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ORIGINAL RESEARCH

Treatment and Implications of Vascular Endothelial Growth Factor Inhibitor-Induced Blood Pressure Rise: A Clinical Cohort Study

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BACKGROUND: Anti-cancer vascular endothelial growth factor inhibitors (VEGFI) frequently induce a rise in blood pressure (BP). The most effective treatment of this BP rise is currently unknown, and risk factors and its association with survival remain inconclusive.

METHODS AND RESULTS: Baseline characteristics and BP readings were retrospectively collected from oncology patients who received oral VEGFI treatment (sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib, or cabozantinib). Risk factors for a clinically relevant BP rise (increase of ≥20 mm Hg in systolic BP or ≥10 mm Hg in diastolic BP) were investigated via logistic regression (relative), efficacy of antihypertensives via unpaired t-tests, and association of BP rise with survival via Cox regression analysis. In total, 162 (47%) of 343 included patients developed a clinically relevant BP rise ≥7 days after VEGFI treatment initiation. Both calcium channel blockers and renin-angiotensin system inhibitors effectively reduced systolic BP (–24.1 and –18.2 mm Hg, respectively) and diastolic BP (–12.0 and –11.0 mm Hg, respectively). Pazopanib therapy (odds ratio, 2.71 [95% CI, 1.35–5.42; *P*=0.005], compared with sorafenib) and estimated glomerular filtration rate <60 mL/min per 1.73 m^2 (OR, 1.75 [95% CI, 0.99–3.18, *P*=0.054]) were risk factors for a BP rise, whereas a baseline BP ≥140/90 mm Hg associated with a lower risk (OR, 0.39 [95% CI, 0.25–0.62, *P*<0.001]). Only for renal cell carcinoma, BP rise was associated with a substantially improved median overall survival compared with no BP rise: 45.4 versus 20.3 months, respectively, *P*=0.003.

CONCLUSIONS: The type of VEGFI, baseline BP, and baseline estimated glomerular filtration rate determine the VEGFI-induced BP rise. Both calcium channel blockers and renin-angiotensin system inhibitors are effective antihypertensive treatments. Particularly in patients with renal cell carcinoma, a BP rise is associated with improved overall survival.

Key Words: antihypertensive agents ■ cardio-oncology ■ hypertension ■ survival ■ vascular endothelial growth factor inhibitor

Vascular endothelial growth factor (VEGF) inhibitors (VEGFI) are a cornerstone in the treatment of a variety of advanced solid malignancies. Most available VEGFI are small-molecule tyrosine kinase inhibitors directed at the VEGF receptor(s). By inhibition of VEGF-VEGF receptors signaling, these agents exert powerful anti-tumor effects by impairing tumor angiogenesis. Unfortunately, cardiovascular toxicity is frequently observed during VEGFI treatment.[1,2] Hypertension is the most commonly occurring cardiovascular toxicity: virtually every patient experiences any form of rapid blood pressure (BP) increase upon VEGFI treatment initiation, and hypertension is observed in approximately 20% to 40% but up to 90% of patients depending on the type of VEGFI.[3,4] The BP rise during VEGFI therapy might require initiation of antihypertensive drugs, a reduction

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CLINICAL PERSPECTIVE

What Is New?

- Our study is the first to identify independent risk factors for the development of a substantial blood pressure (BP) rise (rather than only reaching a dichotomous threshold for hypertension) during oral vascular endothelial growth factor inhibitors (VEGFI) therapy: pazopanib, normotension at baseline, and a trend (P=0.054) for estimated glomerular filtration rate <60 mL/min per 1.73 m^2.
- Both calcium channel blockers and renin-angiotensin system inhibitors can establish powerful and similar antihypertensive effects when started during VEGFI therapy, although these results have to be interpreted with caution.
- Particularly the rise in BP during VEGFI therapy (rather than reaching a BP threshold of ≥140/90 mm Hg) is associated with improved overall survival in renal cell carcinoma patients but not in patients with hepatocellular carcinoma.

What Are the Clinical Implications?

- Careful monitoring of a BP rise during VEGFI therapy is essential, particularly during pazopanib therapy, for previously normotensive patients or in case of decreased kidney function.
- Both calcium channel blockers and renin-angiotensin system inhibitors seem suitable and effective options to lower BP during VEGFI therapy and choice of antihypertensive therapy should be based on patient-specific characteristics, until prospective clinical studies indicate otherwise.
- A notable BP rise during VEGFI therapy can be treated promptly given that antihypertensive treatment does not impair anti-cancer treatment efficacy.

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CCB	calcium channel blockers
DBP	diastolic blood pressure
HCC	hepatocellular carcinoma
OS	overall survival
RASI	renin-angiotensin system inhibitor
RCC	renal cell carcinoma
SBP	systolic blood pressure
VEGF	vascular endothelial growth factor
VEGFI	vascular endothelial growth factor inhibitor

of the treatment dosage, or even temporary or permanent treatment discontinuation despite an ongoing anticancer effect. These interventions have the potential to impair patient survival and to reduce quality of life. Also, the rise in BP can directly lead to serious consequences, including hypertensive emergencies in severe cases,[5,6] and predisposes to VEGFI-induced cardiac toxicity.[2]

Despite the frequent occurrence of a VEGFI-induced BP rise, the most effective antihypertensive agent to treat this BP rise remains unknown. Calcium channel blockers (CCB) and renin-angiotensin system inhibitors (RASI) have been recommended as first-line therapies, but this is predominantly based on expert opinion.[7,8] Studies in rats[9,10] and patients[11,12] provide preliminary evidence that CCB are the preferred agents over RASI to treat hypertension during VEGFI therapy, but a formal and adequately powered clinical comparison is currently lacking.

Most previous studies have investigated risk factors and prognostic implications of VEGFI-induced hypertension, which was demonstrated prognostically favorable for patients with metastatic renal cell carcinoma (RCC)[13] but not for all other tumor types.[14] Notably, VEGFI-induced hypertension was defined as a BP reading above predefined thresholds of ≥140/90 mm Hg or ≥160/100 mm Hg or requirement of antihypertensive medication.[12,15] Consequently, patients who did experience a notable VEGFI-induced BP rise but of whom BP readings did not reach the predefined thresholds of hypertension were not classified as having VEGFI-induced hypertension. Currently, it is unknown whether a rise in BP per se associates with survival outcomes and whether absolute BP levels or the magnitude of change in BP during VEGFI is the strongest predictor of (future) hypertensive complications.

The current study aims to characterize the pro-hypertensive effects of a variety of VEGFI and to investigate the relative efficacy of various classes of antihypertensive agents to treat a BP rise during oral VEGFI therapy. In addition, we aim to identify risk factors for the occurrence of a VEGFI-induced rise in BP, rather than reaching a dichotomous threshold for hypertension, and to study its prognostic implications in a representative real-world cohort of patients with various types of cancer.

METHODS

All data and supporting materials have been provided within the published article.

