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ORIGINAL RESEARCH

Increase in Blood Pressure Associated With Tyrosine Kinase Inhibitors Targeting Vascular Endothelial Growth Factor

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ABSTRACT

OBJECTIVES This study quantified the change in blood pressure (BP) during antivascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) therapy, compared BPs between TKIs, and analyzed change in BP during antihypertensive therapy.

BACKGROUND TKIs targeting VEGF are associated with hypertension. The absolute change in BP during anti-VEGF TKI treatment is not well characterized outside clinical trials.

METHODS A retrospective single-center study included patients with metastatic renal cell carcinoma who received anti-VEGF TKIs between 2007 and 2018. Mixed models analyzed 3,088 BPs measured at oncology clinics.

RESULTS In 228 patients (baseline systolic blood pressure [SBP] 130.2 ± 16.3 mm Hg, diastolic blood pressure [DBP] 76.8 ± 9.3 mm Hg), anti-VEGF TKIs were associated with mean increases in SBP of 8.5 mm Hg ($p < 0.0001$) and DBP of 6.7 mm Hg ($p < 0.0001$). Of the anti-VEGF TKIs evaluated, axitinib was associated with the greatest BP increase, with an increase in SBP of 12.6 mm Hg ($p < 0.0001$) and in DBP of 10.3 mm Hg ($p < 0.0001$) relative to baseline. In pairwise comparisons between agents, axitinib was associated with greater SBPs than cabozantinib by 8.4 mm Hg ($p = 0.004$) and pazopanib by 5.1 mm Hg ($p = 0.01$). Subsequent anti-VEGF TKI courses were associated with small increases in DBP, but not SBP, relative to the first course. During anti-VEGF TKI therapy, calcium-channel blockers and potassium-sparing diuretic agents were associated with the largest BP reductions, with decreases in SBP of 5.6 mm Hg ($p < 0.0001$) and 9.9 mm Hg ($p = 0.007$), respectively.

CONCLUSIONS Anti-VEGF TKIs are associated with increased BP; greatest increases are observed with axitinib. Calcium-channel blockers and potassium-sparing diuretic agents were associated with the largest reductions in BP.

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Tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor (VEGF) receptors are a mainstay in the treatment of patients with metastatic renal cell carcinoma (mRCC) because of their efficacy in improving progression-free survival and overall survival (1-3). Sorafenib and sunitinib were the initial anti-VEGF TKIs approved by the United States Food and Drug Administration in 2005 and 2006, respectively, for use in mRCC. Since then, additional anti-VEGF TKIs have been approved for mRCC, including axitinib, cabozantinib, lenvatinib, and pazopanib (4).

Because of their effects on vascular regression, vasoconstrictor levels, and the renal parenchyma, anti-VEGF TKIs are highly associated with hypertension, with a reported incidence in first-time users of 21% to 40% (5-13). The absolute change in blood pressure (BP) during treatment with anti-VEGF TKIs and the time course of change in BP from these agents have not been well characterized because previous studies primarily evaluated hypertension as a dichotomous outcome, usually using Common Terminology Criteria for Adverse Events (CTCAE) version 2 or 3 (14,15). The definition of hypertension as BP >150/100 mm Hg by CTCAE versions 2 and 3 likely underestimates the incidence of hypertension compared with more clinically used 2017 American College of Cardiology and American Heart Association or 2014 Joint National Committee 8 guidelines, which define hypertension as BP >130/80 mm Hg and >140/90 mm Hg, respectively (16,17).

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To the best of our knowledge, no study has directly compared the changes in BP among commonly used anti-VEGF TKIs. Comparing hypertensive effects of different agents may guide monitoring for hypertension and selection of agents. Furthermore, given the chronicity of mRCC, most patients receive multiple courses of anti-VEGF TKIs, either sequentially or with intervening regimens. No studies to date have evaluated whether receiving multiple courses of anti-VEGF TKIs leads to cumulative hypertensive toxicity.

Using 11 years of data from electronic medical records at Stanford Cancer Institute in Stanford, California, we identified patients with mRCC who were treated with anti-VEGF TKIs and analyzed all BPs measured at oncology clinics to quantify the change in BP relative to baseline. We evaluated whether receiving multiple anti-VEGF TKI courses was associated with cumulative increases in BP and compared the changes in BP across anti-VEGF TKIs. Additionally, we analyzed the change in BP according to the various antihypertensive drug classes prescribed during anti-VEGF TKI treatment.

METHODS

STUDY DESIGN. After receiving Institutional Review Board approval, we used the Stanford RCC Database to identify all patients with mRCC who were treated with anti-VEGF TKIs from January 1, 2007 to March 1, 2018. Anti-VEGF TKIs received included axitinib, cabozantinib, pazopanib, sorafenib, sunitinib, and lenvatinib.

Data for this retrospective study were retrieved from the Stanford Medicine Research Data Repository, an electronic warehouse containing data from institutional medical records dating from 1998 for approximately 4 million patients, including International Classification of Diseases diagnoses, medications, outpatient vital signs, and clinic note transcriptions (18).

All cancer treatments received by the cohort were retrieved from the Data Repository pharmacy records. Oncology clinic notes were reviewed to confirm treatment start and end dates and to evaluate adherence. Patients were excluded if they received treatment for mRCC before establishing care at Stanford because their baseline BPs and baseline antihypertensive agents were unknown. The follow-up period started from the date of first treatment received to date of death or date of last follow-up as of May 30, 2018.

OUTCOME: BLOOD PRESSURE MEASUREMENTS. All BP measurements from oncology clinics were retrieved from both the Stanford Data Repository and a comprehensive review of clinic notes. BPs were measured by medical assistants using automated sphygmomanometers (Welch Allyn, Skaneateles Falls, New York) in clinics with a protocol requiring measurement of 1 resting BP after patients had been sitting for 15 min in the clinic room before seeing the oncologist. BPs measured during outpatient visits within 10 days of an inpatient admission were excluded to avoid confounding by comorbid events or short-term discharge medications. Baseline BP was calculated as the mean of BPs measured during the 3 months before the first mRCC treatment start date. For patients with a change in antihypertensive agents during the 3 months before treatment, only BPs measured after the antihypertensive regimen change (but before mRCC treatment start date) were used to determine baseline BP.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin II receptor blocker

