Cardiovasc Surg Int 2025;12(1):21-27
http://dx.doi.org/DOI: 10.5606/e-cvsi.2025.1763
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Effects of vascular endothelial growth factor inhibitors on systemic arterial blood pressure: Evaluation by ambulatory blood pressure measurement

Eren Ozan Bakır[1], Ferhat Ekinci[2], Nurullah Cetin[3]

[1]Department of Cardiology, Bakırçay University Çiğli Training and Research Hospital, İzmir, Türkiye
[2]Department of Oncology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye
[3]Department of Cardiology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye

Received: October 08, 2024 ***Accepted:*** December 01, 2024 ***Published online:*** December 27, 2024

ABSTRACT

Objectives: This study aimed to determine the effects of vascular endothelial growth factor (VEGF) inhibitors on arterial blood pressure levels by performing ambulatory blood pressure measurement evaluation before and after the treatment.

Patients and methods: In this prospective study, A total of 33 patients (13 males, 20 females; mean age: 58.3±10.6 years; range, 33 to 82 years) were selected among those who applied to the cardiology clinic for cardiac evaluation before VEGF inhibitor treatment between September 2020 and November 2021. Twenty-four-hour ambulatory blood pressure examinations were performed before the treatment, and after four to six weeks of treatment (30 days for oral medications; after the third cycle for bevacizumab), ambulatory blood pressure examinations were repeated.

Results: With the evaluation of mean, ambulatory blood pressure measurement results, an increase was found in systolic and diastolic measurements during the day, night, and over 24 h. A statistically significant increase was observed in mean systolic, mean diastolic, daytime systolic, and daytime diastolic measurements.

Conclusion: Findings demonstrate that VEGF inhibitors increased the mean arterial blood pressure (all day mean, day time, and night time) and both systolic and diastolic pressures regardless of hypertension history. In this context, patients receiving VEGF inhibitor therapy should be more closely followed in their oncological evaluation.

Keywords: Ambulatory blood pressure measurement, hypertension side effects, VEGF inhibitors.

Hypertension is a common condition in the daily cardiology practice. Therefore, its management, treatment, and preventive measures are relatively well-defined. Although the diagnosis and treatment of hypertension might slightly differ in different sources and guidelines, a consensus can be reached regarding clinical studies and possible complications of hypertension.[1,2] Along with increasing the coordination and awareness between clinical branches, knowledge and experience of noncardiac hypertensive conditions have been increasing. With the progression of oncological science and research, new drugs and treatment protocols are emerging day by day. However, the usage of these drugs also creates possible side effects. Vascular endothelial growth factor (VEGF) inhibitors' clinical use started in 2004 with the USA Food and Drug Administration approval for the usage of bevacizumab in colorectal carcinoma. They are effective molecules that are increasingly used in cancer treatment by preventing the formation of new vessels.[3,4]

Vascular endothelial growth factor is one of the primary regulators of angiogenesis and triggers and promotes endothelial cell growth following its activation. Vascular endothelial growth factor molecules are encoded by a family of genes, including VEGF-A, VEGF-B, VEGF-C, and VEGF-D, as well as placental growth factor. These are mainly required

Corresponding author: Eren Ozan Bakır, MD. Bakırçay Üniversitesi Çiğli Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, 35620 Çiğli, İzmir, Türkiye.
E-mail: eren.ozan.bakir@gmail.com

Citation: Bakır EO, Ekinci F, Cetin N. Effects of vascular endothelial growth factor inhibitors on systemic arterial blood pressure: Evaluation by ambulatory blood pressure measurement. Cardiovasc Surg Int 2025;12(1):21-27. doi: 10.5606/e-cvsi.2025.1763.

for blood and lymphatic vessel formation.[4] Vascular endothelial growth factor inhibitors were developed to decrease tumor angiogenesis and destabilize existing tumor vascularization by blocking tumor blood flow.[5] Vascular endothelial growth factor causes increased nitric oxide (NO) production by stimulating endothelial NO synthase through the activation of VEGF receptor 2. Therefore, inhibition of the VEGF pathway and decreased NO bioavailability are believed to cause vasoconstriction and the development of hypertension.[6,7]

The clinical appearance of hypertension is relatively well-known. Some signs and symptoms can verify hypertension development besides the arterial blood pressure measurements. For instance, side effects such as headache, fatigue, developing retinopathy, or vascular complications, as well as some unusual metabolical parameters regarding newly developing hypertension, such as asymmetric dimethylarginine levels.[8] Furthermore, sometimes an infective state like the COVID-19 (coronavirus disease 2019) pandemic can cause hypertension-related symptoms.[9] These might be explained by psychological or diet-related factors or the infection itself. Nevertheless, none of the above could make the hypertension side effect diagnosis without obvious evidence. Therefore, with a molecule that relates to the hypertension side effect, these signs and measurements of the arterial blood pressure should be assessed regularly.

