openheart

Effect of renin–angiotensin system inhibitors in patients with cancer treated with anti-VEGF therapy

Shohei Moriyama ,[1] Michinari Hieda ,[1] Megumi Kisanuki,[1] Shotaro Kawano,[2] Taku Yokoyama,[1] Mitsuhiro Fukata ,[1] Hitoshi Kusaba,[3] Toru Maruyama,[4] Eishi Baba,[5] Koichi Akashi,[1] Haruhisa Fukuda[6]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2022-002135).

To cite: Moriyama S, Hieda M, Kisanuki M, *et al*. Effect of renin–angiotensin system inhibitors in patients with cancer treated with anti-VEGF therapy. *Open Heart* 2022;**9**:e002135. doi:10.1136/openhrt-2022-002135

Received 12 October 2022
Accepted 8 November 2022

[1]Department of Haematology, Oncology and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka, Japan
[2]Division of Immunology and Rheumatology, Hamanomachi Hospital, Fukuoka, Japan
[3]Division of Oncology, Hamanomachi Hospital, Fukuoka, Japan
[4]Campus Life Health Center, Kyushu University, Fukuoka, Japan
[5]Department of Oncology and Social Medicine, Kyushu University, Fukuoka, Japan
[6]Department of Health Care Administration and Management, Kyushu University, Fukuoka, Japan

Correspondence to
Dr Michinari Hieda; hieda.michinari.265@m.kyushu-u.ac.jp

ABSTRACT

Background Cancer treatment with vascular endothelial growth factor signalling pathway (VSP) inhibitors frequently causes hypertension. Although previous reports suggested that the antihypertensive drug renin–angiotensin system inhibitor (RASI) may have a positive synergistic effect with VSP inhibitors, the actual impact on clinical outcomes is unknown.

Objectives The study aims to clarify whether RASIs exhibit clinical benefits for patients with cancer with hypertension.

Method From the Longevity Improvement and Fair Evidence Study database, comprising Japanese claims data between 2016 and 2020, we reviewed 2380 patients treated with VSP inhibitors who received antihypertensive treatment during cancer therapy. The patients were classified into two groups: with-RASI (n=883) and without-RASI (n=1497). In addition, 1803 of these patients treated for hypertension with RASI-only (n=707) or calcium channel blocker-only (n=1096) were also reviewed. The time-to-treatment failure (TTF), the interval from initiation of chemotherapy to its discontinuation, was applied as the primary endpoint.

Results The median TTFs were 167 (60–382) days in the with-RASI group and 161 (63–377) days in the without-RASI group (p=0.587). All models, including Cox proportional hazard models and multiple propensity score models, did not reveal the superiority of with-RASI treatment. In the propensity score matching model, the HR for treatment with-RASI compared with that for without-RASI was 0.96 (95% CI 0.86 to 1.06, p=0.386). In addition, the TTFs of RASI-only were not superior to calcium channel blocker-only (p=0.584).

Conclusions RASIs for hypertension do not benefit clinical outcomes during cancer therapy with VSP inhibitors. In addition, RASIs and calcium channel blockers have comparable clinical efficacy as first-line antihypertensive.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vascular endothelial growth factor signalling pathway (VSP) inhibitors have improved the prognosis of patients with cancer but frequently provoke hypertension as an adverse event.
⇒ Renin–angiotensin system inhibitors have been reported to have anti-angiogenesis effects and inhibit cancer progression, which may synergise with VSP inhibitors. However, few studies focus on antihypertensive drugs during cancer therapy with VSP inhibitors.

WHAT THIS STUDY ADDS

⇒ Renin–angiotensin system inhibitors used to treat hypertension do not improve clinical outcomes in patients with advanced cancer treated with VSP inhibitors.
⇒ Renin–angiotensin system inhibitors and calcium channel blockers exhibit comparable clinical efficacy as first-line antihypertensive drugs during cancer therapy with VSP inhibitors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Renin–angiotensin system inhibitors may not always be necessary for patients with advanced cancer treated with vascular endothelial growth factor VSP inhibitors.
⇒ Renin–angiotensin system inhibitors and calcium channel blockers are equally recommended as first-line antihypertensive drugs.

INTRODUCTION

Vascular endothelial growth factor (VEGF) signalling pathway (VSP) inhibitors can improve mortality in patients with solid tumours. Therefore, multiple VSP inhibitors are used to treat various types of cancer.[1] However, VSP inhibitors induce drug-specific adverse events, the most common being hypertension.[2] Blood pressure (BP) elevation is observed after the first administration of VSP inhibitors and persists during the subsequent cycle of administration of anticancer drugs.[3] Therefore, continuous monitoring of BP is recommended during cancer treatment with VSP inhibitors.[4] The goal of controlling BP during cancer treatment is to maintain BP levels below 140/90 mm Hg; if hypertension is not controlled, the intensity of cancer

treatment should be reduced.[1] This reduction in therapeutic dosage may diminish the effect of the anticancer drug and worsen mortality.

According to the guidelines for the treatment of hypertension, renin–angiotensin system inhibitors (RASIs) and non-dihydropyridine calcium channel blockers (CCBs) are the preferred first-line antihypertensive drugs.[5] Previous studies suggested that RASIs provide a favourable prognosis in patients with cancer. Kim *et al* reported the impact of RASIs on mortality in patients with gastric cancer treated with platinum-based chemotherapy.[6] Nakai *et al*[7] and Zhao *et al*[8] reported that RASIs enhanced the prognosis of patients with advanced pancreatic and ovarian cancer. However, there is no definitive consensus regarding antihypertensive drugs during cancer treatment.