Study Design and Participants

In this single-center retrospective cohort study, patients with advanced or metastatic cancer who were prescribed oral VEGFI treatment (ie, sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib, or cabozantinib) in the period of November 2008 until February 2020 for the first time were identified via prescription data of the outpatient pharmacy of the Erasmus MC University

Medical Center. The following baseline characteristics were collected via the corresponding electronical medical records in an anonymous manner: general characteristics (age, sex, body mass index), type of cancer, type and duration of VEGFI treatment, medical history of hypertension, dyslipidemia, and diabetes, history of cardiovascular disease (myocardial infarction, ischemic stroke, or transient ischemic attack), smoking status, usage of antihypertensive drugs, estimated glomerular filtration rate (eGFR), and presence of proteinuria. Patients were excluded from the study and analyses in case of previous VEGFI therapy, VEGFI treatment shorter than 7 days, or in case of incomplete documentation of BP readings or antihypertensive intervention (either on baseline or during VEGFI therapy). Outpatient BP readings were collected and averaged in case multiple measurements were available on the same day. BP readings were excluded if acquired during hospital admissions, during outpatient visits on which the treating physician had also documented the presence of anxiety or uncontrolled pain, and during off-treatment weeks for VEGFI that were administered according to a cyclic, noncontinuous treatment schedule (eg, sunitinib 4-weeks-on, 2-weeks-off for RCC). The Medical Ethics Committee of the Erasmus MC reviewed the study and concluded that our study did not fall under the scope of the Medical Research Involving Human Subjects Act (MEC-2019-0683). No informed consent was obtained because all data were collected and analyzed in an anonymous manner, and a substantial proportion of patients had passed away at the time of study initiation. The study was conducted according to the principles of the Declaration of Helsinki (version July 2018).

Definitions and Study Outcomes

The primary outcomes of the current study were: (1) difference in systolic blood pressure (SBP) and diastolic blood pressure (DBP) collected at 2 timepoints during VEGFI therapy compared with baseline: first reading (≥7 days) after start of VEGFI treatment, and highest reading (throughout the entire VEGFI treatment period). Baseline BP was collected at the day of VEGFI treatment initiation or ≤90 days prior if BP was not available on that same day. (2) The efficacy of different classes of antihypertensive drugs to reduce BP, defined as the reduction in SBP and DBP ≥7 days after start of the antihypertensive(s), compared with the reading closest before antihypertensive treatment initiation. The per-patient analyzed treatment period encompassed the period until permanent VEGFI treatment discontinuation or treatment interruption for ≥5 times the elimination half-life of the corresponding VEGFI.

Secondary outcomes were (1) risk factors for the occurrence of a clinically relevant VEGFI-induced BP rise (≥20 mm Hg in SBP or ≥10 mm Hg in DBP) on the first BP measurement and (2) the association between a clinically relevant BP rise and overall survival (OS). The threshold for a clinically relevant BP was chosen to account for a substantial BP increase, natural variability of BP measurements,[16] and has been used previously.[17]

Statistical Analysis

Continuous variables are reported as mean±SD or median with interquartile ranges in case of a normal and non-normal distribution, respectively. Categorical data are expressed in frequencies with percentages. To compare patient characteristics between the group with and without a BP rise, the Pearson χ^2-test or Fisher exact test was used. Changes in SBP and DBP between the different VEGFI were compared with 1-way ANOVA followed by Tukey multiple comparison test. To characterize the efficacy of antihypertensive agents, BP readings before and after antihypertensive initiation were compared with paired t-tests, and the relative efficacy of the different antihypertensive classes was compared with unpaired t-tests. Clinical risk factors for the occurrence of a VEGFI-induced rise in BP were identified by dichotomizing the rise in BP (presence or absence of ≥20 mm Hg SBP or ≥10 mm Hg DBP increase) and performing a univariable logistic regression to calculate odds ratios (OR). Unique predictor variables with a value of P <0.10 in the univariable analysis were included in a multivariable model.

OS was calculated from VEGFI initiation until death or censored at the last follow-up survival and compared between patients with and without a VEGFI-induced BP rise with Kaplan–Meier analysis and the log-rank test. Univariable Cox proportional hazard regression analysis was performed to calculate hazard ratios (HR) with 95% CI. Also, multivariable Cox proportional hazard regression analysis was performed to adjust for relevant factors (age, body mass index, and a history of cardiovascular disease). P values <0.05 were considered to indicate statistical significance. SPSS 26.0 software (IBM SPSS, Chicago, IL) and GraphPad Prism Software Version 8.0 (GraphPad Software Inc., San Diego, CA) were used for statistical evaluation of the data and design of the figures.

RESULTS

General Characteristics of the Study Population

From 2008 until 2020, a total of 563 patients were prescribed sorafenib, sunitinib, pazopanib, regorafenib, lenvatinib, or cabozantinib in the Erasmus MC University Medical Center. From these, 220 patients were excluded from the study and analyses because of the following

reasons: missing BP measurements on baseline or during VEGFI therapy (n=157), incomplete information on date of initiation, type, or dosage of VEGFI treatment (n=49), and VEGFI treatment duration <7 days (n=14) (Figure 1). The molecular targets and daily starting dosages of included VEGFI are displayed in Table S1.

In total, 343 patients were included, of whom baseline characteristics are displayed in Table 1. Hepatocellular carcinoma (HCC) and RCC were the most common tumor types, and sorafenib and sunitinib were the most frequently prescribed VEGFI. The median age was 64 years, and most included patients were men (72%). Subsequently, characteristics were compared between patients with and without a clinically relevant rise in BP during VEGFI therapy (Table 1). Overall, 162 (47%) patients experienced a clinically relevant VEGFI-induced BP rise on the first measurement. This was most frequently observed in patients with gastrointestinal stromal tumors (62%) and RCC (56%) and least frequently in thyroid cancer (27%). Also, the BP rise was significantly more common in women compared with men (57% versus 44%, respectively, P=0.031) and less often observed in patients with a baseline reading of hypertension (≥140/90 mm Hg) compared with patients with a normotensive baseline reading (<140/90 mm Hg): 59% versus 37%, respectively, P<0.001. Median treatment duration, baseline SBP and DBP, main cardiovascular risk factors, and baseline eGFR did not differ significantly between patients with and without a substantial BP rise.

Prohypertensive Effects of Studied VEGFI

The first and highest available BP measurements after start of VEGFI treatment were collected after a median treatment duration of 14 and 28 days, respectively (Figure 2A and 2B). Baseline BP was similar between the different VEGFI treatment groups (Table S2). In the total cohort, mean increases of SBP and DBP were 8.8±19 and 5.4±13 mm Hg at first measurement and 17.4±20 mm Hg and 9.0±13 at highest measurement, respectively. Pazopanib was associated with the most substantial increases in SBP and DBP on both first (+14.6 and +10.4 mm Hg, respectively) and highest measurements (+22.2 and +13.6 mm Hg, respectively). This was significantly higher than the BP rise induced by sorafenib (Figure 2A and 2B). Moreover, 3 cases of a hypertensive emergency were observed in the current study, which occurred during pazopanib (n=2) and sunitinib (n=1) therapy. This required discontinuation of the VEGFI treatment. Patients who already used CCB or RASI at baseline experienced a less substantial rise in SBP at first measurement during VEGFI therapy, compared with patients without baseline antihypertensive use: −6.3 mm Hg (95% CI, −12.2 to −0.42;

