors, TTF: time to treatment failure, VSP: vascular endothelial growth factor signalling pathway

* Adjusting age, sex, primary cancer lesion, type of VSP inhibitors, and past medical histories

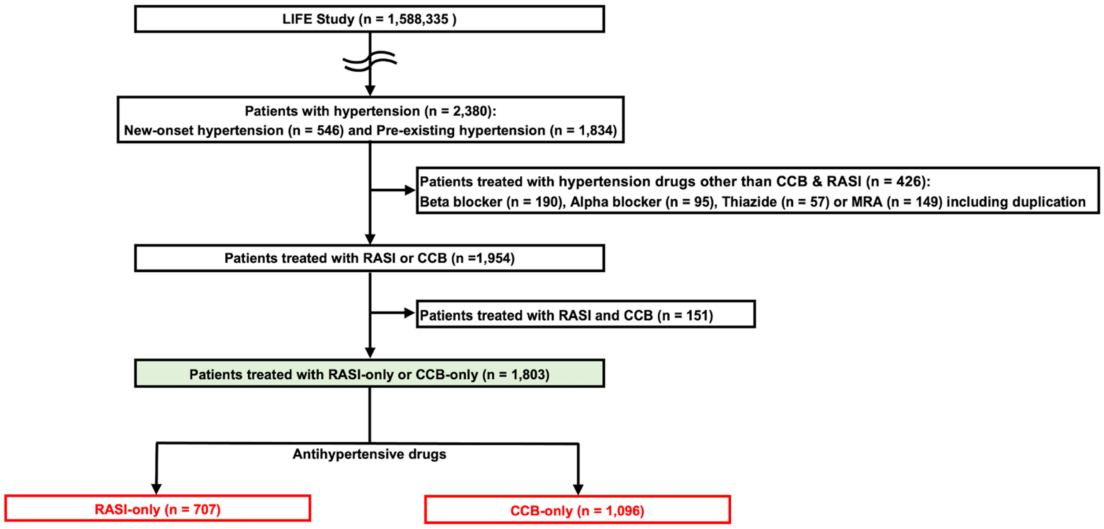
Supplemental Table 5. TTF and unadjusted analysis among RASI-only and CCB-only

	TTF [IQR] (days)		HR [95% CI]
	RASI-only	CCB-only	
Treatment			
non RASI group	-	168 [69–389]	-
RASI group	171 [63–396]	-	-
Age			
< 50 years old	356 [239–665]	164 [110–547]	0.87 [0.33–2.25]
50–70 years old	250 [91–547]	187 [80–468]	0.86 [0.72–1.02]
≥ 70 years old	146 [57–349]	154 [63–364]	1.03 [0.92–1.15]
Sex			
Female	220 [84–469]	168 [70–389]	0.89 [0.76–1.03]
Male	146 [60–366]	168 [66–387]	1.04 [0.92–1.17]
Timing of hypertension onset			
Pre-existing	127 [53–331]	147 [57–309]	1.00 [0.89–1.11]
New-onset	321 [143–594]	308 [126–562]	0.99 [0.83–1.19]
Cancer site			
Colorectal	260 [91–546]	245 [107–518]	0.96 [0.83–1.11]
Stomach	83 [42–169]	80 [42–161]	0.90 [0.71–1.16]
Liver	149 [56–346]	133 [49–329]	0.93 [0.76–1.12]
Lung	175 [81–367]	152 [75–284]	0.93 [0.74–1.16]
VSP Inhibitors			
Ramucirumab	78 [42–168]	100 [42–180]	0.99 [0.80–1.23]
Bevacizumab	252 [98–525]	229 [103–490]	0.95 [0.84–1.07]
Lenvatinib	109 [38–234]	112 [47–288]	1.14 [0.81–1.61]
Sorafenib	96 [36–250]	78 [32–272]	0.93 [0.65–1.32]
Past medical history			
Chronic pulmonary disease	146 [58–384]	183 [84–448]	1.10 [0.95–1.27]
Psychoses	186 [63–434]	196 [84–363]	0.98 [0.75–1.28]
CHF	156 [56–380]	161 [58–388]	1.02 [0.85–1.23]
Valvular disease	156 [56–380]	161 [58–388]	1.02 [0.79–1.33]
Cardiac arrhythmias	158 [63–359]	147 [63–324]	1.08 [0.86–1.35]
Depression	182 [61–415]	169 [68–371]	0.92 [0.72–1.16]
Diabetes	150 [61–371]	147 [62–350]	1.03 [0.86–1.23]
Renal failure	151 [58–425]	128 [49–322]	0.94 [0.69–1.27]
Peripheral vascular disorders	132 [49–301]	132 [58–300]	1.01 [0.80–1.28]
Hypothyroidism	145 [56–319]	154 [61–344]	1.05 [0.77–1.44]
Liver disease	148 [63–364]	168 [63–378]	1.03 [0.91–1.17]