This study aimed to determine the effects of VEGF inhibitors on arterial blood pressure levels by performing ambulatory blood pressure measurement evaluation before and after the treatment.

PATIENTS AND METHODS

In this prospective study, the patients included in the study group were selected from patients who were referred to the cardiology outpatient clinic at the Manisa Celal Bayar University Faculty of Medicine between September 2020 and November 2021 after an assessment by the oncology outpatient clinic and were decided to commence a VEGF inhibitor treatment. A total of 57 patients who were diagnosed with colorectal, ovarian, renal cell, breast, gastrointestinal stromal tumor, and rectum carcinoma were included in our study. However, within the first assessments, a total of 24 patients were excluded. Among these patients, those who already had a hypertension diagnosis, those taking antihypertensive drugs, and those who were diagnosed with systolic or diastolic heart failure were excluded. Subsequently, some patients were excluded due to a hypertensive state at the first ambulatory measurement during the follow-up. Among these patients, there were no additional symptoms, except for headaches some patients had described. All the patients who had hypertension were treated with oral antihypertensive drugs according to the guidelines, and subsequently, all the arterial blood pressure measurements were controlled within normal ranges. Finally, 33 patients (13 males, 20 females; mean age: 58.3±10.6 years; range, 33 to 82 years) were included in the study. The baseline characteristics and demographic characteristics of the patients are summarized in Table 1. Twenty-four-hour ambulatory blood pressure measurements were performed before the treatment, and the results were evaluated. Blood tests were requested during the patient's routine outpatient examinations. After approximately four to six weeks of treatment (30 days for oral medications; after the third cycle for bevacizumab treatment), 24-h ambulatory blood pressure measurements were repeated, and the results before and after the treatments were compared. Twent-four-hour ambulatory blood pressure measurements were performed with hourly measurements during the day and night (12 daytime and 12 nighttime measurements). Valid measurements from 22 to 24 hours were accepted for evaluation. The study protocol was approved by the Manisa Celal Bayar University Ethics Committee (date: 31.12.2020, no: E-85252386-050.04.04-10360). Written informed

Table 1
Baseline characteristics of patients (n=33)

	n	%	Mean±SD
Age (year)			58.3±10.6
Sex			
Female	20	60.6	
Body mass index (kg/m^2)			27.59±3.63
Comorbidities			
Diabetes mellitus	10	10.3	
Coronary artery disease	5	15.2	
Chronic kidney disease	1	3	
Smoking	3	9.1	
Medications			
Bevacizumab	28	84.84	
Sunitinib	4	12.12	
Sorafenib	1	3	

SD: Standard deviation.

consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA), and figures were constructed using GraphPad Prism version 8 (GraphPad Software, La Jolla, CA, USA). The Shapiro-Wilk test was used to assess whether the continuous variables were distributed normally. Categorical variables were summarized with the use of frequencies and proportions and were compared with the use of Pearson's chi-square test or Fisher exact test in cases where applicability conditions were not met. Continuous variables were summarized as mean ± standard deviation (SD) and were compared using paired or unpaired Student's t-tests or nonparametric Wilcoxon rank-sum tests if the normal distribution of the variables could not be demonstrated. A p-value <0.05 was considered statistically significant.

RESULTS

Basal blood values of the patients were examined before and after the treatment. The mean hemoglobin values were 12.5±1.6 before the treatment and 12.7±1.5 after the treatment (p=0.132). The mean creatinine values were 0.72±0.2 before the treatment and 0.71±0.2 after the treatment (p=0.718). Similarly, glucose and other electrolytes of the patients, along with other hemogram parameters were examined, and no statistically significant change was found before and after the treatment. Blood values changes are summarized in Table 2.