Hypertension related to VSP inhibitors is caused by inhibition of the VEGF family in normal tissue and has been reported to be an indicator of favourable clinical outcomes.[9] However, few studies focused on antihypertensive drugs during cancer therapy with VSP inhibitors. Therefore, we hypothesised that there might be clinical benefits associated with treatment with RASIs when used as an antihypertensive drug during VSP inhibitor therapy. The study aimed to assess whether the with-RASI group achieved a more favourable clinical outcome than the without-RASI group.

METHODS

Data sources and study design

The Longevity Improvement and Fair Evidence (LIFE) Study database consisted of 14 municipality-level sources primarily from claims data between 2016 and 2020, involving 1 588 335 patients (figure 1).[10] In this study, 4004 patients fulfilled the inclusion criteria: (A) patients diagnosed with target cancer and received corresponding VSP inhibitor therapy, (B) patients who were treated with a single VSP inhibitor during cancer treatment and (C) age ≥18 years. Target primary cancer lesions and corresponding VSP inhibitors were determined as follows: colorectal and bevacizumab or ramucirumab, gastric and ramucirumab, liver and lenvatinib, bevacizumab, ramucirumab or sorafenib, and lung and bevacizumab or ramucirumab. 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=1198), a total of 2380 patients (new-onset hypertension: n=546; pre-existing hypertension: n=1834) were eligible. With respect to antihypertensive drugs, the clinical outcomes of the with-RASI group (n=883) were compared with those of the without-RASI group (N=1497) (figure 1). RASIs were either ACE

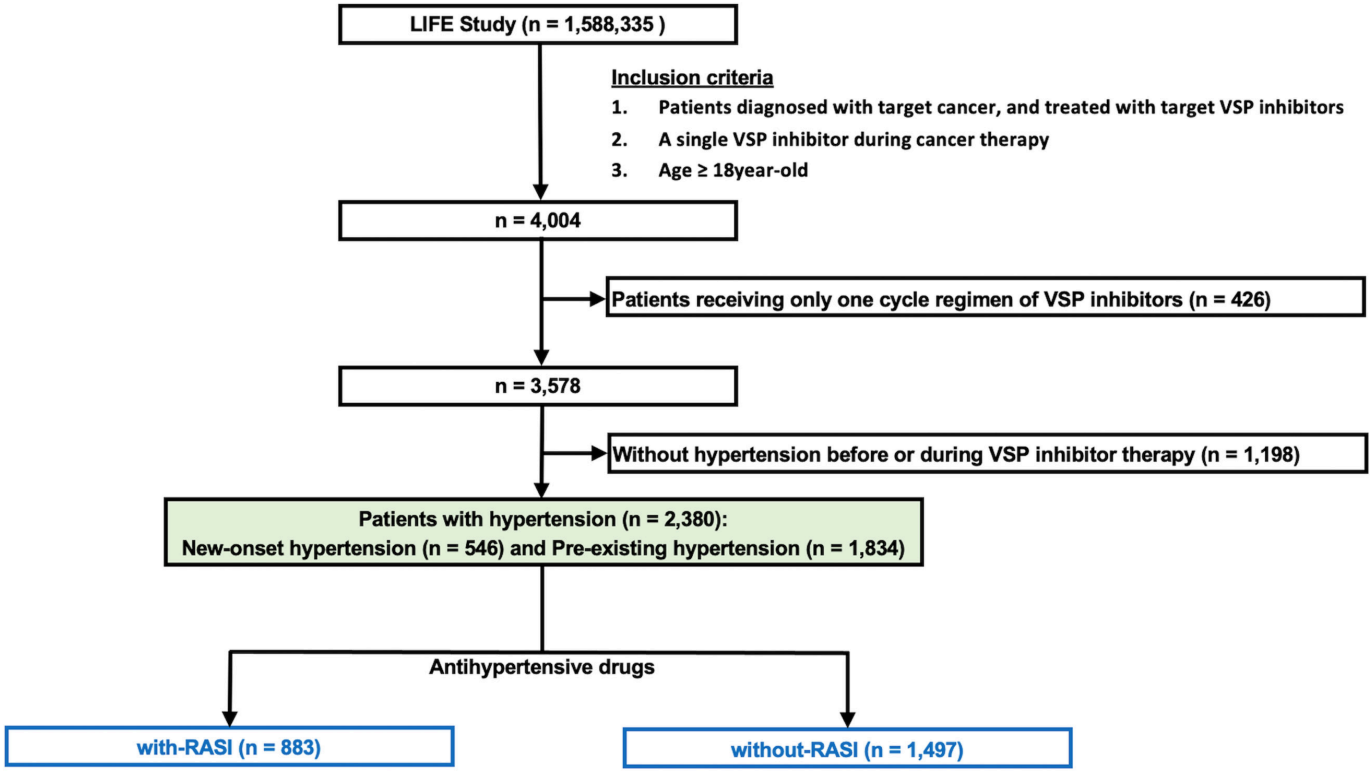

Figure 1 Patient selection from the LIFE study database. The LIFE study database comprised 1 588 335 patients. In this study, 4004 patients fulfilled the inclusion criteria. After excluding patients who received only one cycle of VSP inhibitors (n=426) and those who were not diagnosed with hypertension before or during VSP inhibitor therapy (n=1198), a total of 2380 patients with hypertension were eligible (new-onset hypertension: n=546 and pre-existing hypertension: n=1834). The patients with hypertension were stratified into two groups, according to antihypertensive drugs: with-RASI (n=883) vs without-RASI group (n=1497). LIFE, Longevity Improvement and Fair Evidence; RASI, renin–angiotensin system inhibitors; VSP, vascular endothelial growth factor signalling pathway.

inhibitors or angiotensin II receptor blockers (online supplemental table 1).