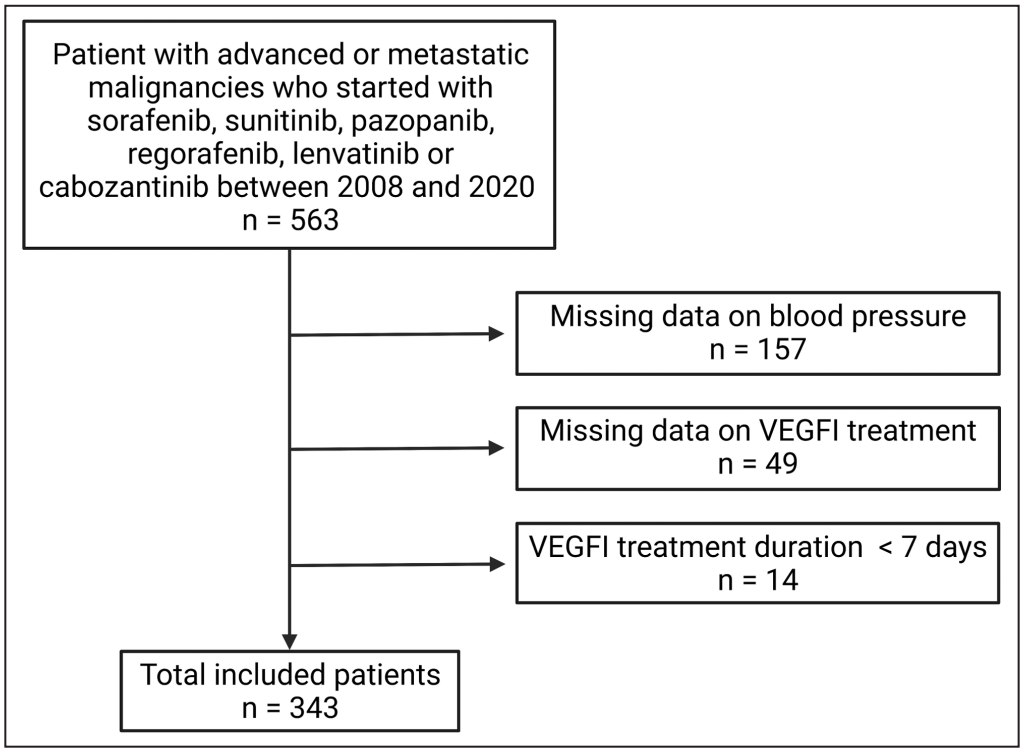

Figure 1. Flowchart of included patients.
VEGFI indicates vascular endothelial growth factor inhibitor. This flowchart was created with Biorender.com.

Table 1. Baseline Characteristics of the Study Population

Patient characteristic	Total cohort	BP rise*	No BP rise*	*P* value
Patients, n (%)	343 (100)	162 (47)	181 (53)	
Median age, y [IQR]	64 [56–70]	64 [56–70]	64 [57–70]	0.977
Sex, n (%)				0.031†
Men	246 (72)	107 (43)	139 (57)	
Women	97 (28)	55 (57)	42 (43)	
Median BMI, kg/m^2 [IQR]	26 [24–29]	26.3 [23.6–29.6]	25.8 [23.7–29.2]	0.258
Tumor type, n (%)				0.023†
HCC	127 (37)	47 (37)	80 (63)	
RCC	97 (28)	54 (56)	43 (44)	
GIST	39 (11)	24 (62)	15 (39)	
CRC	25 (7)	11 (44)	14 (56)	
Sarcoma	22 (6)	12 (55)	10 (46)	
pNET	17 (5)	7 (42)	10 (59)	
Thyroid cancer	11 (3)	3 (27)	8 (73)	
Other	5 (2)	4 (80)	1 (20)	
VEGFI therapy, n (%)				0.011†
Sorafenib	143 (42)	55 (39)	88 (62)	
Sunitinib	118 (34)	60 (51)	58 (49)	
Pazopanib	55 (16)	35 (64)	20 (36)	
Regorafenib	25 (7)	11 (44)	14 (56)	
Lenvatinib	1 (0.3)	1 (100)	0 (0)	
Cabozantinib	1 (0.3)	0 (0)	1 (100)	
Median VEGFI treatment duration, days [IQR]	111 [46–281]	105 [45–282]	112 [46–283]	0.889
Baseline SBP, mm Hg ±SD	137 ± 18	133 ± 17	141 ± 17	0.375
Baseline DBP, mm Hg ±SD	80 ± 11	76 ± 11	84 ± 10	0.327
Pre-existing hypertension, n (%)	170 (50)	74 (41)	96 (60)	0.348
Medical record history	16 (5)	9 (56)	7 (44)	
Antihypertensive use	49 (14)	19 (39)	30 (61)	
Both	105 (31)	46 (44)	59 (56)	
Hypertensive reading (≥140/90) at baseline, n (%)				<0.001†
Yes	183 (53)	68 (37)	115 (63)	
No	160 (47)	94 (59)	66 (41)	
Antihypertensives, n (%)				0.103
0	182 (53)	97 (53)	85 (47)	
1	66 (19)	26 (39)	40 (61)	
2	54 (16)	20 (37)	34 (63)	
3	29 (9)	13 (45)	16 (55)	
>3	12 (4)	6 (50)	6 (50)	
Antihypertensive drug class, n (%)				
β-blocker	82 (24)	36 (44)	46 (56)	0.527
ACEI/ARB	81 (24)	35 (43)	46 (57)	0.446
Diuretic				
Total	72 (18)	29 (60)	43 (40)	0.189
Loop/thiazide	63 (19)	25 (40)	38 (60)	0.210
MRA	9 (2.6)	4 (45)	5 (56)	1.00
Loop/thiazide+MRA	15 (4.4)	4 (27)	11 (73)	0.119
CCB	9 (2.6)	19 (40)	28 (60)	0.348

(*Continued*)

Table 1. Continued

Patient characteristic	Total cohort	BP rise*	No BP rise*	*P* value
Cardiovascular risk factors, n (%)				
History of CVD	46 (13)	22 (48)	24 (52)	1.000
Smoking				0.052
Current	65 (19)	21 (32)	44 (68)	
Former	109 (32)	57 (52)	52 (48)	
Never	142 (41)	72 (51)	70 (49)	
Unknown	27 (8)	12 (45)	15 (56)	
Dyslipidemia	74 (22)	39 (53)	35 (47)	0.296
Diabetes	78 (23)	34 (44)	44 (56)	0.519
Median eGFR, mL/min per 1.73 m^2 [IQR]	80 [62–90]	78 [59–90]	81 [65–92]	0.665
Median proteinuria, g/L [IQR]‡	0 [0–0.25]	0.0 [0.0–0.25]	0.0 [0.0–0.26]	0.932

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CRC, colorectal cancer; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; pNET, pancreatic neuro-endocrine tumor; RCC, renal cell carcinoma; and SBP, systolic blood pressure.

*Blood pressure rise was defined as ≥20 mm Hg increase in systolic or ≥10 mm Hg increase in diastolic blood pressure on the first measurement during vascular endothelial growth factor inhibitor therapy compared with baseline. Percentages (%) in blood pressure rise and no blood pressure rise columns display percentages within subcategories specified in the second column.

†*P* values <0.05.

‡Baseline proteinuria status missing for 140 (41%) patients.