The patients included in the study were receiving bevacizumab, sunitinib, and sorafenib treatment. The number of patients who received treatment was 28 patients with bevacizumab, four patients with sunitinib, and one patient with sorafenib. When the ambulatory blood pressure measurements were evaluated, after the VEGF inhibitor treatment, it was observed that a total of 12 patients had blood pressure measurements above the hypertension limit values. Of these, 10 were receiving bevacizumab, and two were receiving sunitinib. When the patient's mean ambulatory blood pressure measurement results were evaluated, an increase was found in all the systolic and diastolic measurements during the day, night, and over 24 h. The mean systolic (118.3±10.9 - 123.8±14.5, p=0.017), mean diastolic (69.8±8.2 - 73.4±10.0, p=0.018), daytime systolic (120.5±10.9 - 126.3±14.1, p=0.011), and daytime diastolic (72.1±8.1 - 75.8±10.1, p=0.023) measurements showed a statistically significant increase (Table 3).

When the blood pressure values were examined before and after VEGF inhibitor treatment, there was a statistically significant increase in the mean systolic (117.8±11.6 - 123.6±17.2, p=0.044), mean diastolic (69.7±7.9 -73.6±11.0, p=0.049), and daytime mean

Table 2
Laboratory parameters of the study population

	Pretreatment		Posttreatment		
	n	%	n	%	*p*
Glucose (mg/dL)	103	36	102	33	0.922
Creatinine (mg/dL)	0.67	0.27	0.69	0.34	0.879
Sodium (mEq/L)	138	1.5	139	2.7	0.119
Potassium (mEq/L)	4.2	0.3	4.2	0.6	0.139
AST (u/L)	21	9.5	22	13	0.875
ALT (u/L)	16	19	16	17	0.868
Hemoglobin (g/dL)	13	2	13.3	1.9	0.203
CRP (mg/dL)	0.56	0.77	0.63	0.78	0.903

AST: Aspartate transaminase; ALT: Alanine aminotransferase; CRP: C-reactive protein. Changes of parameters from pre-treatment to post-treatment were analyzed using paired samples Wilcoxon signed-rank test.

Table 3
Comparison of ambulatory blood pressure parameters before and after treatment with VEGF inhibitors

	Pretreatment	Posttreatment	Delta		
	Mean±SD	Mean±SD	Mean±SD	*p*	Cohen's d
24-h-systolic ABP (mmHg)	118.33±10.92	123.81±14.54	5.48±11.58	**0.017**	0.439
24-h-diastolic ABP (mmHg)	69.85±8.26	73.43±10.04	3.58±7.18	**0.018**	0.434
Daytime systolic ABP (mmHg)	120.52±10.96	126.36±14.17	5.84±12.0	**0.011**	0.469
Daytime diastolic ABP (mmHg)	72.17±8.19	75.87±10.11	3.70±8.38	**0.023**	0.417
Nighttime systolic ABP (mmHg)	113.43±11.94	117.66±16.59	4.60±14.19	0.081	0.325
Nighttime diastolic ABP (mmHg)	64.74±8.47	67.15±10.32	2.67±8.71	0.098	0.307

SD: Standard deviation; ABP: 24h-ambulatory blood pressure; Changes of parameters from pretreatment to posttreatment were analyzed using paired samples Student's t-test. Delta: value at posttreatment subtracted from the value at pretreatment. P<0.05 was regarded significant (bold type). Cohen´s d is reported for the effect size.

systolic (119.6±11.4 - 125.6±16.7, p=0.049) values in females and the mean diastolic (70.0±9.0 - 73.1±8.7, p=0.017) values in males. All day, daytime, and nighttime blood pressure changes are shown in Figure 1.

DISCUSSION

The findings of this study showed a progression in ambulatory blood pressure measurements. Compared to the pretreatment measurements, there was a statistically significant increase in the mean systolic, mean diastolic, daytime systolic, and daytime diastolic blood pressure measurements throughout the day after the treatment. In addition, when the distribution of these data was examined according to sex, we found a statistically significant increase in mean all day systolic and diastolic and daytime systolic measurements in females, as well as in daytime diastolic measurements in males. Some previous studies mentioned sex differences in ambulatory blood pressure measurement differences. One study found that diastolic pressures were higher in males than females.[10] Another ambulatory blood pressure study revealed that males had higher mean ambulatory diastolic and mean arterial blood pressures than females.[11] However, there were no studies that specifically mentioned sex differences in patients using VEGF inhibitors and its hypertension side effects. This topic needs further evaluation.