The diagnostic criteria for hypertension were determined as the registration of the disease of hypertension and the administration of antihypertensive drugs. The date of diagnosis was determined as the first administration day of antihypertensive drugs. As an indicator of clinical outcome, time-to-treatment failure (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.[11]

This was a cohort-based retrospective study, and patients or the public were not involved in the study's design, conduct, reporting or dissemination plans. All procedures performed in this study conformed to the guidelines of the updated Declaration of Helsinki (2013).

Statistical analysis

Continuous variables were presented as median (IQR) and compared using the Mann-Whitney U test. The χ^2 test was used to compare the categorical variables between the two groups. The Kaplan-Meier method with a log-rank test was conducted to describe event-free survival analysis. Cox proportional hazards model adjusted for age, sex, medical history, primary cancer lesion and type of VSP inhibitor was conducted.

Propensity score models were also conducted to adjust the confounding covariates. Multivariable logistic regression was used to predict the treatment groups based on

Table 1 Patient characteristics of with-RASI and without-RASI groups

	Total (n=2380)	with-RASI (n=883)	without-RASI (n=1497)	P value
Age	74 (68–78)	74 (69–78)	74 (68–78)	0.186
Age				0.070
<50 years old	32 (1.3%)	6 (0.7%)	26 (1.7%)	
50–70 years old	673 (28.3%)	243 (27.5%)	430 (28.7%)	
≥70 years old	1675 (70.4%)	634 (71.8%)	1041 (69.5%)	
Male	1457 (61%)	539 (61%)	918 (61%)	0.892
Timing of hypertension onset				0.655
Pre-existing	1834 (77.1%)	676 (76.6%)	1158 (77.4%)	
New onset	546 (22.9%)	207 (23.4%)	339 (22.6%)	
Cancer site				0.206
Colorectal	1004 (42.2%)	356 (40.3%)	648 (43.3%)	
Stomach	353 (14.8%)	129 (14.6%)	224 (15.0%)	
Liver	608 (25.5%)	226 (25.6%)	382 (25.5%)	
Lung	415 (17.4%)	172 (19.5%)	243 (16.2%)	
VSP Inhibitors				0.076
Ramucirumab	484 (20.3%)	183 (20.7%)	301 (20.1%)	
Bevacizumab	1481 (62.2%)	556 (63.0%)	925 (61.8%)	
Lenvatinib	197 (8.3%)	80 (9.1%)	117 (7.8%)	
Sorafenib	218 (9.2%)	64 (7.2%)	154 (10.3%)	
Medical history				
Chronic pulmonary disease	1022 (42.9%)	384 (43.5%)	638 (42.6%)	0.679
Psychoses	288 (12.1%)	106 (12.0%)	182 (12.2%)	0.912
CHF	716 (30.1%)	253 (28.7%)	463 (30.9%)	0.242
Valvular disease	320 (13.4%)	115 (13.0%)	205 (13.7%)	0.643
Cardiac arrhythmias	471 (19.8%)	160 (18.1%)	311 (20.8%)	0.116
Depression	375 (15.8%)	142 (16.1%)	233 (15.6%)	0.738
Diabetes	702 (29.5%)	278 (31.5%)	424 (28.3%)	0.102
Renal failure	234 (9.8%)	91 (10.3%)	143 (9.6%)	0.551
Peripheral vascular disorders	376 (15.8%)	155 (17.6%)	221 (14.8%)	0.071
Hypothyroidism	260 (10.9%)	94 (10.6%)	166 (11.1%)	0.738
Liver disease	1346 (56.6%)	508 (57.5%)	838 (56.0%)	0.460

CHF, congestive heart failure; RASI, renin–angiotensin system inhibitors; VSP, vascular endothelial growth factor signalling pathway.

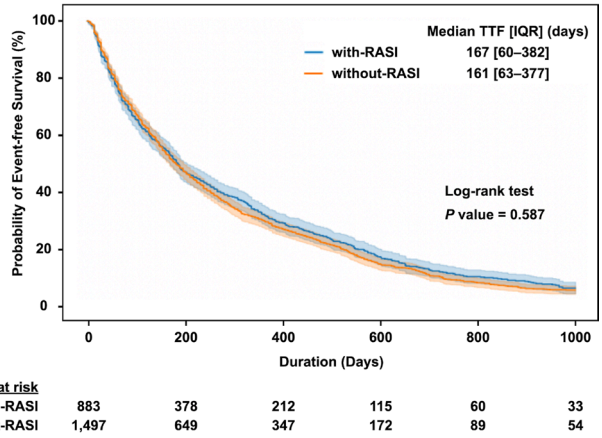

Figure 2 Comparison of TTF between with-RASI and without-RASI groups. TTFs were described using the Kaplan-Meier method with a log-rank test. Median TTFs were 167 (60–382) days in the with-RASI group and 161 (63–377) days in the without-RASI group (p=0.587). RASI, renin–angiotensin system inhibitors; TTF, time to treatment failure.

confounders, including age, sex, the timing of hypertension onset, primary cancer lesion, type of VSP inhibitor and medical history. All patients were allocated estimated propensity scores that predicted the probability of receiving with-RASI treatment in the primary analysis and RASI-only treatment in the secondary analysis. Several Cox proportional hazard models were conducted to adjust for between-group differences by applying propensity scores: (1) inverse probability of treatment weighting (IPTW) model using propensity scores to create weights for treatment selection, (2) regression adjustment model in which propensity scores were used as a linear predictor of outcome, (3) propensity score matching model with 1:1 pairs of patients created using a k-nearest neighbour algorithm and (4) stratification model in which patients were stratified into five groups by propensity scores (1: lowest to 5: highest), and the therapeutic effect in each group and effect of combined groups were estimated. The analyses were conducted (1) in all patients, (2) in those who survived at least 4 weeks after initiation of VSP inhibitor therapy and (3) in those diagnosed with de novo hypertension after the administration of VSP inhibitors.