P=0.036) and −5.1 mm Hg (95% CI; −9.9 to −0.35, *P*=0.036) respectively (Table S3).

Efficacy of Various Antihypertensive Agents to Treat the VEGFI-Induced Rise in BP

Antihypertensive treatment was initiated in 81 (24%) of the included patients. This comprised new antihypertensive treatment (n=67) or intensification of previously prescribed antihypertensive treatment (n=14). For 51 of these 81 patients (63%), a clinically relevant BP rise was the main reason to start antihypertensive therapy, whereas 31 (38%) patients received new antihypertensives for elevated BP readings during VEGFI therapy but which had not increased substantially compared with baseline.

CCB were the most prescribed drugs to treat a VEGFI-induced BP rise (n=42), followed by RASI (n=27), β-blockers (n=4), diuretics (n=3), and α-blockers (n=1). In 4 patients, ≥2 classes of antihypertensives were started simultaneously. Given the low prescription numbers of other antihypertensive agents, the efficacy to lower BP was only compared between CCB and RASI, which could be analyzed for 39 and 25 patients, respectively. These antihypertensive effects were determined after a median treatment duration of 17 days with CCB and 14 days with RASI. As displayed in Figure 3, both CCB and RASI were able to establish powerful antihypertensive effects: CCB decreased SBP and DBP by 24.1±23 and 12.0±15 mm Hg, respectively, whereas RASI lowered SBP and DBP by 18.2±22 and 11.0±10 mm Hg, respectively. Although CCB thus numerically had more powerful effects than RASI, particularly in reducing SBP (Δ5.9 mm Hg, 95% CI −5.7 to 17.6, *P*=0.314) compared with DBP (Δ1.0 mm Hg, 95% CI −6.0 to 8.0, *P*=0.773), this did not reach statistical significance.

Risk Factors for the Development of a BP Rise During VEGFI Therapy

The associations between clinical parameters and a clinically relevant rise in BP are shown in Table 2. This included a comparison of the risk between the most prescribed VEGFI. For this, sorafenib was used as the reference group (given that this was the most common prescribed VEGFI). Unique predictor variables with a value of *P*<0.10 in the univariable analysis were included in a multivariable model. Although significant in the univariable analysis, female sex and usage of antihypertensive drugs at baseline were not significantly associated with the risk of BP rise in the multivariable model, nor were age, paracetamol use, and main cardiovascular risk factors, including history of cardiovascular disease and smoking. Tumor type could not be added to the multivariable model because of multicollinearity with VEGFI type.

In the multivariable model, pazopanib treatment was associated with a significantly increased odds of inducing a rise in blood pressure compared with sorafenib (OR, 2.71 [95% CI, 1.35–5.42; *P*=0.005]). Also, eGFR <60 mL/mL per 1.73 m^2 demonstrated a trend to an increased odds for a rise in BP (OR, 1.75 [95% CI, 0.99–3.18; *P*=0.054]). In contrast, a hypertensive reading (≥140 mm Hg SBP and/or ≥90 DBP mm Hg) at baseline was associated with a decreased odds to develop a

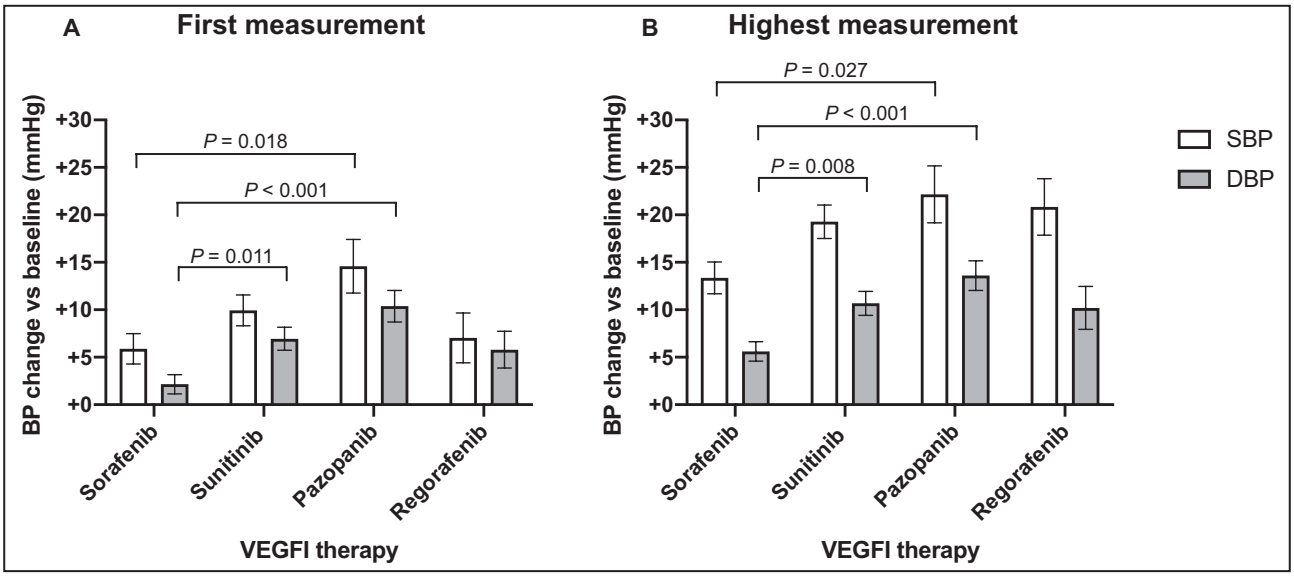

Figure 2. Changes of BP during VEGFI therapy.
BP values are compared with baseline at **A**, first measurement after start of VEGFI, and **B**, highest measurement after start of VEGFI. BP indicates blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; and VEGFI, vascular endothelial growth factor inhibitor. Bars indicate mean and error bars indicate SEM.

VEGFI-induced BP rise (OR, 0.39 [95% CI, 0.25–0.62; *P*<0.001]).

Tumor-Specific Association Between VEGFI-Induced Blood Pressure Rise and Improved Survival Outcomes

Subsequently, the association between a BP rise during VEGFI therapy and survival outcomes was studied. This was assessed separately for the 2 most common tumor types in our study: RCC and HCC. This was done as RCC was a more prognostically favorable tumor compared with HCC (median OS 25.2 versus 9.4 months, respectively, *P*<0.001) with a higher incidence of a VEGFI-induced BP rise (56% versus 37%, respectively, *P*=0.007). This indicates that tumor type could be a confounder for the observed association between a BP rise and improved OS in the total cohort. RCC patients who demonstrated a BP rise had a more than 2-fold longer median OS compared with patients with RCC without a BP rise (median OS 45.4 versus 20.3 months, respectively, *P*=0.003) (Figure 4A). In contrast, median OS did not differ significantly in patients with HCC who did (8.9 months) versus who did not (11.9 months) develop