The incidence of hypertension after VEGF inhibitor treatment was observed in a total of 10 patients, with the ambulatory blood pressure limit values taken as the basis (mean 130/80 mmHg for mean measurement, 135/85 mmHg for mean daytime, and 120/70 mmHg for mean night time). Ten of 28 patients taking bevacizumab and two of four taking sunitinib were hypertensive. However, because the number of patients who received sorafenib and sunitinib treatment in the study was very small, it is not possible to draw conclusion about such a proportional relationship. For bevacizumab, this rate was found to be 35%, and this rate is similar to previous studies in the literature.[12] However, the design of our study and the difference from most previous studies was not to just determine the number of patients who crossed the absolute hypertension limit as the endpoint. Moreover, the ambulatory measurements of patients who did not exceed the hypertensive limit were compared before and after treatment. Additionally, the mean arterial blood pressure measurements of the whole patient group, with the normotensive patients included, showed statistically significant progression.

Hypertension is one of the common side effects that encountered with the usage of VEGF inhibitors.[13] It was determined that the hypertension side effect was observed from the first week at the beginning of the treatment.[14] In a different study with 313 patients comparing IFL (irinotecan, fluorouracil, and leucovorin) treatment and IFL + bevacizumab treatment, the hypertension side effect was observed approximately 2.75 times more in patients with bevacizumab treatment added.[15] In another study with VEGF inhibitors, the patients were evaluated with ambulatory