BP = blood pressure

CCB = calcium-channel blocker

CTCAE = Common Terminology Criteria for Adverse Events

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

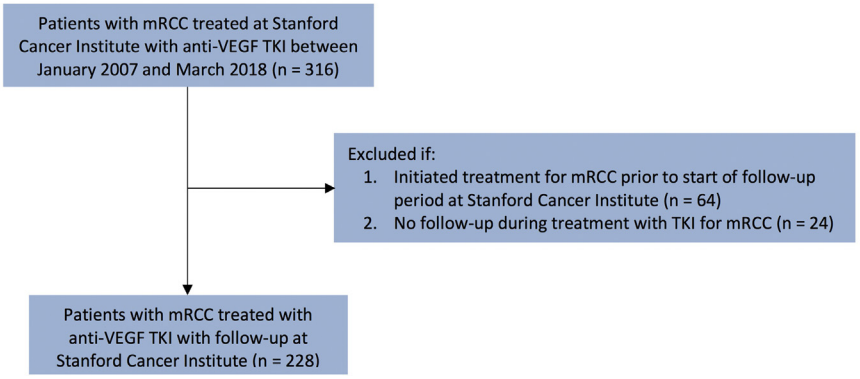
mRCC = metastatic renal cell carcinoma

SBP = systolic blood pressure

TKI = tyrosine kinase inhibitor

VEGF = vascular endothelial growth factor

FIGURE 1 Patient Cohort Selection



mRCC = metastatic renal cell carcinoma; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

COVARIATES. We retrieved demographic characteristics and comorbid cardiovascular risk factors. Outpatient creatinine measurements at baseline and during follow-up were retrieved and used to calculate estimated glomerular filtration rates (eGFR) by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; eGFR values were matched by date to BP measurements from oncology clinics. The outpatient creatinine measurement most closely preceding the mRCC treatment start date was used to calculate baseline eGFR.

Data were retrieved from pharmacy records in the Data Repository on all outpatient antihypertensive medications received at baseline and during follow-up, including medication name, dosage, start date, and end date. Antihypertensive agents were classified as angiotensin-converting-enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta blockers, calcium channel blockers (CCBs), loop diuretics, thiazide diuretics, potassium-sparing diuretics, and other. Oncology clinic notes were reviewed to confirm accuracy of pharmacy data and to evaluate medication adherence. These data were used to determine the number of ambulatory antihypertensive agents used at the date of each BP measurement. A covariate value for number of antihypertensive agents was specified for each BP and was attributed as 0 for BPs measured when the patient was not taking antihypertensive agents.

Because of the high frequency of antihypertensive dose changes during follow-up, a separate time-varying covariate for dose change was included. Dosages of antihypertensive agents at the date of each BP measurement were retrieved; relative to the first dose received of each medication, dose changes were categorized as +1 for increases, 0 for no change, and −1 for decreases. A covariate value was specified for each BP and was attributed as 0 for each BP measured when the patient was not taking antihypertensives.

TABLE 1 Baseline Characteristics of Patients (N = 228)

Age, yrs	61.2 (18-91)
Sex	
Male	159 (69.7)
Female	69 (30.3)
Race	
Non-Hispanic white	127 (55.7)
Hispanic	37 (16.2)
African-American	7 (3.1)
Asian	34 (14.9)
Unknown or other	23 (10.1)
Comorbid cardiovascular risk factors	
Pre-existing hypertension (by 2017 ACC/AHA criteria)	183 (80.3)
Pre-existing hypertension (by 2014 JNC 8 criteria)	144 (63.2)
Hyperlipidemia	99 (43.4)
Diabetes	57 (25.0)
Pre-existing congestive heart failure	12 (5.3)
Baseline blood pressure (mm Hg) before first treatment	
Systolic	130.2 ± 16.3
Diastolic	76.8 ± 9.3
Baseline antihypertensive agents	
ACE inhibitor or ARBs	61 (26.8)
Beta-blockers	59 (25.9)
Calcium-channel blockers	45 (19.7)
Other	33 (14.5)
Baseline estimated glomerular filtration rate (ml/min/1.73 m^2) before first treatment	63.7 ± 21.2

Values are mean (range), n (%), or mean ± SD.

ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; JNC = Joint National Committee.

STATISTICAL ANALYSIS. Linear mixed-effects models with an unstructured covariance matrix compared repeated BP measurements during treatment with anti-VEGF TKIs relative to baseline BP. As an active control, models also compared BPs measured in our cohort during treatment with agents that did not have any anti-VEGF activity. Additional analyses restricted to BPs measured during anti-VEGF TKI treatment were performed to: 1) compare BPs among different TKIs; 2) evaluate whether second and third anti-VEGF TKI courses were associated with increased BP relative to the first course; 3) evaluate change in BP during use of different antihypertensive agents; and 4) evaluate the time course of BP changes during treatment with anti-VEGF TKIs.

Covariates for multivariate analyses included age, eGFR, nephrectomy status, number of antihypertensive agents, antihypertensive dosage changes, number of prior cancer treatments received for mRCC, pre-existing heart failure, and sex; the first 6 covariates were time-varying predictors with values corresponding to each BP measurement at baseline and during follow-up. For analyses in which baseline BPs were not the reference group, multivariate models additionally adjusted for baseline BP. Intercept and slope of change over time were modeled as random effects. Analyses were performed using Statistical Analysis Systems software version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Between January 2007 and March 2018, 316 patients with mRCC were treated with anti-VEGF TKIs. We excluded 64 patients who received treatment for mRCC before their first clinic visit at Stanford because of a lack of data on baseline BP. We excluded 24 patients with no follow-up during anti-VEGF TKI treatment. The remaining 228 patients comprised the study cohort (Figure 1).

PATIENT CHARACTERISTICS. Mean age at the start of first treatment was 61.2 years (range 18 to 91 years), and 159 (69.7%) patients were male (Table 1). Mean baseline SBP and DBP were 130.2 ± 16.3 mm Hg and 76.8 ±9.3 mm Hg, respectively; 115 (50.4%) patients were taking antihypertensive agents before starting treatment for mRCC.

Over 359.5 person-years of follow-up, patients received a mean of 2.4 (range 1 to 8) different cancer therapies, with 143 (62.7%) patients receiving more than 1 treatment. Treatments included: 1) single-agent anti-VEGF TKIs; 2) monoclonal antibody to VEGF (bevacizumab); 3) agents without anti-VEGF activity (chemotherapy, immune checkpoint inhibitors, mTOR inhibitors, TKIs without anti-VEGF activity); and 4) combination therapy of an anti-VEGF TKI with another agent (lenvatinib and everolimus, sunitinib and gemcitabine, sorafenib and erlotinib, axitinib and nivolumab, or lenvatinib and nivolumab) (Table 2).