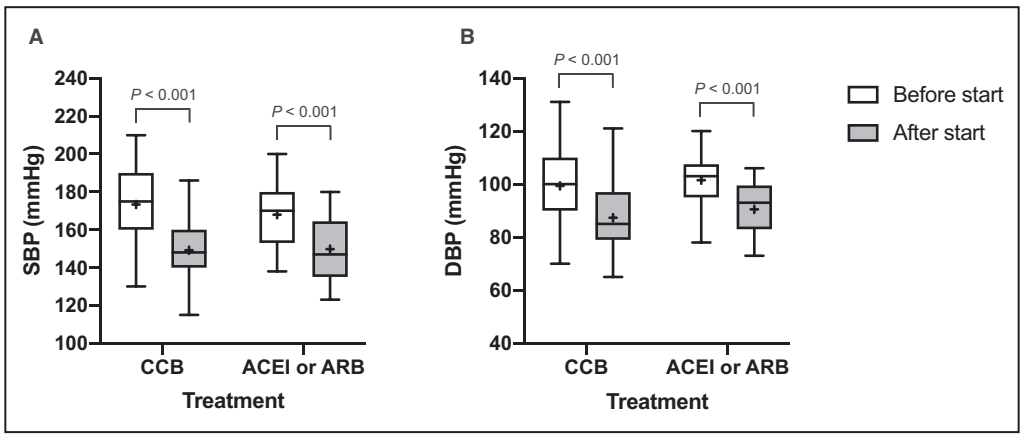

Figure 3. Effects of calcium channel blocker (n=39) and angiotensin-converting-enzyme inhibitor or angiotensin II receptor blocker (n=25) for the treatment of hypertension during vascular endothelial growth factor inhibitor therapy.
A, Systolic blood pressure and **B**, diastolic blood pressure before and ≥7 days after start of antihypertensive treatment. ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; DBP, diastolic blood pressure; and SBP, systolic blood pressure. Plus signs indicate mean values, whiskers indicate ranges.

Table 2. Univariable and Multivariable Logistic Regression Analysis of Risk Factors for the Development of a BP Rise During VEGFI Therapy

Variables	No. (%)	Univariable analysis			Multivariable analysis		
		OR	95% CI	*P* value	OR	95% CI	*P* value
Patient characteristics							
Sex (women)	96 (28)	1.70	1.06–2.73	0.028†	1.58	0.95–2.62	0.080
Age (≥65 y)	167 (49)	1.01	0.66–1.54	0.978			
Tumor type (vs HCC)	343 (100%)			0.011†	NA*		
RCC	97 (28%)	2.14	1.25–3.66	0.006†	NA*		
GIST	39 (11%)	2.72	1.30–5.70	0.008†	NA*		
Other	80 (23%)	1.47	0.83–2.56	0.188	NA*		
VEGFI type (vs sorafenib)	343 (100%)			0.013†			0.046*
Sunitinib	118 (34%)	1.66	1.01–2.71	0.045†	1.43	0.83–2.46	0.195
Pazopanib	55 (16%)	2.80	1.47–5.33	0.002†	2.71	1.35–5.42	0.005*
Other	27 (8%)	1.26	0.53–2.97	0.601	1.29	0.53–3.15	0.583
Hypertension							
Hypertension at baseline (≥140/90 mm Hg)	183 (53%)	0.42	0.79–0.64	<0.001†	0.39	0.25–0.62	<0.001*
Antihypertensive use at baseline vs none	161 (47%)	0.59	0.39–0.91	0.017†	0.66	0.41–1.07	0.092
β-blocker	82 (24%)	0.84	0.51–1.38	0.489			
ACEI/ARB	81 (24%)	0.81	0.49–1.34	0.407			
Diuretic							
Total	72 (18%)	0.70	0.41–1.19	0.185			
Loop/thiazide	48 (14%)	0.69	0.39–1.20	0.186			
MRA	9 (2.6%)	0.54	0.22–1.29	0.163			
Loop/thiazide+MRA	15 (4.4%)	0.39	0.12–1.25	0.114			
CCB	47 (14%)	0.73	0.39–1.36	0.316			
CVD risk factors							
History of CVD	46 (13%)	1.03	0.55–1.91	0.931			
BMI >25	195 (57%)	1.39	0.88–2.19	0.156			
Ever smoked	174 (55%)	0.79	0.51–1.23	0.298			
Dyslipidemia	84 (22%)	1.32	0.79–2.22	0.288			
Diabetes	78 (23%)	0.83	0.50–1.38	0.464			
Kidney function							
eGFR <60 mL/min per 1.73 m^2	76 (22%)	1.73	1.03–2.89	0.038†	1.75	0.99–3.18	0.054
Creatinine ≥90	132 (39%)	1.12	0.78–1.85	0.416			
Proteinuria at baseline (≥0.15 g/L)‡	58 (29%)	1.18	0.64–2.18	0.593			
Comedication							
Paracetamol	79 (23%)	0.61	0.37–1.02	0.060	0.60	0.34–1.05	0.075
Aspirin	37 (11%)	1.36	0.69–2.69	0.380			
Antiplatelet drugs§	15 (4%)	0.98	0.35–2.76	0.964			

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; CCB, calcium channel blocker; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; and RCC, renal cell carcinoma.

*Not applicable, tumor type could not be entered in the multivariable model because of multicollinearity with vascular endothelial growth factor inhibitor type.

†*P* values <0.05.

‡Baseline proteinuria status missing for 140 (41%) patients.

§P2Y12 inhibitors and dipyridamole.

a BP rise (*P*=0.228) (Figure 4B). Compared with the unadjusted model, adjustment for age, body mass index, and history of cardiovascular disease did not significantly change the HR for the risk of death in RCC patients with a rise in BP (HR, 0.49 [95% CI, 0.31–0.79; *P*=0.003] and HR, 0.52 [95% CI, 0.32–0.87; *P*=0.012]), respectively, nor for patients with HCC (HR, 1.26 [95% CI, 0.86–1.85; *P*=0.228] and HR, 1.31 [95% CI, 0.88–1.95; *P*=0.184]), respectively.

Given the demonstrated prognostic implications of this BP rise for at least RCC, we analyzed if treatment of this hypertensive response with antihypertensive drugs could interfere with the anti-tumor effects of VEGFI in this population. Therefore, OS was compared among patients with RCC with a BP rise who did and did not receive new antihypertensive therapy during VEGFI treatment. We found no significant differences in OS between patients with and without new antihypertensives in the RCC cohort (median OS 29.6 versus 47.4 months, *P*=0.904), HR for death in BP rise group with new antihypertensives versus no new antihypertensives 1.04 (95% CI, 0.52–2.08; *P*=0.904) (Figure 4C). In the total cohort of patients, addition of antihypertensives did not significantly impact OS either (median OS 21.9 versus 18.5 months, *P*=0.143) (Figure S1A).

Finally, we investigated whether an elevated BP reading specifically (SBP ≥140 or DBP ≥90 mm Hg) at first measurement after VEGFI initiation had prognostic implications. We found no association between an elevated BP reading and OS in the total cohort nor in patients with RCC and HCC separately, although power was limited for the RCC patient subgroup analysis (Figure S1B through S1D).

DISCUSSION

Hypertension induced by VEGFI is a commonly encountered clinical problem. We found that almost 50% of patients receiving oral VEGFI therapy experience a clinically relevant rise in BP. This was most frequently observed in response to pazopanib (64%), which also numerically induced the strongest prohypertensive effects of the studied VEGFI. Furthermore, out of the 3 cases of a hypertensive emergency observed in the current study, 2 occurred during pazopanib therapy. This illustrates that the VEGFI-induced blood pressure rise is not just a numerical phenomenon but can have clear clinical implications.