A p<0.05 was considered statistically significant for all other statistical analyses. Statistical calculations were performed using Python, V.3.8.5 (Python Software Foundation, Beaverton, Oregon, USA).

RESULTS

Patient characteristics

Overall, 2380 patients were included in the primary analysis (with-RASI: 883 patients (37%) vs without-RASI: 1497 patients (63%) (figure 1). Patients' characteristics are summarised in table 1. Approximately 60% of the patients were aged >70 years in both groups. There were no significant between-group differences regarding age, sex and the timing of hypertension onset. No significant difference was detected in medical history between groups. Primary cancer site and type of VSP inhibitor also exhibited no significant difference between groups.

Comparison of TTFs

With-RASI versus without-RASI

Median TTFs were 167 (60–382) days in the with-RASI group and 161 (63–377) days in the without-RASI group (p=0.587). Kaplan-Meier curves for TTF are shown in figure 2. Unadjusted and adjusted Cox proportional hazard models also obtained comparable TTFs (HR: 0.98 (95% CI 0.90 to 1.06); p=0.584 and HR: 0.96 (95% CI 0.88 to 1.04); p=0.295, respectively) (table 2). Further, the propensity score model using IPTW did not demonstrate significant efficacy of RASIs on TTF (HR: 0.94 (95% CI 0.6 to 1.03); p=0.186). Other propensity models with regression adjustment, matching and stratification also failed to detect a greater clinical effect of RASIs.

In the patients who received VSP inhibitors for >4 weeks, we could not identify the benefit of RASIs in an unadjusted model (HR: 0.95 (95% CI 0.87 to 1.04); p=0.255) (table 2). Although the multivariate analysis and propensity score-adjusted IPTW model shifted the HR leftward, neither revealed a significant benefit of RASIs on TTF in the multivariate model (HR: 0.92 (95% CI 0.85 to 1.01); p=0.082 and HR: 0.91 (95% CI 0.83 to 1.00); p=0.053, respectively). Even when confined to the patients with de-novo hypertension after the administration of VSP inhibitors, the clinical impact of RASIs was not significant in all models. We described the TTF and unadjusted HR of the RASI groups categorised according to baseline characteristics (table 3). TTFs were comparable between the with-RASI and without-RASI groups even when classified by age, sex, cancer site, type of VSP inhibitor and medical history (All p>0.05).

In addition, different RASIs and CCBs were evaluated to determine which would be more effective regarding clinical outcomes (online supplemental material and figure 1). The TTFs of RASI-only and CCB-only were also comparable (p=0.584, log-rank test) (online supplemental figure 2).

DISCUSSION

We assessed whether RASIs provided clinical benefits during VSP inhibitor therapy in these patients with hypertension. In addition, we clarified whether RASIs or CCBs should be the first-line antihypertensive drug. In the primary analysis, TTF was compared between the with-RASI and without-RASI groups. RASIs in patients with hypertension did not demonstrate a substantial clinical benefit regarding the response to cancer therapy (figure 3). Even when restricting the study to patients who received VSP inhibitors for more than 4 weeks or were newly diagnosed with hypertension after the administration of VSP inhibitors, we identified no significant advantage of RASIs. This study clarified that RASIs for hypertension do not improve clinical outcomes in patients with cancer treated with VSP. In addition, RASIs and CCBs

Table 2 TTF analyses between with-RASI and without-RASI groups with multiple models

Analysis models	Sample size		HR (95% CI)	P value
	With-RASI	Without-RASI		
All patients				
Unadjusted analysis	883	1497	0.98 (0.90 to 1.06)	0.584
Multivariate analysis*	883	1497	0.96 (0.88 to 1.04)	0.295
Propensity score-adjusted model				
IPTW	882	1494	0.94 (0.86 to 1.03)	0.186
Regression adjustment	882	1494	0.94 (0.86 to 1.03)	0.198
Matching 1:1	879	879	0.96 (0.86 to 1.06)	0.386
Stratification	882	1494	0.95 (0.86 to 1.04)	0.224
Within-propensity score quintile				
1 (lowest propensity score)	126	349	0.84 (0.68 to 1.05)	0.128
2	179	296	0.95 (0.77 to 1.16)	0.586
3	180	295	1.02 (0.84 to 1.25)	0.827
4	196	279	1.12 (0.92 to 1.37)	0.262
5 (highest propensity score)	201	275	0.82 (0.67 to 1.00)	0.047
Patients who were treated for >4 weeks with VSP inhibitor administrated				
Unadjusted analysis	788	1369	0.95 (0.87 to 1.04)	0.255
Multivariate analysis*	788	1369	0.92 (0.85 to 1.01)	0.082
Propensity score-adjusted model (IPTW)	788	1367	0.91 (0.83 to 1.00)	0.053
Patients with de-novo hypertension after VSP inhibitor administration				
Unadjusted analysis	207	339	0.96 (0.81 to 1.15)	0.683
Multivariate analysis*	207	339	0.90 (0.76 to 1.08)	0.271
Propensity score-adjusted model (IPTW)	205	330	0.85 (0.70 to 1.04)	0.107

*Adjusting age, sex, primary cancer lesion, type of VSP inhibitors and medical histories.
IPTW, inverse probability of treatment weighting; RASI, renin–angiotensin system inhibitors; TTF, time to treatment failure; VSP, vascular endothelial growth factor signalling pathway.

have comparable clinical efficacy as first-line antihypertensive drugs during VSP inhibitor therapy (figure 3).