TABLE 2 Cancer Agents Included in Each Treatment Category

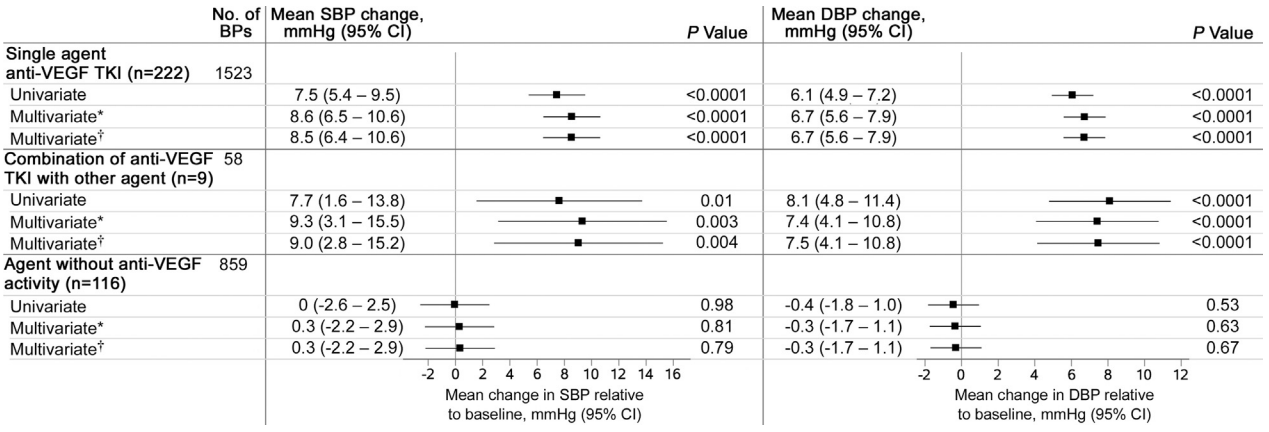
Agent Without Anti-VEGF Activity* (n = 116)		Single-Agent Anti-VEGF TKI* (n = 222†)		Combination of Anti-VEGF TKI With Other Agent* (n = 9)	
Agent	**n**	**Agent**	**n**	**Agent**	**n**
Immune checkpoint inhibitors		Pazopanib	127	Lenvatinib/everolimus	5
Nivolumab	54	Sunitinib	106	Sunitinib/gemcitabine	4
Nivolumab/ipilimumab	4	Axitinib	45	Sorafenib/erlotinib	1
Atezolizumab	1	Sorafenib	31	Axitinib/nivolumab	1
Nivolumab/varlilumab	1	Cabozantinib	21	Lenvatinib/nivolumab	1
Pembrolizumab	1	Lenvatinib	2		
mTOR inhibitors					
Everolimus	52				
Temsirolimus	13				
Everolimus/CB-839 glutaminase inhibitor	2				
Interleukin-2	8				
Chemotherapy					
Capecitabine/gemcitabine	3				
Carboplatin/paclitaxel	2				
Gemcitabine	2				
Capecitabine	1				
Gemcitabine/doxorubicin	1				
Capecitabine/gemcitabine	1				
Vincristine/cyclophosphamide/ dacarbazine	1				
CB-839 glutaminase inhibitor	1				
BCR-ABL TKI					
Imatinib	1				
MET inhibitors					
Savolitinib	1				

Values are n. Sample sizes indicate the number of patients who received each treatment agent or each treatment category. *The total number of patients who received each treatment category is less than the sum of the sample sizes for the corresponding treatment agents because most patients received more than 1 treatment agent over the follow-up period. †Of the cohort of 228 patients, 222 received single-agent anti-VEGF TKIs; 6 received combination treatment (anti-VEGF TKI with another agent) but no single-agent anti-VEGF TKIs.

MET = mesenchymal epithelial transition; mTOR = mammalian target of rapamycin; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

BLOOD PRESSURE MEASUREMENTS. Patients had 4,355 outpatient oncology visits from 3 months before the start date of the first treatment to the date of death or date of last follow-up as of May 30, 2018. A total of 4,301 (98.8%) BP measurements were available from those visits. Of available BPs, we excluded 117 measured within 10 days of an inpatient admission and 960 measured during treatment breaks. Given the study focus on anti-VEGF TKIs, 136 BPs measured during treatment with bevacizumab were excluded. The remaining 3,088 BP values were analyzed, including 648 baseline values and 2,440 values measured during treatment.

FIGURE 2 Change in BP During Treatment With Anti-VEGF TKIs and Agents Without Anti-VEGF Activity Relative to Baseline

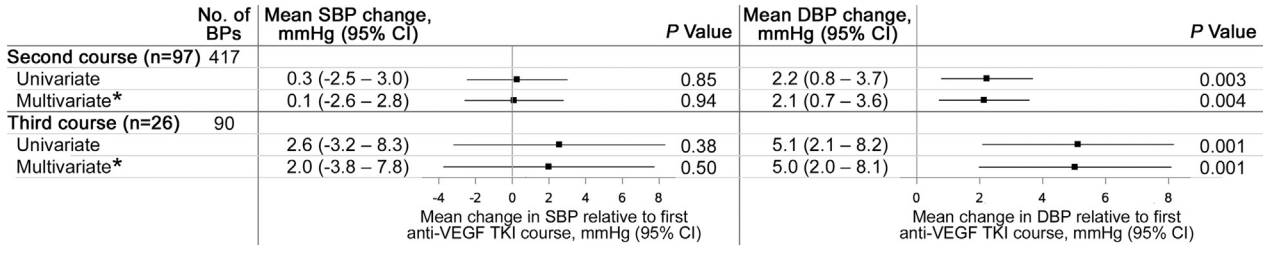


*Adjusted for age, number of antihypertensive agents, changes in antihypertensive dosage, number of prior cancer therapies, nephrectomy status, baseline estimated glomerular filtration rate, pre-existing congestive heart failure, and sex; first 5 covariates were time-varying predictors. †Adjusted for aforementioned variables and time-varying estimated glomerular filtration rate. The p values indicate significance of change in blood pressure (BP) relative to baseline. CI = confidence interval; DBP = diastolic blood pressure; SBP = systolic blood pressure; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

CHANGE IN BLOOD PRESSURE DURING TREATMENT RELATIVE TO BASELINE. Baseline characteristics were similar between patients who received single-agent anti-VEGF TKIs, combination therapy, and agents without anti-VEGF activity (Supplemental Table 1). In multivariate models, relative to baseline BP, single-agent anti-VEGF TKIs were associated with an increase in SBP and DBP of 8.5 mm Hg ($p < 0.0001$) and 6.7 mm Hg ($p < 0.0001$), respectively (Figure 2). Combination therapy was associated with a significant increase in SBP and DBP of 9.0 mm Hg ($p = 0.004$) and 7.5 mm Hg ($p < 0.0001$), respectively, relative to baseline. Results were similar between partially and fully adjusted multivariate models. Interactions between treatment category and time were not significant and were not included in adjusted models. Agents without anti-VEGF activity were not associated with increased BP relative to baseline (nonsignificant change of 0.3 and −0.3 mm Hg for SBP and DBP, respectively).