We identified that patients with a normotensive BP reading (<140/90 mm Hg) at baseline had an almost 3-fold higher odds to experience a VEGFI-induced BP rise. This most likely indicates that VEGFI trigger prohypertensive physiological mechanisms in previously normotensive patients, which might already be active in patients with pre-existing hypertension. Although the exact reason remains unclear, various mechanisms have been implicated in the BP rise during VEGFI therapy, including increased endothelin-1 signaling, suppression of the nitric oxide pathway,[18] oxidative stress, and microvascular dysfunction.[19] Our observation is in accordance with a previous study that demonstrated a higher BP rise in patients with lower baseline BP values in response to sunitinib[20] but seems to conflict with previous studies which have identified pre-existing hypertension as a risk factor for VEGFI-induced hypertension.[12,15]

This apparent latter discrepancy is most likely explained by differences in primary study outcomes: in our study, we identified risk factors for a numerical rise in BP (≥20 mm Hg SBP or ≥10 mm Hg DBP), whereas previous studies analyzed risk factors for VEGFI-induced hypertension (thresholds of ≥140/90 mm Hg, ≥160/100 mm Hg, or requirement of antihypertensive medication).[12,15] Consequently, in previous studies, patients with a notable VEGFI-induced BP rise but of whom BP readings did not reach the predefined thresholds of hypertension were not classified as having VEGFI-induced hypertension. Given that it is currently unknown whether absolute BP levels or the magnitude of change in BP is the strongest predictor for future cardiovascular events during VEGFI therapy, close BP monitoring in all patients receiving these anticancer agents remains important, regardless of baseline hypertensive status.[19,21] In addition, eGFR <60 mL/min per 1.73 m^2 demonstrated a trend as an additional risk factor (OR, 1.75; *P*=0.054). Although we were unable to measure VEGFI plasma concentrations, decreased renal clearance could result in higher VEGFI plasma concentrations, which has been associated with increased incidence of VEGFI-induced toxicity, including prohypertensive effects.[22]

In the analysis of baseline characteristics and the univariable logistic regression analysis, we identified female sex as a risk factor for a BP rise during VEGFI therapy, which has been described before as a risk factor for bevacizumab-induced high-grade hypertension.[23] However, female sex was not a significant predictor for BP rise in the multivariable logistic analysis. Notably, pazopanib, which induced the strongest prohypertensive effects, was more frequently administered to women compared with men (22% versus 14%), and women were less likely to have a diagnosis of HCC (24% versus 42%), a tumor type with a low incidence of a substantial BP rise (37%). This indicates that most likely characteristics other than sex had predisposed the female cohort of patients to a rise in BP.

Our study is the first to demonstrate the importance of distinguishing between a substantial BP rise during oral VEGFI therapy and reaching a threshold for VEGFI-induced hypertension in a tumor-specific manner. Next to differences in risk factors for the occurrence of any of these events, we found that only the occurrence of BP rise is associated with a remarkably longer OS in the cohort of patients with RCC but not in patients with HCC. In contrast, specifically having a BP reading indicating hypertension (≥140/90 mm Hg) during VEGFI therapy was not predictive for OS in our total cohort, either for patients with RCC or HCC separately. Yet, for patients with RCC this latter finding must be

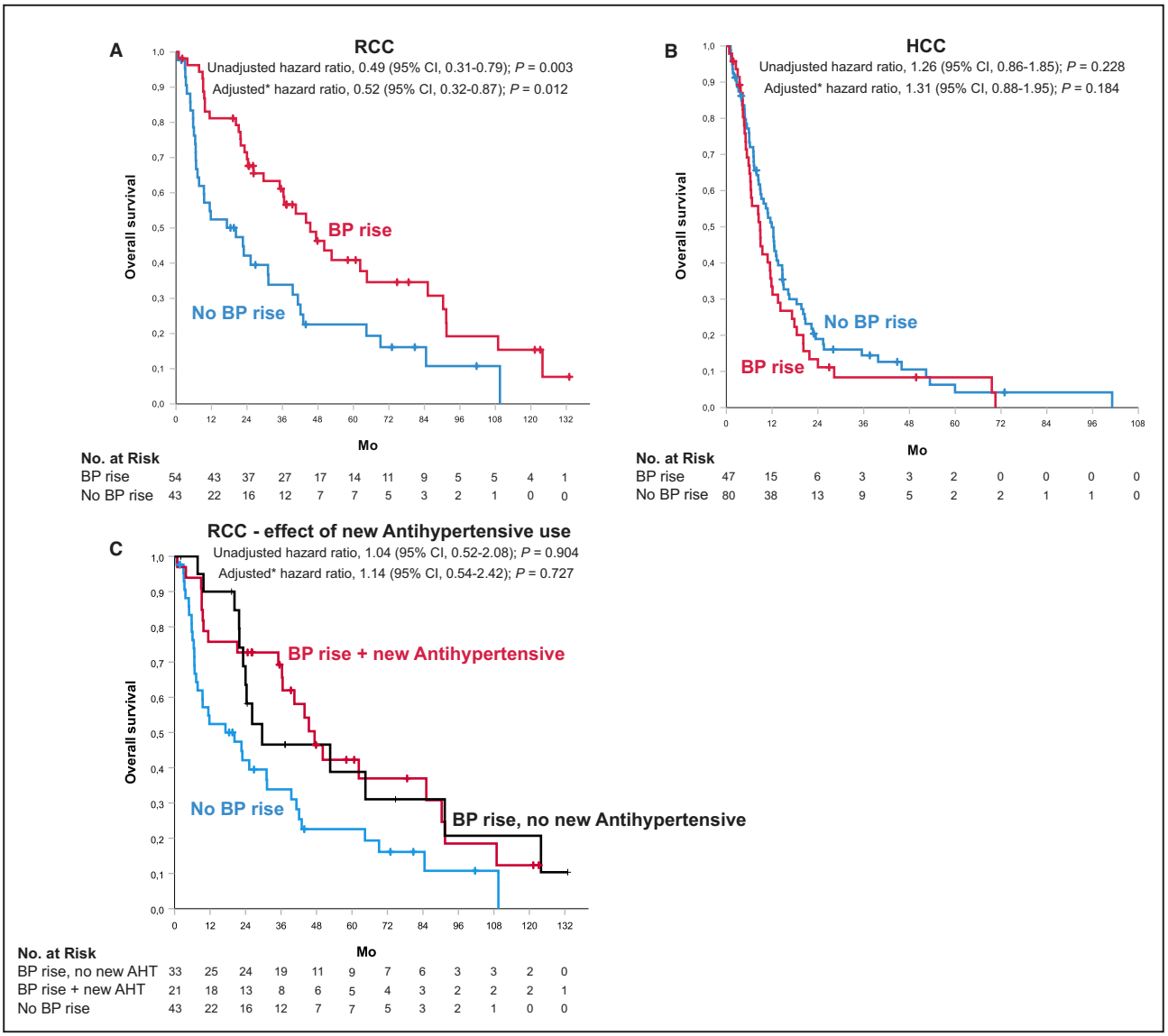

Figure 4. Kaplan–Meier curves of overall survival of patients with and without a blood pressure rise (≥20 mm Hg systolic blood pressure or ≥10 mm Hg diastolic blood pressure) at first measurement after vascular endothelial growth factor inhibitor therapy initiation.