Clinical implication of RASIs in patients with cancer

The relation between RASIs and clinical outcomes in patients treated with VSP inhibitors has been discussed extensively in renal cell carcinoma. However, even in renal cancer, the efficacy of RASIs is inconclusive. Izzedine *et al* reported that RASIs improved overall survival and progression-free survival in patients with metastatic renal cell carcinoma treated with sunitinib.[12] Likewise, McKay *et al* also reported that RASIs reduced the hazard of overall survival by approximately 30% in patients with renal cancer with hypertension treated with VSP inhibitors.[13] On the other hand, another study failed to reveal a relation between RASIs and prognosis in patients with renal cell carcinoma treated with sunitinib or pazopanib.[14] Furthermore, there is a lack of evidence clarifying the effect of RASIs during VSP inhibitor therapy in patients with other malignancies. Since the nephroprotective effect of RASIs may be more assertively reflected in clinical response in renal cancer than in other malignancies, we focused on malignancies other than renal carcinoma in this study. This study is one of the most extensive cohort studies investigating the effect of antihypertensive agents on clinical outcomes in patients with cancer, other than renal cancer, treated with VSP inhibitors.

Should RASIs be used for patients with cancer treated with VSP inhibitors?

Advantages of RASIs on hypertension in patients with advanced cancer treated with VSP inhibitors

In solid tumours, disorganised vasculature controlled by VEGF plays an essential role in tumour growth and maintenance.[15–17] Preclinical research has also reported that angiotensin- II promotes cell proliferation and angiogenesis and suppresses cell apoptosis through the angiotensin-2-AT1 receptor.[18 19] The administration of angiotensin-II type 1 (AT1) receptor inhibitor to cancer model mice suppressed VEGF expression and angiogenesis and inhibited tumour progression.[20] ACE inhibitors have also been reported to inhibit cancer progression due to the antiangiogenesis effects.[21 22] Egami *et al* reported that the inhibition of angiotensin-II type 1 receptor played a complementary role to VSP inhibitors and that a

Table 3 TTF and unadjusted analysis among with-RASI and without-RASI

	TTF (IQR) (days)		
	With-RASI	Without-RASI	HR (95% CI)
Treatment			
Non-RASI group	–	161 (63–377)	–
RASI group	167 (60–382)	–	–
Age			
<-50 years	356 (239–665)	158 (89–547)	0.76 (0.31 to 1.87)
50–70 years	204 (76–530)	183 (76–447)	0.87 (0.75 to 1.02)
≥-70 years	146 (56–340)	154 (63–344)	1.02 (0.92 to 1.13)
Sex			
Female	198 (70–445)	168 (70–380)	0.91 (0.80 to 1.04)
Male	142 (56–352)	160 (63–371)	1.02 (0.92 to 1.14)
Timing of hypertension onset			
Pre-existing	126 (49–326)	143 (56–306)	0.99 (0.90 to 1.09)
New onset	322 (141–590)	287 (125–553)	0.96 (0.81 to 1.15)
Cancer site			
Colorectal	255 (89–535)	252 (105–518)	0.98 (0.86 to 1.11)
Stomach	83 (42–169)	91 (42–168)	0.88 (0.71 to 1.10)
Liver	140 (49–321)	136 (49–314)	0.96 (0.81 to 1.13)
Lung	160 (66–343)	148 (66–287)	0.97 (0.80 to 1.18)
VSP inhibitors			
Ramucirumab	77 (42–164)	93 (42–177)	0.97 (0.80 to 1.16)
Bevacizumab	236 (91–502)	229 (102–488)	0.96 (0.87 to 1.07)
Lenvatinib	84 (27–232)	102 (46–294)	1.19 (0.90 to 1.59)
Sorafenib	90 (35–247)	97 (34–286)	1.02 (0.76 to 1.37)
Medical history			
Chronic pulmonary disease	146 (56–388)	190 (77–439)	1.11 (0.97 to 1.25)
Psychoses	154 (56–402)	172 (79–317)	0.95 (0.75 to 1.21)
CHF	154 (52–362)	159 (57–374)	1.03 (0.88 to 1.20)
Valvular disease	165 (60–357)	153 (63–329)	1.02 (0.81 to 1.28)
Cardiac arrhythmias	130 (42–345)	154 (63–371)	1.10 (0.91 to 1.33)
Depression	176 (60–376)	168 (61–371)	0.95 (0.77 to 1.17)
Diabetes	146 (54–348)	147 (57–343)	1.07 (0.92 to 1.24)
Renal failure	145 (49–428)	132 (44–312)	0.95 (0.73 to 1.24)
Peripheral vascular disorders	131 (49–300)	145 (56–329)	1.07 (0.87 to 1.32)
Hypothyroidism	151 (54–336)	152 (57–309)	0.95 (0.74 to 1.23)
Liver disease	146 (56–358)	168 (63–377)	1.03 (0.92 to 1.15)

CHF, congestive heart failure; CRC, colorectal cancer; RASI, renin–angiotensin system inhibitors; TTF, time to treatment failure; VSP, vascular endothelial growth factor signalling pathway.

combination of these agents prevented tumour progression in the mice model.[23] Another pathology regarding the anticancer effect of RASIs, similar to that of VSP inhibitors, was also suggested to be that RASIs released the compression of tumour vessels and improved drug transport into the cancer cell.[7 24] These results suggested that RASIs exerted an anticancer effect and were particularly effective during VSP inhibitor therapy. In addition, VSP inhibitors often induce proteinuria and subsequent glomerular dysfunction due to VEGF suppression in the kidney.[25] The nephroprotective effect of RASIs in patients with proteinuria supports the use of RASIs in patients with cancer being treated with VSP inhibitors and may support its remarkable efficacy on renal cancer.[12 13 26] However, these advantages of RASIs did not contribute to enhancing TTF in this study.