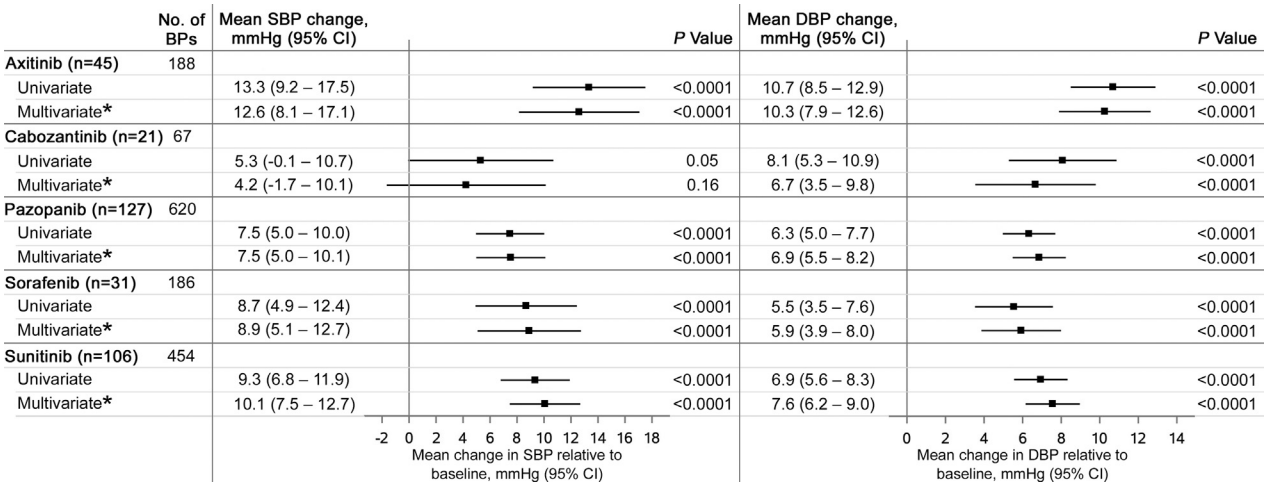
Because more than one-half of the patient cohort received more than 1 cancer therapy during the follow-up period, a sensitivity analysis limited to BPs measured during the first treatment regimen was conducted to avoid confounding by prior treatments. During treatment with single-agent anti-VEGF TKIs, this analysis determined an increase in SBP and DBP, respectively, of 10.3 mm Hg ($p < 0.0001$) and 7.5 mm Hg ($p < 0.0001$) relative to baseline on univariate analysis and of 10.8 mm Hg ($p < 0.0001$) and 8.1 mm Hg ($p < 0.0001$) in the fully adjusted model.

FIGURE 3 Change in BP During Second and Third Anti-VEGF TKI Courses Relative to First Anti-VEGF TKI Course



*Adjusted for age, number of antihypertensive agents, changes in antihypertensive dosage, nephrectomy status, estimated glomerular filtration rate, baseline blood pressure (BP), pre-existing heart failure, and sex; first 5 covariates were time-varying. The p values indicate significance of blood pressure change relative to the first tyrosine kinase inhibitor (TKI) course. Abbreviations as in Figure 2.

FIGURE 4 Change in BP Relative to Baseline Stratified by Specific Anti-VEGF TKI Agent



*Adjusted for age, number of antihypertensive agents, changes in antihypertensive dosage, number of prior cancer therapies, nephrectomy status, estimated glomerular filtration rate, pre-existing heart failure, and sex; first 6 covariates were time-varying. The p values indicate significance of blood pressure (BP) change relative to baseline. Abbreviations as in Figure 2.

COMPARISON OF BLOOD PRESSURE MEASUREMENTS BETWEEN ANTI-VEGF TKI COURSE SEQUENCES. Of 222 patients treated with single-agent anti-VEGF TKIs, a second TKI course was received by 85 patients, a third course by 22, and a fourth course by 5 (Supplemental Table 2). In mixed models limited to BPs measured during single-agent anti-VEGF TKI treatment, relative to the first TKI course (mean SBP 138.1 ± 19.1 mm Hg), second and third courses were not associated with changes in SBP (**Figure 3**). However, relative to the first course (mean DBP 81.4 ± 10.7 mm Hg), second and third TKI courses were associated with statistically significant increases in DBP of 2.1 mm Hg ($p = 0.004$) and 5.0 mm Hg ($p = 0.001$), respectively, on multivariate analysis. Because of the small sample size, the fourth course was excluded from this analysis. Although second and third TKI courses were not associated with increased SBP relative to the first course, all 3 courses were associated with significant increases in SBP of 8 to 10 mm Hg ($p < 0.001$) relative to baseline on multivariate analyses.

A separate mixed model evaluated whether patients who received only 1 anti-VEGF TKI experienced greater hypertensive toxicity compared with patients who received additional anti-VEGF TKI courses. In an analysis limited to BPs measured during the first TKI course, no significant differences were found in BPs between those 2 groups of patients.

COMPARISON OF BLOOD PRESSURE MEASUREMENTS BETWEEN SINGLE-AGENT ANTI-VEGF TKIs. The 5 most commonly received single-agent anti-VEGF TKIs in our cohort were pazopanib ($n = 127$), sunitinib ($n = 106$), axitinib ($n = 45$), sorafenib ($n = 31$), and cabozantinib ($n = 21$). Baseline demographic characteristics were comparable among patients who received those agents (Supplemental Table 3).