A, patient with renal cell carcinoma; **B**, patients with hepatocellular carcinoma; and **C**, patients with renal cell carcinoma with and without a blood pressure rise +/– new antihypertensive therapy during vascular endothelial growth factor inhibitor therapy. AHT indicates antihypertensive; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HCC, hepatocellular carcinoma; and RCC, renal cell carcinoma. *Adjusted for age, body mass index, and history of cardiovascular disease.

interpreted with caution, given that only a small number of patients within our RCC cohort (n=16) had a BP reading <140/90 mm Hg during VEGFI therapy and that this finding contrasts with a previous study.[13]

Previous studies indicate that increased VEGF signaling positively correlates with tumor growth[24] and that, consequently, effective blockade of VEGF/VEGF receptor-induced angiogenesis decelerates tumor progression. The prohypertensive effects of VEGFI have been proposed as an on-target mechanism.[25] Thus, the simplest explanation of the association between a VEGFI-induced BP rise and improved OS is that this BP rise is indicative of effective VEGF receptors blockade. At least for RCC, this BP rise could therefore serve as a biomarker for effective anti-tumor efficacy. Indeed, a clear relationship between systemic exposure and anti-tumor response was found previously for currently approved VEGFI for the treatment of RCC, sunitinib[22] and pazopanib,[26] and higher circulating concentrations of these agents were associated with more treatment-related toxicity, including hypertension.[22,26] In contrast, the relationship between sorafenib exposure and anti-tumor response is less clear for patients with HCC: a previous study failed to demonstrate a clear

association between treatment dose and anti-tumor response in this patient group.[27] This could be an explanation for the lack of association between a rise in BP and OS for patients with HCC (who predominantly received sorafenib) in the current study.

In our cohort, antihypertensive intervention was initiated in almost 25% of patients receiving VEGFI. Interestingly, patients who already used CCB or RASI before VEGFI initiation experienced a lower rise in SBP during VEGFI therapy, and both classes of antihypertensives were able to induce substantial and similar antihypertensive effects when started during VEGFI therapy. This contrasts with preclinical studies that demonstrate superiority of CCB over RASI for the treatment of sunitinib- and cediranib-induced hypertension.[9,10] Also, a small clinical study demonstrated that CCB were the most effective to treat VEGFI-induced hypertension.[12]

The substantial antihypertensive effect of RASI during VEGFI therapy was unexpected, given that clinical data generally argue against an important role of renin in the pathophysiology of a VEGFI-induced BP rise: plasma renin levels remained stable[28] or even decreased[29] during therapy with sunitinib. Neither does aldosterone seem to play a key role in VEGFI-induced hypertension, given that its plasma levels remained stable during sunitinib-induced hypertension in rats,[29] increased only slightly in patients with RCC receiving sunitinib,[28] and based on clinical evidence that sunitinib was still able to induce a notable BP rise in a patient who previously underwent an adrenalectomy (resulting in undetectable aldosterone concentrations).[30]

Our results now indicate that both CCB and RASI are effective interventions to treat a VEGFI-induced BP rise. In this regard, mineralocorticoid receptor antagonists (MRA) might be another promising treatment strategy, antagonizing aldosterone signaling downstream of RASI. Unfortunately, we could not assess the antihypertensive effect of MRA because none of the patients started an MRA during VEGFI treatment. Until prospective clinical studies are performed, both CCB and RASI seem suitable antihypertensives, and choice of therapy should therefore be predominantly based on patient-specific comorbidities (eg, RASI in case of pre-existing kidney disease or concomitant VEGFI-induced proteinuria), possible drug–drug interactions with pre-existing comedication, and patient tolerability. Importantly, we observed that antihypertensives do not impair VEGFI-induced anti-tumor effects, which is in concordance with previous studies.[13,31]

The current study merits several limitations. First, because of the retrospective design, a substantial number of patients had to be excluded from our analyses because of missing BP data. This is an important observation, because adequate BP monitoring is an essential first step in effective detection and treatment of a VEGFI-induced BP rise.[7,26] Second, BP readings were collected from outpatient visits, which did not always take place on standardized time points during VEGFI therapy. Therefore, we had to select the first and highest BP measurements during therapy to keep collection of readings as standardized as possible. Third, despite the usage of validated BP monitors and cuffs, the exclusion of inpatient readings, and the exclusion of outpatient BP readings that were obtained on visits during which the treating physician had also documented the presence of anxiety or pain, ideally 24-hour ambulatory blood pressure monitoring or home BP monitoring are used to obtain the most reliable BP measurements and to rule out white-coat hypertension. We aimed to minimize the influence of these factors on our study outcomes by analyzing the changes in outpatient BP readings as a primary outcome rather than analyzing absolute BP levels alone.

Future studies should use prospectively collected 24-hour ambulatory blood pressure monitoring or home BP measurements and should separately investigate the associations between survival and either experiencing a BP rise or having/reaching BP thresholds for hypertension. Also, future studies should investigate the relative efficacy of various antihypertensives in a prospective manner and, more importantly, whether timely and prompt antihypertensive treatment has the potential to prevent preliminary discontinuation of VEGFI therapy attributable to cardiovascular toxicity. In this way, patients with cancer can hopefully optimally benefit from their effective anti-cancer therapy while minimizing hypertensive risks.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Targets and starting daily dosage of included VEGFI treatments

VEGFI therapy	N (% of total cohort)	Targets	Starting daily dosage	N (% of VEGFI subtype)
Sorafenib	143 (42)	BRAF, $BRAF^{V600E}$, c-Kit, CRAF, FLT3, PDGFR, VEGFR2-3		
			200 mg	3 (2)
			400 mg	128 (90)
			600 mg	2 (1)
			800 mg	10 (7)
Sunitinib	118 (34)	c-Kit, CSF-1R, FLT-3, PDGFR, RET, VEGFR1-3		
			12.5 mg	1 (1)
			25 mg	12 (10)
			37.5 mg	25 (21)
			50 mg	80 (68)
Pazopanib	55 (16)	c-Kit, PDGFR, VEGFR1-3		
			600 mg	5 (9)
			800 mg	50 (91)
Regorafenib	25 (7)	BRAF, $BRAF^{V600E}$, c-Kit, CSF-1R, FGFR, PDGFR, RAF-1, RET, TIE-2, VEGFR1-3		
			120 mg	22 (88)
			160 mg	3 (12)
Lenvatinib	1 (0.3)	c-Kit, FGFR, PDGFR, RET, VEGFR1-3	4 mg	1 (100)
Cabozantinib	1 (0.3)	AXL, c-Kit, FLT-3, MER, RET, ROS1, TIE-2, TRKB, TYRO3, VEGFR1-3	40 mg	1 (100)

Abbreviations: BRAF: v-raf murine sarcoma viral oncogene homologue B1, CSF-1R: colony stimulating factor 1 receptor, FGFR: fibroblast growth factor receptor, FLT: fetal liver tyrosine kinase, MET: mesenchymal-epithelial transition factor, TRKB: tropomyosin receptor kinase B, PDGFR: platelet-derived growth factor receptor, RET, rearranged during transfection, VEGF: vascular endothelial growth factor, VEGFI: vascular endothelial growth factor inhibitor, VEGFR: vascular endothelial growth factor receptor.