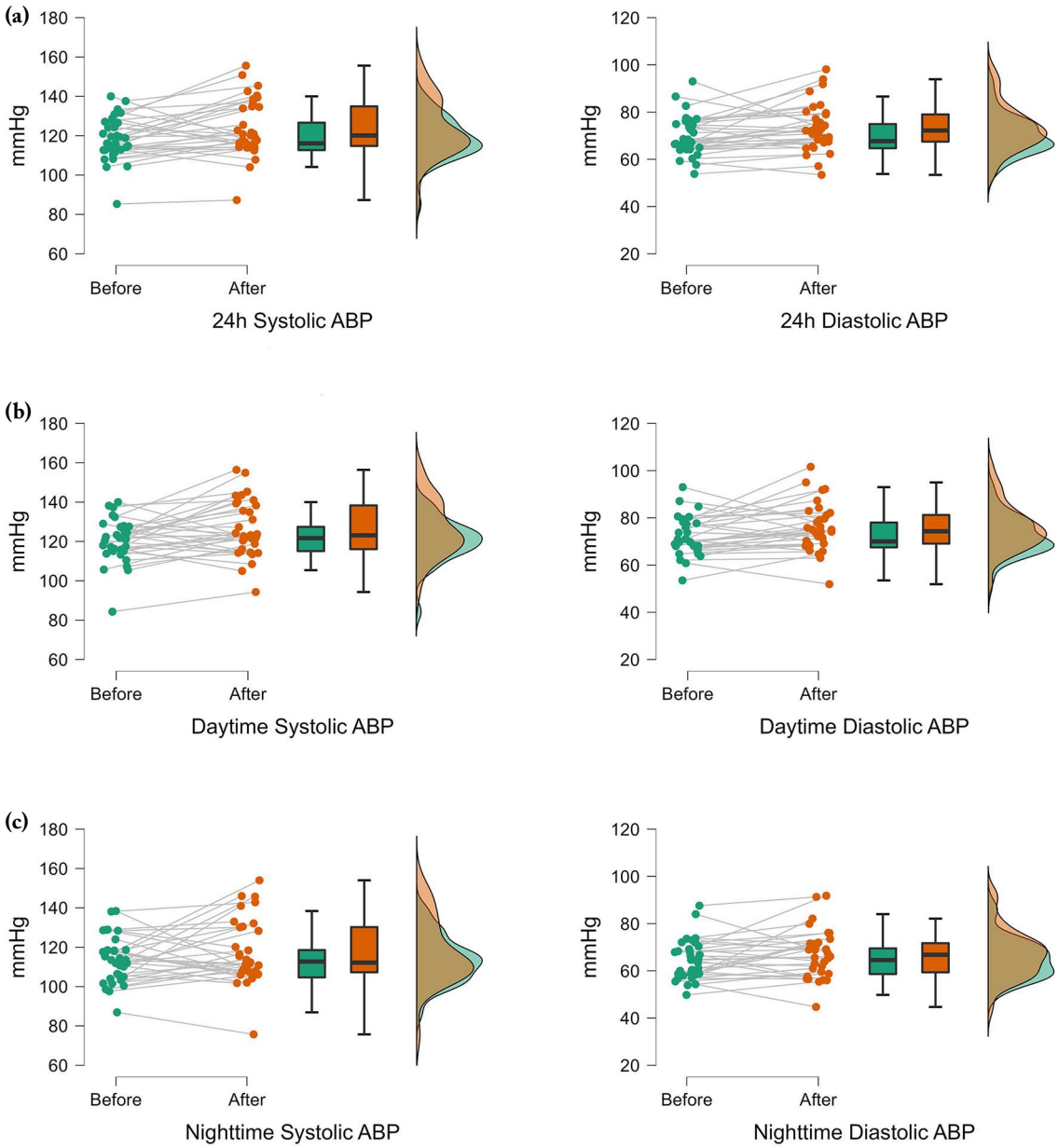

Figure 1. All day, daytime, and nighttime blood pressure measurement changes.

blood pressure measurements and were found to be hypertensive within six to 10 days after the treatment. Furthermore, it was found that this hypertensive effect started in the first 24-h of the treatment.[16] However, within the results of other trials, regardless of the specific molecules, with VEGF inhibitor-related hypertension, the rise of arterial blood pressure was observed by four weeks, and it could be reversible.[6,17]

Ambulatory mean arterial blood pressure changes with sunitinib were previously demonstrated before and after treatment, and an increase of 10.8 mmHg in mean systolic blood pressure and 8 mmHg in mean diastolic blood pressure was observed in that study.[12] In a study, in which bevacizumab treatment was given intraocularly and ambulatory blood pressures were measured before the treatment after 72 h, it was observed that

the arterial blood pressure values progressed.[18] However, when the literature was reviewed, it was observed that similar ambulatory blood pressure measurement evaluations before and after treatment with systemic bevacizumab treatment were not performed as much. In this sense, we believe that our study is important, although more voluminous clinical studies are needed in the future in terms of the number of patients.

It was observed that VEGF inhibitors increased the mean arterial blood pressure (all day mean, daytime, and nighttime measurements) and both systolic and diastolic blood pressure, regardless of hypertension history. When the results obtained by ambulatory blood pressure measurement are evaluated, it should be noticed that even if the blood pressure was below the limit values determined by the guidelines for the diagnosis of hypertension, the progression could have occurred after the treatment. Although it is thought that ambulatory blood pressure measurement brings more burden in terms of time and finance, it could be more cost-effective. For instance, in the case of white coat hypertension, it ensures that patients are correctly diagnosed (not misdiagnosed as hypertension) and that antihypertensive medication that would not normally be required is not prescribed. In addition, it is stated that adjusting antihypertensive treatment according to ambulatory blood pressure measurement rather than office blood pressure results in less antihypertensive drug prescribing without affecting the target organ involvement rate, and thus may be more cost-effective.[19]

This study had several limitations, including its small sample size. The most important factor is that it is a single-center study and the oncology clinic has limited patient capacity. These results need to be verified by further studies with a larger number of patients.