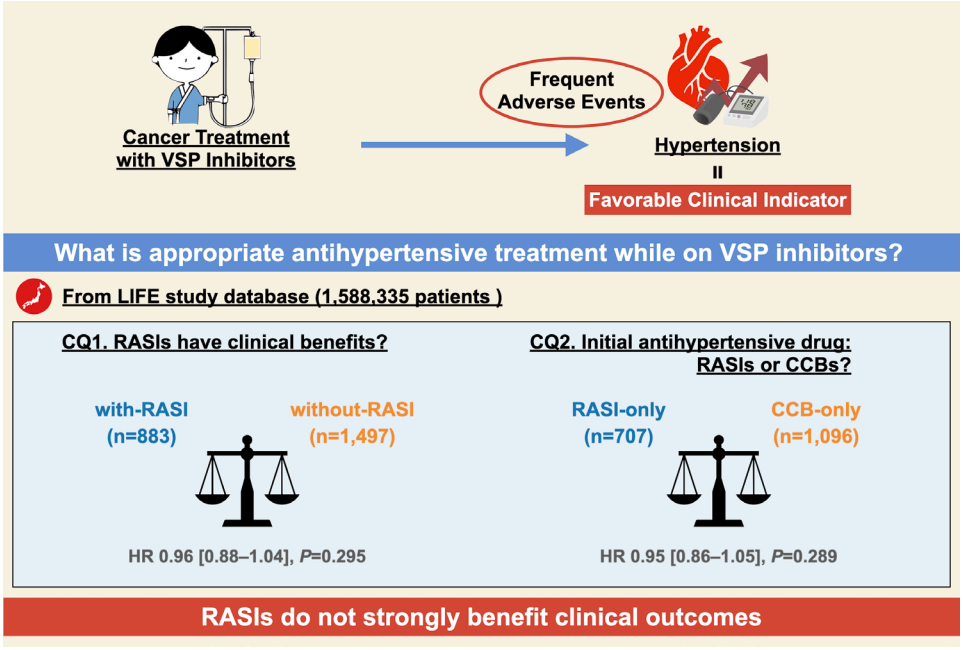

Figure 3 Renin–angiotensin system inhibitors (RASIs) have no clinical benefits during cancer treatment with VSP inhibitor therapy. VSP inhibitor-related hypertension has been reported to be a favourable clinical indicator, but the optimal antihypertensive therapy has not been elucidated. In this study, we analysed the impact of RASI on clinical outcomes in patients with cancer treated with VSP inhibitors using CQ1 (whether RASIs have clinical benefits) and CQ2 (whether RASIs or CCBs are more appropriate as initial antihypertensive drugs). However, no superiority of RASIs was indicated in both CQs, suggesting that RASIs do not strongly contribute to clinical outcomes. CCB, calcium channel blocker; CQ, clinical question; LIFE, Longevity Improvement and Fair Evidence; VSP, Vascular endothelial growth factor signalling pathway.

Disadvantages of RASIs on hypertension in patients with advanced cancer treated with VSP inhibitors

Several previous studies support our findings that combined RASI with VSP inhibitor therapy did not significantly affect clinical outcomes. Kappers *et al* reported that plasma renin and aldosterone were not linked to BP in patients treated with sunitinib, a VSP inhibitor.[27] Facemire *et al* reported that in the mice model with the administration of VSP inhibitors, renin messenger-RNA expression in the kidney and excretion of aldosterone in urine decreased.[28] These results suggested that the renin–angiotensin–aldosterone system is unlikely to influence VSP inhibitor-related hypertension strongly and that there is no specific effect of RASIs on VSP inhibitor-related hypertension. In addition, although VSP inhibitors related proteinuria was caused by reduced abundant of VEGF family in podocytes and endothelial cells, most of the proteinuria reduction by RASIs is due to haemodynamic reduction of glomerular hypertension.[25 29] Thus, RASIs may not reduce the VSP inhibitors-related proteinuria. Besides, Walther *et al* reported that RASIs promote angiogenesis via angiotensin-II AT2 receptor in mice implanted with cancer cells.[30] This result conflicted with previous reports suggesting favourable effects of RASIs on cancer progression.[20–22] In addition, median TTF was shorter than 6 months in our study, and usual doses of RASI may not have a significant effect on the VEGF pathway and cancer progression in this short period. The extent to which the renin–angiotensin system influences the VEGF pathway, cancer progression and the mechanisms involved have not been fully elucidated; therefore, further research is required.