Relative to baseline BP, axitinib was associated with the highest increase in BP on multivariate analysis, with an increase in SBP of 12.6 mm Hg ($p < 0.0001$) and in DBP of 10.3 mm Hg ($p < 0.0001$) (**Figure 4**). On multivariate analysis, an increase in SBP of 10.1 mm Hg ($p < 0.0001$) was noted during treatment with sunitinib, 8.9 mm Hg ($p < 0.0001$) during sorafenib, and 7.5 mm Hg ($p < 0.0001$) during pazopanib. Cabozantinib, pazopanib, sorafenib, and sunitinib were associated with increases in DBP of 6 to 8 mm Hg relative to baseline. Interactions between TKI and time were not significant and were excluded from the adjusted model. An analysis stratified by TKI agent and dose demonstrated a dose-dependent increase in SBP and DBP by axitinib, cabozantinib, pazopanib, and sunitinib (Supplemental Table 4).

In adjusted mixed models comparing BPs among TKIs, axitinib was associated with higher SBP than cabozantinib by 8.4 mm Hg ($p = 0.004$) and pazopanib by 5.1 mm Hg ($p = 0.01$), and with higher DBPs than sorafenib by 4.3 mm Hg ($p = 0.001$), cabozantinib by 3.6 mm Hg ($p = 0.02$), pazopanib by 3.4 mm Hg

FIGURE 5 Change in BP Stratified by Classification of Antihypertensive Agent Received During Treatment With Anti-VEGF TKI

	No. of BPs	Mean SBP change, mmHg (95% CI)	*P* Value	Mean DBP change, mmHg (95% CI)	*P* Value
ACEi (n=66)	348				
Univariate		-1.9 (-4.9 – 1.1)	0.22	-1.1 (-2.7 – 0.5)	0.18
Multivariate*		-2.4 (-5.3 – 0.4)	0.10	-0.2 (-1.7 – 1.3)	0.80
Multivariate†		-3.0 (-5.9 – 0.0)	0.05	-0.7 (-2.2 – 0.9)	0.40
ARB (n=39)	308				
Univariate		2.3 (-1.6 – 6.2)	0.25	-1.9 (-3.9 – 0.2)	0.08
Multivariate*		0.7 (-2.9 – 4.3)	0.71	-1.5 (-3.4 – 0.3)	0.11
Multivariate†		0.7 (-3.1 – 4.5)	0.71	-1.5 (-3.4 – 0.5)	0.15
Beta Blocker (n=87)	561				
Univariate		1.5 (-1.5 – 4.5)	0.32	-0.9 (-2.5 – 0.8)	0.30
Multivariate*		2.3 (-0.5 – 5.2)	0.11	-0.2 (-1.7 – 1.3)	0.81
Multivariate†		2.8 (-0.2 – 5.7)	0.07	-0.1 (-1.6 – 1.4)	0.90
CCB (n=115)	738				
Univariate		-4.8 (-7.1 – -2.5)	<0.0001	-2.2 (-3.4 – -1.0)	0.0005
Multivariate*		-5.1 (-7.3 – -2.9)	<0.0001	-1.9 (-3.1 – -0.8)	0.001
Multivariate†		-5.6 (-7.8 – -3.4)	<0.0001	-2.1 (-3.2 – -1.0)	0.0005
Loop diuretic (n=23)	63				
Univariate		-0.9 (-6.1 – 4.4)	0.75	-0.4 (-3.2 – 2.5)	0.80
Multivariate*		-0.3 (-5.4 – 4.8)	0.90	1.3 (-1.5 – 4.0)	0.36
Multivariate†		1.0 (-4.3 – 6.3)	0.71	2.1 (-0.7 – 4.9)	0.15
Thiazide diuretic (n=40)	290				
Univariate		-0.5 (-3.9 – 3.0)	0.79	0.0 (-1.8 – 1.9)	0.96
Multivariate*		-0.6 (-3.8 – 2.7)	0.74	0.5 (-1.2 – 2.2)	0.56
Multivariate†		-0.6 (-4.0 – 2.8)	0.74	1.1 (-0.7 – 2.9)	0.23
Potassium-sparing diuretic (n=10)	42				
Univariate		-7.9 (-15.4 – -0.4)	0.04	-5.5 (-9.5 – -1.4)	0.008
Multivariate*		-8.0 (-14.9 – -1.0)	0.03	-4.2 (-7.9 – -0.6)	0.02
Multivariate†		-9.9 (-17.2 – -2.7)	0.007	-4.8 (-8.5 – -1.0)	0.01

*Adjusted for age, number of prior cancer therapies, nephrectomy status, estimated glomerular filtration rate, baseline blood pressure (BP), pre-existing congestive heart failure, and sex; first 4 covariates were time-varying. †Adjusted for aforementioned variables and all antihypertensive classes used at each blood pressure measurement. The p values indicate significance of blood pressure change during use of each antihypertensive class relative to blood pressures measured without use of that class. ACEi = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium-channel blocker; other abbreviations as in Figure 2.