Table S2. Baseline blood pressure prior to VEGFI treatment

		N (%)	SBP	DBP
Total		343 (100)	138 ± 18 mmHg	80 ± 11 mmHg
Per VEGFI therapy				
	Sorafenib	143 (42)	136 ± 17 mmHg	79 ± 11 mmHg
	Sunitinib	118 (34)	137 ± 19 mmHg	80 ± 12 mmHg
	Pazopanib	55 (16)	141 ± 17 mmHg	80 ± 10 mmHg
	Regorafenib	25 (7)	138 ± 17 mmHg	85 ± 11 mmHg

Abbreviations: DBP: diastolic blood pressure, SBP: diastolic blood pressure, VEGFI: vascular endothelial growth factor inhibitor.

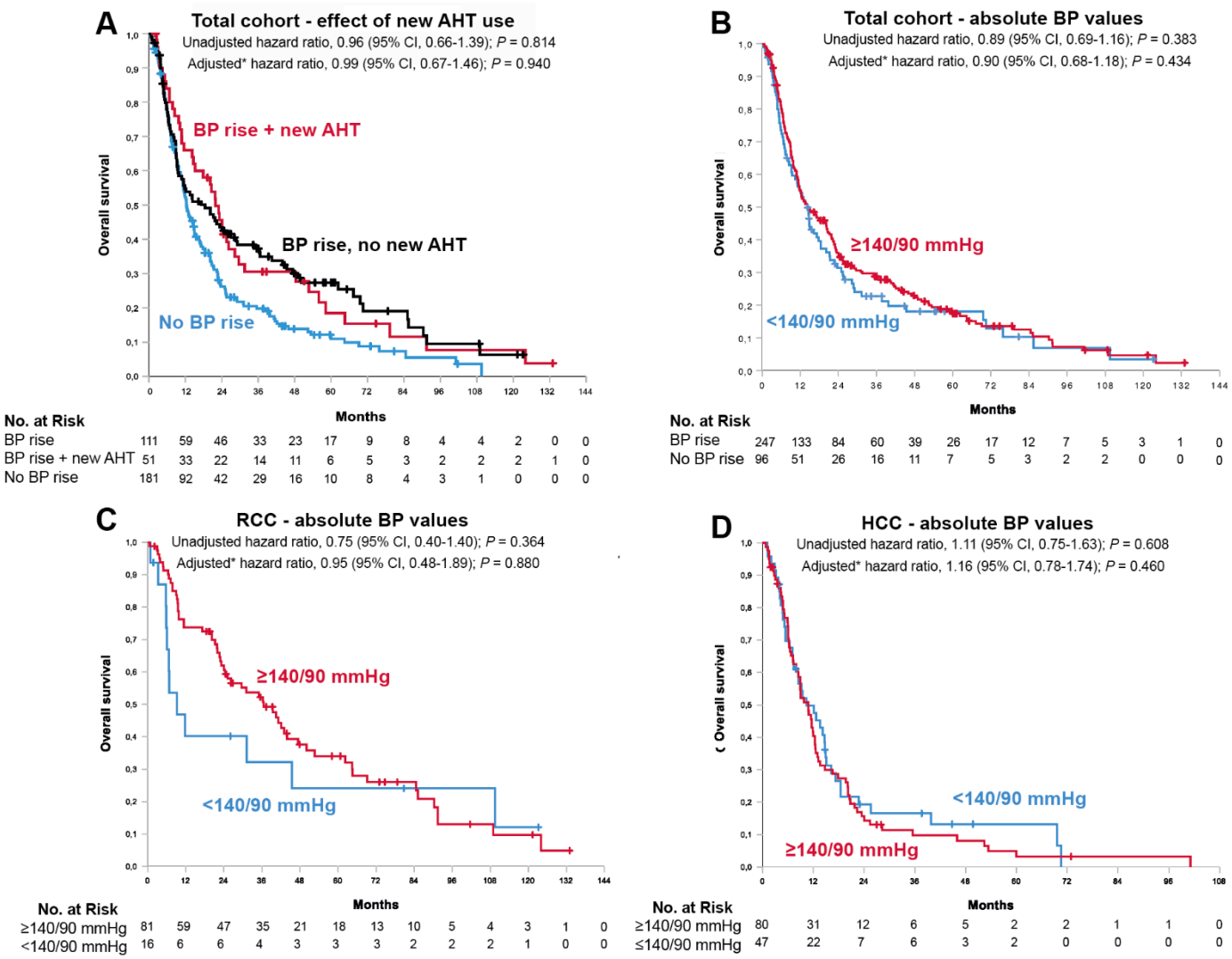
Table S3. Mean blood pressure increase on first measurement during VEGFI therapy compared to baseline, depending on baseline use of antihypertensives

Baseline use of antihypertensive(s)			**N (%)**	**ΔSBP ± SD**	***P value* ΔSBP***	**ΔDBP ± SD**	***P value* ΔDBP***
No			182 (53)	10.9 ± 17 mmHg		6.8 ± 13 mmHg	
Yes	Total		161 (47)	6.4 ± 13 mmHg	**0.027**	3.9 ± 12 mmHg	**0.037**
	β-blocker		82 (24)	7.6 ± 20 mmHg	0.167	3.8 ± 13 mmHg	0.081
	ACEI/ARB		81 (24)	5.8 ± 20 mmHg	**0.036**	3.8 ± 13 mmHg	0.083
	Diuretic	Total	72 (21)	6.1 ± 19 mmHg	0.053	3.7 ± 12 mmHg	0.082
		Loop/thiazide	63 (18)	6.6 ± 20 mmHg	0.100	4.2 ± 12 mmHg	0.160
		MRA	9 (3)	2.4 ± 17 mmHg	0.153	0.44 ± 12 mmHg	0.151
		Loop/thiazide + MRA	15 (4)	3.5 ± 17 mmHg	0.111	2.8 ± 12 mmHg	0.252
	CCB		47 (14)	4.6 ± 22 mmHg	**0.036**	4.9 ± 12 mmHg	0.364

**P* value vs. no baseline use of antihypertensive(s).

Abbreviations: ACEI/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, CCB: calcium channel blocker, DBP: diastolic blood pressure, MRA: mineralocorticoid receptor antagonist, SBP = systolic blood pressure.

Figure S1. Kaplan Meier Curves of overall survival (OS) of **A,** total cohort of included patients with and without a blood pressure (BP) rise (≥20 mmHg SBP and/or ≥10 mmHg DBP) at first measurement after vascular endothelial growth factor inhibitor (VEGFI) therapy +/- new antihypertensive therapy during VEGFI, and OS of patients with and without a reading of hypertension (≥140 mmHg and/or DBP ≥90 mmHg) at first measurement after VEGFI initiation in **B,** total cohort of patients, **C,** renal cell carcinoma (RCC) patients and **D,** hepatocellular carcinoma (HCC) patients.



*Adjusted for age, BMI, and history of CVD.

Abbreviations: AHT: antihypertensive, BMI: body mass index, CI: confidence interval, CVD: cardiovascular disease, DBP: diastolic blood pressure, SBP: systolic blood pressure.