Antihypertensive drugs for patients with cancer treated with VSP inhibitors

How should we select antihypertensive drugs in patients with cancer treated with VSP inhibitors from our study? Importantly, this study does not recommend that RASIs should not be used during cancer therapy with VSP inhibitors. RASIs exert cardioprotective and nephroprotective effects.[26 31] In addition, because of the strong antihypertensive effect and adherence, a recent hypertension guideline recommended a combination of RASIs and CCB using a fixed-dose drug as initial antihypertensive therapy.[32] Therefore, once BP has stabilised after the administration of VSP inhibitors, RASI and CCB combination therapy should be considered. Moreover, although this study did not reveal significantly favourable effects of RASIs, the use of RASIs tended to reduce the HR. This result suggested that RASIs may have a positive clinical impact during cancer treatment, though not strong. A specific population of patients with cancer may respond well to RASIs, and further research is required to investigate specific subpopulations.

Study strengths and limitations

To our knowledge, this is one of the largest cohort studies to comprehensively evaluate the impact of

antihypertensive drugs on clinical outcomes in patients with cancer treated with VSP inhibitors. The statistical power (1-β) was sufficiently large, and multiple models were applied to confirm the robustness. The results of this study are precious because it is challenging to analyse the prognosis of large cohorts in randomised controlled trials, such as that evaluated in this study.

This study has several limitations. First, it was a cohort-based retrospective study, and laboratory data at baseline and during cancer treatment could not be assessed. A previous meta-analysis reported that RASIs are nephroprotective in patients with proteinuria but not those without proteinuria.[26] Although we could not assess renal laboratory data, renal function at baseline detected by the Elixhauser Comorbidity Index system was adjusted in the multivariate models and used to calculate propensity scores. Echocardiographic or electrocardiographic parameters were also challenging to collect, but heart failure, arrhythmia and valvular disease were incorporated into the covariates. Besides, high statistical power in big data, which can withstand statistical methods even after adjusting for multiple background factors, can compensate for the limitation that this study could not assess detailed clinical data. Second, the age distribution could have reduced the clinical impact of RASIs in our results. The median age in this study was higher than that in other studies.[12 13] In the subgroup analysis of a younger cohort, there was a trend towards more prolonged TTF in the RASI group than in the others. This age-related difference in RASI response suggests that the mechanism of VSP inhibitor-related hypertension may differ according to age. Alternatively, there could be an age-related difference in the renin–angiotensin–aldosterone system, regardless of VSP inhibitors. Further study including a wide range of age groups is desirable. Third, we comprehensively analysed the combination of primary cancer lesions and VSP inhibitors, but they usually differ in treatment effect and TTF. This bias was mitigated as much as possible by adding cancer type and VSP inhibitor as covariates. Fourth, we could not assess the actual change in BP in this study. The degree of BP elevation may influence the choice of antihypertensive drugs, and the profile of BP after antihypertensive drug initiation may influence the clinical course of cancer treatment. Fifth, the LIFE study was limited to the 14 major Japanese municipalities, which may not necessarily represent real-world clinical data. However, the LIFE study encompassed urban and rural areas, and we were able to evaluate patients receiving standard cancer treatment. Finally, the LIFE study database did not contain all the mortality information of all patients, and we adopted TTF as an alternative indicator. TTF is a clinical indicator that considers the efficacy and toxicity of anticancer treatment and is one of the essential composite measures of real-world outcomes.[33]

CONCLUSION

RASIs do not benefit clinical outcomes during cancer therapy with VSP inhibitors. In addition, RASIs are not superior CCBs as first-line antihypertensive drugs. Nevertheless, our results can be used to guide the selection of antihypertensive drugs during cancer treatment with VSP inhibitors. Future prospective clinical trials are required to address this study's limitations and identify the subpopulations of patients that could benefit most from RASI therapy.

Twitter Shohei Moriyama @mori__1986

Acknowledgements We gratefully acknowledge all staff associated with the LIFE Study.

Contributors SM, MH and HF were responsible for study conception and design. SM, MH, MK, SK, TY, MF, HK, TM, EB and KA were involved in the data analysis. SM acquired data and drafted the manuscript. All authors reviewed the draft manuscript and provided critique and feedback on the manuscript. All authors read and approved the final version of the manuscript. MH accepts full resonsibility for the the work and/or conduct of the study, had access to the data, and controlled the decision to publish.

Funding This work was supported by grants provided by the Japan Science and Technology Agency (JST) Fusion Oriented Research for disruptive Science and Technology (FOREST) Program (Grant Number: JPMJFR205J) and the Japan Society for the Promotion of Science (JSPS) Grants-in-Aid for Scientific Research (KAKENHI) Program (Grant Numbers: JP20H00563 and JP19K21590).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The protocol of this study was approved by the internal review board (approval number: 2021-399), and patient consent was obtained via an opt-out method.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Public access to the registry cannot be provided due to limitations in data use agreements.

ORCID iDs
Shohei Moriyama http://orcid.org/0000-0002-0503-175X
Michinari Hieda http://orcid.org/0000-0003-3434-6184
Mitsuhiro Fukata http://orcid.org/0000-0002-6201-6054

REFERENCES

1 Izzedine H, Ederhy S, Goldwasser F, *et al*. Management of hypertension in angiogenesis inhibitor-treated patients. *Ann Oncol* 2009;20:807–15.
2 Versmissen J, Mirabito Colafella KM, Koolen SLW, *et al*. Vascular cardio-oncology: vascular endothelial growth factor inhibitors and hypertension. *Cardiovasc Res* 2019;115:904–14.
3 Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving sunitinib. *N Engl J Med* 2008;358:95–7.
4 Chang H-M, Okwuosa TM, Scarabelli T, *et al*. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: Part 2. *J Am Coll Cardiol* 2017;70:2552–65.