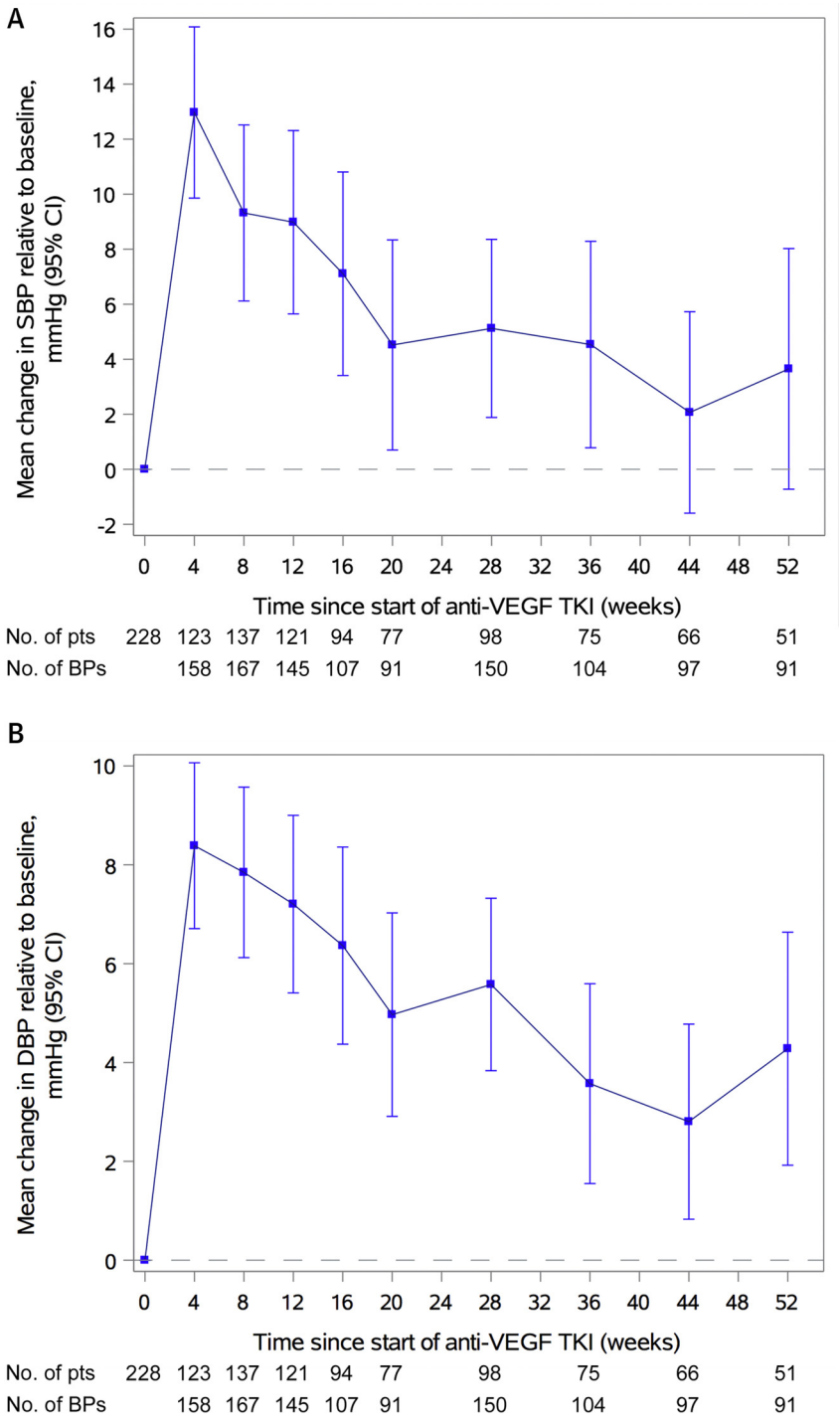
(p = 0.001), and sunitinib by 2.7 mm Hg (p = 0.03). Other pairwise comparisons between anti-VEGF TKIs revealed no statistically significant difference in BPs.

CHANGE IN BLOOD PRESSURE MEASUREMENTS DURING USE OF ANTIHYPERTENSIVE AGENTS. Of the 115 patients receiving baseline antihypertensives, 94 (81.7%) required antihypertensive adjustments during treatment with anti-VEGF TKIs, with 34 receiving additional antihypertensive agent(s) only, 1 receiving only a dose increase of a baseline antihypertensive agent, and 59 requiring both. Of 113 patients not taking baseline antihypertensives, 74 (65.5%) were initiated on antihypertensives during anti-VEGF TKI treatment.

During treatment with single-agent anti-VEGF TKIs, antihypertensive classes received by patients included CCBs (n = 115), beta-blockers (n = 87), ACE inhibitors (n = 66), thiazide diuretic agents (n = 40), ARBs (n = 39), loop diuretic agents (n = 23), and potassium-sparing diuretic agents (n = 10); more than 1 antihypertensive class was required by 86 (38.7%) patients. On fully adjusted multivariate analysis, CCBs were associated with a decrease in SBP of 5.6 mm Hg (p < 0.0001) and in DBP of 2.1 mm Hg (p < 0.0001) relative to BPs measured without CCB use (Figure 5); potassium-sparing diuretic agents were associated with a decrease in SBP of 9.9 mm Hg (p = 0.007) and in DBP of 4.8 mm Hg (p = 0.01). ACE inhibitors and ARBs were not associated with decreased BP during anti-VEGF TKI treatment.

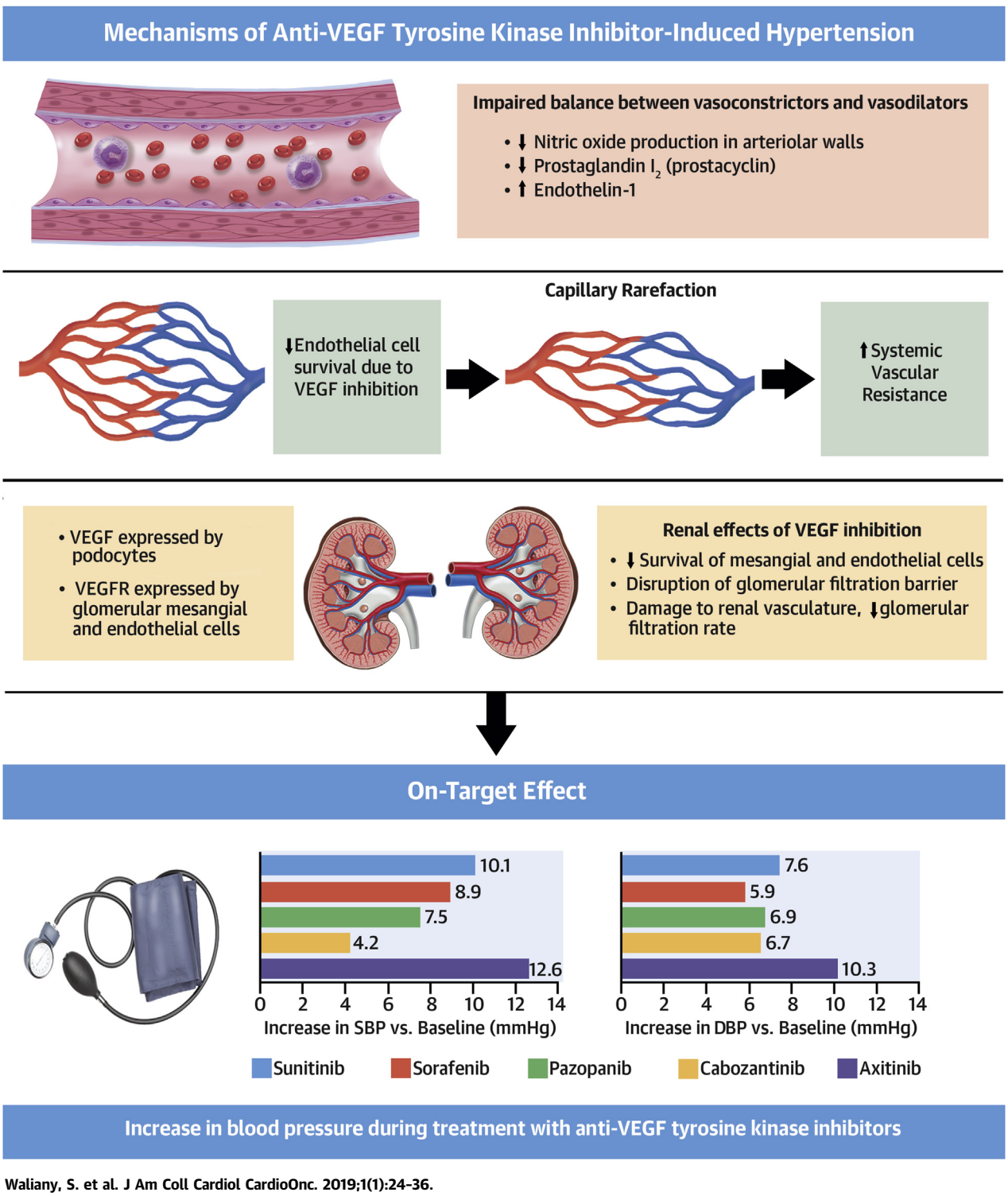
TIME COURSE OF CHANGES IN BLOOD PRESSURE DURING USE OF SINGLE-AGENT ANTI-VEGF TKIs. Single-agent anti-VEGF TKIs were received by 222 patients in our cohort for a mean duration of 11.5 ± 13.8 months. In analyses limited to BPs measured during single-agent anti-VEGF TKI treatment, BPs were stratified according to time since start of TKI therapy (Figures 6A and 6B). The greatest increase in SBP relative to baseline occurred during the first 4 weeks of treatment, with an increase of 13.0 mm Hg (p < 0.0001). This increase gradually declined to 7 to 9 mm Hg between 4 and 16 weeks and to 2 to 5 mm Hg between 16 and 52 weeks.