CCB: Calcium channel blocker, CHF: congestive heart failure, CRC: colorectal cancer, HCC: Hepatocellular carcinoma, RASI: renin-angiotensin system inhibitors, TTF: time to treatment failure, VSP: vascular endothelial growth factor signalling pathway

Figure and Figure Legends

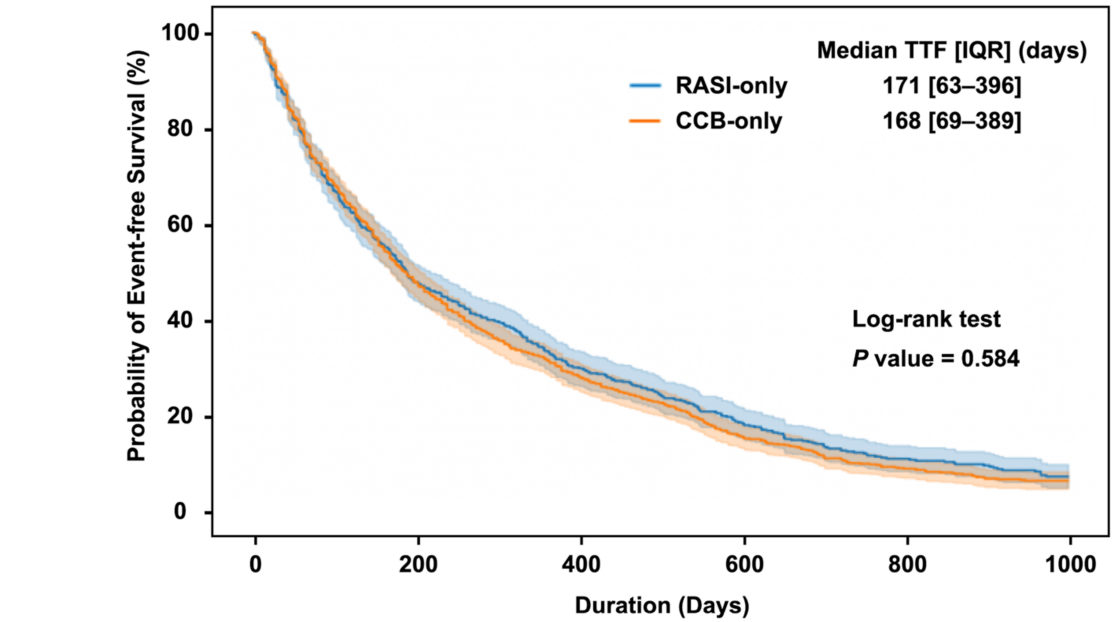
Supplemental Figure 1. Patient selection from the LIFE Study database



The LIFE Study database comprised 1,588,335 patients. In this study, 4,004 patients fulfilled the inclusion criteria (see method section). After excluding patients who received only one cycle of VSP inhibitors (n=426) and those who were not diagnosed with hypertension before or during VSP inhibitor therapy (n=1,198), a total of 2,380 patients with hypertension were eligible. Among them, 1,954 patients treated with RASI and CCB were selected. After the exclusion of 151 patients treated with both RASI and CCB, a total of 1,803 patients were finally eligible: RASI-only (n=707) and CCB-only (n=1,096).

CCB: calcium channel blocker, MRA: mineralocorticoid receptor antagonists, RASI: renin-angiotensin system inhibitors.

Supplemental Figure 2. Comparison of TTF between RASI-only and CCB-only groups



Number at risk						
RASI-only	707	311	176	98	50	29
CCB-only	1,096	481	265	133	73	46

Kaplan–Meier curve showing TTF between groups. Median TTFs in the RASI-only (171 [63–396] days) and the CCB-only (168 [69–389] days) groups were equivalent (log-rank *P*=0.584).
CCB: calcium channel blocker, RASI: renin-angiotensin system inhibitors, IQR: interquartile range, TTF: time to treatment failure