5 Unger T, Borghi C, Charchar F, *et al*. 2020 International Society of hypertension global hypertension practice guidelines. *Hypertension* 2020;75:1334–57.
6 Kim ST, Park KH, Oh SC, *et al*. How does inhibition of the renin-angiotensin system affect the prognosis of advanced gastric cancer patients receiving platinum-based chemotherapy? *Oncology* 2012;83:354–60.
7 Zhao Y, Cao J, Melamed A, *et al*. Losartan treatment enhances chemotherapy efficacy and reduces ascites in ovarian cancer models by normalizing the tumor stroma. *Proc Natl Acad Sci U S A* 2019;116:2210–9.
8 Nakai Y, Isayama H, Ijichi H, *et al*. Inhibition of renin-angiotensin system affects prognosis of advanced pancreatic cancer receiving gemcitabine. *Br J Cancer* 2010;103:1644–8.
9 Dienstmann R, Braña I, Rodon J, *et al*. Toxicity as a biomarker of efficacy of molecular targeted therapies: focus on EGFR and VEGF inhibiting anticancer drugs. *Oncologist* 2011;16:1729–40.
10 Fukuda H, Ishiguro C, Ono R, *et al*. The longevity improvement & fair evidence (LIFE) study: overview of the study design and baseline participant profile. *J Epidemiol* 2022. doi:10.2188/jea.JE20210513. [Epub ahead of print: 24 Jun 2022].
11 Elixhauser A, Steiner C, Harris DR, *et al*. Comorbidity measures for use with administrative data. *Med Care* 1998;36:8–27.
12 Izzedine H, Derosa L, Le Teuff G, *et al*. Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma. *Ann Oncol* 2015;26:1128–33.
13 McKay RR, Rodriguez GE, Lin X, *et al*. Angiotensin system inhibitors and survival outcomes in patients with metastatic renal cell carcinoma. *Clin Cancer Res* 2015;21:2471–9.
14 Sorich MJ, Kichenadasse G, Rowland A, *et al*. Angiotensin system inhibitors and survival in patients with metastatic renal cell carcinoma treated with VEGF-targeted therapy: a pooled secondary analysis of clinical trials. *Int J Cancer* 2016;138:2293–9.
15 Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol* 2005;23:1011–27.
16 Jain RK. Barriers to drug delivery in solid tumors. *Sci Am* 1994;271:58–65.
17 Dallas NA, Fan F, Gray MJ, *et al*. Functional significance of vascular endothelial growth factor receptors on gastrointestinal cancer cells. *Cancer Metastasis Rev* 2007;26:433–41.
18 Pupilli C, Lasagni L, Romagnani P, *et al*. Angiotensin II stimulates the synthesis and secretion of vascular permeability factor/vascular endothelial growth factor in human mesangial cells. *J Am Soc Nephrol* 1999;10:245–55.
19 Leung PS, Suen PM, Ip SP, *et al*. Expression and localization of AT1 receptors in hepatic Kupffer cells: its potential role in regulating a fibrogenic response. *Regul Pept* 2003;116:61–9.
20 Miyajima A, Kosaka T, Asano T, *et al*. Angiotensin II type I antagonist prevents pulmonary metastasis of murine renal cancer by inhibiting tumor angiogenesis. *Cancer Res* 2002;62:4176–9.
21 Volpert OV, Ward WF, Lingen MW, *et al*. Captopril inhibits angiogenesis and slows the growth of experimental tumors in rats. *J Clin Invest* 1996;98:671–9.
22 Neo JH, Malcontenti-Wilson C, Muralidharan V, *et al*. Effect of ACE inhibitors and angiotensin II receptor antagonists in a mouse model of colorectal cancer liver metastases. *J Gastroenterol Hepatol* 2007;22:577–84.
23 Egami K, Murohara T, Shimada T, *et al*. Role of host angiotensin II type 1 receptor in tumor angiogenesis and growth. *J Clin Invest* 2003;112:67–75.
24 Chauhan VP, Martin JD, Liu H, *et al*. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. *Nat Commun* 2013;4:2516.
25 Izzedine H, Massard C, Spano JP, *et al*. VEGF signalling inhibition-induced proteinuria: mechanisms, significance and management. *Eur J Cancer* 2010;46:439–48.
26 Mishima E, Haruna Y, Arima H. Renin-angiotensin system inhibitors in hypertensive adults with non-diabetic CKD with or without proteinuria: a systematic review and meta-analysis of randomized trials. *Hypertens Res* 2019;42:469–82.
27 Kappers MHW, van Esch JHM, Sluiter W, *et al*. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. *Hypertension* 2010;56:675–81.
28 Facemire CS, Nixon AB, Griffiths R, *et al*. Vascular endothelial growth factor receptor 2 controls blood pressure by regulating nitric oxide synthase expression. *Hypertension* 2009;54:652–8.
29 Hisada Y, Sugaya T, Yamanouchi M, *et al*. Angiotensin II plays a pathogenic role in immune-mediated renal injury in mice. *J Clin Invest* 1999;103:627–35.
30 Walther T, Menrad A, Orzechowski H-D, *et al*. Differential regulation of in vivo angiogenesis by angiotensin II receptors. *Faseb J* 2003;17:2061–7.
31 Yancy CW, Jessup M, Bozkurt B, *et al*. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. *Circulation* 2017;136:e137–61.
32 Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH guidelines for the management of arterial hypertension. *J Hypertens* 2018;36:1953–2041. doi:10.1097/HJH.0000000000001940
33 Gajra A, Zemla TJ, Jatoi A, *et al*. Time-to-treatment-failure and related outcomes among 1000+ advanced non-small cell lung cancer patients: comparisons between older versus younger patients (alliance A151711). *J Thorac Oncol* 2018;13:996–1003.