FIGURE 6 **Time Course of Increase in BP Relative to Baseline During Treatment With Anti-VEGF TKIs**



Adjusted for age, number of antihypertensive agents, changes in antihypertensive dosage, number of prior cancer therapies, nephrectomy status, estimated glomerular filtration rate, pre-existing congestive heart failure, and sex; first 6 covariates were time-varying predictors. The mean change in blood pressure (BP) (relative to baseline) and numbers of patients and blood pressures at each time point represent data for the interval since the last time point with displayed data. **(A)** Systolic blood pressure (SBP). **(B)** Diastolic blood pressure (DBP). Error bars indicate 95% confidence intervals (CIs). Abbreviations as in Figure 2.

CENTRAL ILLUSTRATION **Hypertension Induced by Anti-Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitors: Mechanisms and Outcomes**



Waliany, S. et al. J Am Coll Cardiol CardioOnc. 2019;1(1):24-36.

Anti-vascular endothelial growth factor tyrosine kinase inhibitors result in increased vasoconstrictor levels, decreased vasodilator levels, vascular rarefaction, and renal damage, which are possible mechanisms behind antiangiogenic-induced hypertension.

The increase in DBP showed a similar pattern, peaking at 8.4 mm Hg ($p < 0.0001$) above baseline during the first 4 weeks of treatment and declining over time but remaining significantly elevated relative to baseline.

DISCUSSION

In a large cohort of patients with mRCC, we analyzed more than 1,500 BPs to evaluate changes in hypertension during treatment with anti-VEGF TKIs. Our primary findings indicate that: 1) anti-VEGF TKIs are associated with increases in SBP of 8 to 10 mm Hg and in DBP of 6 to 8 mm Hg relative to baseline; 2) hypertensive effects vary among different TKIs, with axitinib associated with the largest BP increase; 3) second and third TKI courses are associated with increases in DBP of 2 to 5 mm Hg relative to the first course; and 4) CCBs and potassium-sparing diuretic agents are associated with significant decreases in BP during anti-VEGF TKI treatment.

Our analyses of BP as a continuous outcome provide insight into hypertensive effects of anti-VEGF TKIs. Furthermore, mixed models allowed analysis of multiple BPs per patient and adjustment for time-varying factors such as eGFR, antihypertensive use, number of prior cancer therapies, and nephrectomy status. This study compared hypertensive changes among 5 commonly used anti-VEGF TKIs. Furthermore, we determined that using multiple courses of anti-VEGF TKIs incurs cumulative increases in DBP but not SBP.

Our findings were consistent with results from the few prior TKI studies that evaluated changes in BP in small samples of patients with mRCC, colorectal cancer, or multiple tumor types (19–22). In a prospective study of 84 patients with mRCC, Catino et al. (19) found an increase in SBP of 9.5 mm Hg and in DBP of 7.2 mm Hg relative to baseline after 3.5 weeks of sunitinib. Maitland et al. (22) detected a similar increase in SBP of 10.8 mm Hg and in DBP of 8.0 mm Hg in 54 patients with different solid tumors, including 19 (35%) with mRCC.

Preclinical studies have demonstrated possible mechanisms behind hypertensive effects of VEGF inhibition, including effects on endogenous vasoconstrictors and vasodilators, vascular rarefaction, and glomerular damage (**Central Illustration**). Given the role of VEGF in endothelial cell survival, inhibiting VEGF initiates endothelial cell apoptosis, resulting in vascular rarefaction, or reduction in capillary bed density, and subsequently increasing systemic vascular resistance (9,10). VEGF also increases nitric oxide levels through transcription of endothelial nitric oxide synthase; it promotes prostacyclin production by endothelial cells; and it decreases levels of vasoconstrictor endothelin-1. Inhibiting VEGF consequently promotes an imbalance between vasoconstrictors and vasodilators, thus enhancing vascular tone (11,12).

Renal effects of VEGF inhibition may contribute to hypertension through disruption of the glomerular filtration barrier, damage of renal vasculature, and effects on sodium natriuresis (23–26). In our analysis of BP change during treatment with anti-VEGF TKIs, our partially adjusted model controlled for baseline eGFR, whereas our fully adjusted model controlled for baseline and time-varying eGFR. The similar findings of the 2 models suggest that the increase in BP during anti-VEGF TKI treatment occurs even after accounting for changes in renal function from VEGF inhibition.