In conclusion, it should be kept in mind that, as in patients in our study group, in cases where the incidence of hypertension side effects significantly increases with treatment, ambulatory blood pressure measurement should be considered in the foreground. Moreover, although office blood pressure measurements may be normal in the pretreatment evaluations, there may be a progression in the arterial blood pressure values during the follow-up of patients during their treatment. Patients should be informed about this issue and encouraged to adapt to their follow-up and lifestyle changes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, writing the article: E.O.B., F.E., N.C.; Control/supervision: N.C.; Data collection and/or processing, literature review, materials: E.O.B., F.E.; Analysis and/or interpretation, critical review: E.O.B., N.C.; References and fundings: E.O.B.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. McEvoy JW, McCarthy CP, Bruno RM, Brouwers S, Canavan MD, Ceconi C, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. Eur Heart J 2024;45:3912-4018. doi: 10.1093/eurheartj/ehae178.
2. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;71:e127-248. doi: 10.1016/j.jacc.2017.11.006.
3. Tocchetti CG, Gallucci G, Coppola C, Piscopo G, Cipresso C, Maurea C, et al. The emerging issue of cardiac dysfunction induced by antineoplastic angiogenesis inhibitors. Eur J Heart Fail 2013;15:482-489. doi: 10.1093/eurjhf/hft008.
4. Homsi J, Daud AI. Spectrum of activity and mechanism of action of VEGF/PDGF inhibitors. Cancer Control 2007;14:285-94. doi: 10.1177/107327480701400312.
5. Duda DG, Batchelor TT, Willett CG, Jain RK. VEGF-targeted cancer therapy strategies: Current progress, hurdles and future prospects. Trends Mol Med 2007;13:223-30. doi: 10.1016/j.molmed.2007.04.001.
6. Pandey AK, Singhi EK, Arroyo JP, Ikizler TA, Gould ER, Brown J, et al. Mechanisms of VEGF (Vascular Endothelial Growth Factor) inhibitor-associated hypertension and vascular disease. Hypertension 2018;71:e1-8. doi: 10.1161/HYPERTENSIONAHA.117.10271.
7. Kappers MH, de Beer VJ, Zhou Z, Danser AH, Sleijfer S, Duncker DJ, et al. Sunitinib-induced systemic vasoconstriction in swine is endothelin mediated and does not involve nitric oxide or oxidative stress. Hypertension 2012;59:151-7. doi: 10.1161/HYPERTENSIONAHA.111.182220.

8. Altuntaş E, Bengü AŞ, Kiraz ZK, Mertoğlu C, Dalar L, Usalp S, et al. Association between newly diagnosed essential hypertension, smoking, assymetric dimethylarginine and ischemia-modified albumin. İstanbul Med J 2017;18:86-90. doi:10.5152/imj.2017.76258.
9. Senoz O, Yapan Emren Z, Erseckin A, Yurdam FS, Gurses E, Demir Y. Effect of COVID-19 pandemic and coronavac vaccine on blood pressure regulation in chronic hypertensive patients- Ege Klinikleri Tıp Dergisi 2021;59:327-333.
10. Kontogiorgos I, Georgianos PI, Vaios V, Vareta G, Apostolos Karligkiotis EF, Sgouropoulou V, et al. Gender-related differences in the levels of ambulatory BP and intensity of antihypertensive treatment in patients undergoing peritoneal dialysis. Life 2023;13:1140. doi: 10.3390/life13051140.
11. Khoury S, Y'avows SA, O'Brien TK, Sowers JR. Ambulatory blood pressure monitoring in a nonacademic setting effects of age and sex. AJH 1992;5:616-623.
12. Escalante CP, Zalpour A. Vascular endothelial growth factor inhibitor-induced hypertension: Basics for primary care providers. Cardiol Res Pract 2011;2011:816897. doi: 10.4061/2011/816897.
13. Bair SM, Choueiri TK, Moslehi J. Cardiovascular complications associated with novel angiogenesis inhibitors: Emerging evidence and evolving perspectives. Trends Cardiovasc Med 2013;23:104-13. doi: 10.1016/j.tcm.2012.09.008.
14. Touyz RM, Herrmann SMS, Herrmann J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. J Am Soc Hypertens 2018;12:409-25. doi: 10.1016/j.jash.2018.03.008.
15. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42. doi: 10.1056/NEJMoa032691.
16. Maitland ML, Kasza KE, Karrison T, Moshier K, Sit L, Black HR, et al. Ambulatory monitoring detects sorafenib-induced blood pressure elevations on the first day of treatment. Clin Cancer Res 2009;15:6250-7. doi: 10.1158/1078-0432.CCR-09-0058.
17. Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving sunitinib. N Engl J Med 2008;358:95-7. doi: 10.1056/NEJMc072330.
18. Ziemssen F, Zhu Q, Peters S, Grisanti S, El Wardani M, Szurman P, et al. Tuebingen Bevacizumab Study Group; Ziemssen T. Intensified monitoring of circadian blood pressure and heart rate before and after intravitreous injection of bevacizumab: preliminary findings of a pilot study. Int Ophthalmol 2009;29:213-24. doi: 10.1007/s10792-008-9221-7.
19. O'Brien E, Parati G, Stergiou G. Ambulatory blood pressure measurement: what is the international consensus? Hypertension 2013;62:988-94. doi: 10.1161/HYPERTENSIONAHA.113.02148.