Anti-VEGF TKIs are multitargeted agents that inhibit not only VEGF, but also other growth factors and kinases including c-kit protein, platelet-derived growth factor receptor, and FMS-like tyrosine kinase-3 (25,26). Comparing hypertensive effects of anti-VEGF TKIs allows clinicians to anticipate when patients may require more surveillance or more aggressive antihypertensive management. Our study detected that axitinib was associated with the largest BP increase relative to other TKIs. Past studies have detected a 40.1% incidence of hypertension from axitinib compared with 35.9% for pazopanib, 32.9% for cabozantinib, 23.1% for sorafenib, and 21.6% for sunitinib (6–8,27,28). Compared with other multitargeted TKIs evaluated in our study, axitinib had higher selectivity for VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3, a finding suggesting that selectivity for VEGFR may be associated with greater hypertensive effects (25,29–31). Alternatively, because of selectivity for VEGFR, axitinib may be associated with fewer off-target side effects, thus allowing tolerability of higher dosage and leading to enhanced on-target hypertensive effects.

With mRCC treatment, patients often receive multiple treatment courses, with each regimen continued until disease progression or intolerable adverse events. In our study, two-thirds of patients received more than 1 treatment. Prior studies have demonstrated favorable tumor response from use of sequential courses of anti-VEGF TKIs. Consequently, understanding adverse effects of receiving multiple courses is critical in guiding management of toxicities, thereby allowing patients to derive maximal therapeutic benefit. Relative to the first course of anti-VEGF TKIs, second and third courses were associated with increases in DBP of 2 and 5 mm Hg,

respectively, but not with increases in SBP. However, because second and third TKI courses are still associated with increased SBP relative to baseline, patients receiving multiple TKIs still experience hypertensive effects of VEGF inhibition during those courses.

Evaluating the association between different antihypertensive classes and changes in BP may guide management of anti-VEGF TKI–induced hypertension. Our findings indicate that CCBs and potassium-sparing diuretic agents may be effective in lowering BP during treatment with anti-VEGF TKIs. The analysis of potassium-sparing diuretic agents is limited by the small sample size of patients and requires confirmation by larger studies.

Currently no clear guidelines exist for selecting antihypertensive agents in patients with anti-VEGF TKI–induced hypertension, largely because of a paucity of clinical studies evaluating antihypertensive agents in these patients. However, ACE inhibitors, ARBs, and CCBs are frequently used by clinicians in managing antiangiogenic-induced hypertension (32). Previous studies have shown effectiveness of CCBs in managing bevacizumab-induced hypertension (33,34). In a preclinical study in rats comparing nifedipine and captopril in managing hypertension induced by the anti-VEGF TKI cediranib, both antihypertensive agents were effective in lowering a 10 mm Hg increase in BP; however, only nifedipine controlled severe increases in BP of 35 to 50 mm Hg (35). The authors of that study proposed that the renin-angiotensin-system may downregulate in response to large BP increases, potentially making ACE inhibitors less effective in those cases. In contrast, because of an increase in vascular tone by antiangiogenic agents, vasodilatory effects of CCBs may be beneficial in lowering BP in patients with anti-VEGF TKI–induced hypertension. Overall, additional studies are needed to compare CCBs with other antihypertensive classes in patients with anti-VEGF TKI–induced hypertension.

Our study directly quantified the change in BP during treatment with anti-VEGF TKIs. Our findings of differences in hypertensive changes from 5 commonly used TKIs, the decrease in SBP associated with CCBs and potassium-sparing diuretic agents, and the cumulative increase in DBP from using multiple TKI courses should be confirmed in future studies. A strength of our analysis is the use of mixed effects models, thus allowing adjustment for time-varying confounders and analysis of multiple BPs per patient, including more than 1,500 BPs measured during treatment with anti-VEGF TKIs.

STUDY LIMITATIONS. Limitations of this study are related to the retrospective methodology. Data on medications received, including anti-VEGF TKIs, other cancer therapies, and antihypertensive agents, were obtained from medical records. Evaluating adherence to treatments is challenging in a retrospective analysis. We used both pharmacy data and a thorough review of clinic notes to evaluate adherence to antihypertensive agents and cancer therapies.

Another limitation is the potential for error in BP measurements. All BP measurements were made in the same genitourinary oncology clinic using Welch Allyn automated sphygmomanometers with a protocol instructing medical assistants to allow a 15-min resting period before measuring BP. There may have been variability in protocol adherence that we were unable to assess. Although we have 1 BP measurement per clinic visit per patient, we have analyzed multiple BP measurements over multiple clinic visits during the follow-up period for each patient. BP measurements from 1.2% of clinic encounters were not retrievable. This low percentage of missing data is unlikely to have affected our results.

CONCLUSIONS

As patients with mRCC experience longer survival as a result of improvements in treatment, monitoring and managing adverse events such as treatment-related hypertension have become critical in preventing morbidity from cardiovascular events. In our cohort, axitinib was associated with greater increases in SBP than cabozantinib and pazopanib, and with greater increases in DBP than sunitinib, sorafenib, cabozantinib, and pazopanib. Overall, anti-VEGF TKIs were associated with increases in SBP of 8 to 10 mm Hg and in DBP of 6 to 8 mm Hg relative to baseline, with subsequent anti-VEGF TKI courses further increasing DBP but not SBP relative to the first course. CCBs and potassium-sparing diuretic agents were associated with significant decreases in BP during treatment with anti-VEGF TKIs.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: TKIs targeting VEGF receptors are associated with significant, 8 to 10 mm Hg increases in SBP and with 6 to 8 mm Hg increases in DBP relative to baseline. Of the antihypertensive therapies commonly prescribed, CCBs and potassium-sparing diuretic agents are associated with decreases in SBP of 5.6 mm Hg and 9.9 mm Hg, respectively, in patients treated with anti-VEGF TKIs. Receiving multiple courses of anti-VEGF TKIs is associated with cumulative increases in DBP but not SBP.

TRANSLATIONAL OUTLOOK: Further studies should focus on elucidating the different mechanisms of action that result in greater hypertensive effects with certain anti-VEGF TKIs but not others. Moreover, studies are needed to evaluate the mechanisms of CCBs, ACE inhibitors, ARBs, and potassium-sparing diuretic agents in managing anti-VEGF TKI–induced hypertension and corroborate the effectiveness of CCBs and potassium-sparing diuretic agents in BP reduction.

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APPENDIX For supplemental tables, please see the online version of this paper.