بسم الله الرحمن الرحيم

ONCO-HYPERTENSION

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AHA SCIENTIFIC STATEMENT

Cancer Therapy–Related Hypertension: A Scientific Statement From the American Heart Association

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Hypertension is available at www.ahajournals.org/journal/hyp

Hypertension. 2023;80:e46–e57. DOI: 10.1161/HYP.0000000000000224

STATE-OF-THE-ART REVIEW

Hypertension in Cancer Patients and Survivors

Epidemiology, Diagnosis, and Management

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JACC: CARDIOONCOLOGY JOURNAL CME/MOC/ECME

REVIEW

New Concept of Onco-Hypertension and Future Perspectives

Satoshi Kidoguchi, Naoki Sugano, Gorou Tokudome, Takashi Yokoo, Yuichiro Yano, Kiyohiko Hatake, Akira Nishiyama

ABSTRACT: Owing to aging populations, the prevalence of hypertension and associated cardiovascular events has been increasing worldwide. The morbidity and mortality due to cancer have also been increasing with aging populations. Several

- *Hypertension.* 2021;77:16–27. DOI: 10.1161/HYPERTENSIONAHA.120.16044

Review Article

Hypertension in Patients with Cancer

Vinicius Barbosa de Souza, Eduardo Nani Silva, Mario Luiz Ribeiro, Wolney de Andrade Martins
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- Arq Bras Cardiol. 2015; 104(3):246-252

Cancer and the Heart

Hypertension in Cancer Patients

Epidemiology

- Hypertension is increasing… 1.3 billion in adults in 2019.
- Inadequately controlled in almost 50% of those known to have hypertension.
- New cancer cases worldwide will increase from 19.3 million in 2020 to >28 million in 2040.
- Similar prevalence of hypertension in patients with solid and neuroendocrine tumors before sorafenib therapy compared with the general population. One exception is Wilms tumor.
- New-onset hypertension in a population of 25,090 adults with solid malignancies… one-third
- RCC: moderate hypertension gastric and ovarian cancers: severe HTN
- median time : 96 days from the time of their initial diagnosis with cancer.

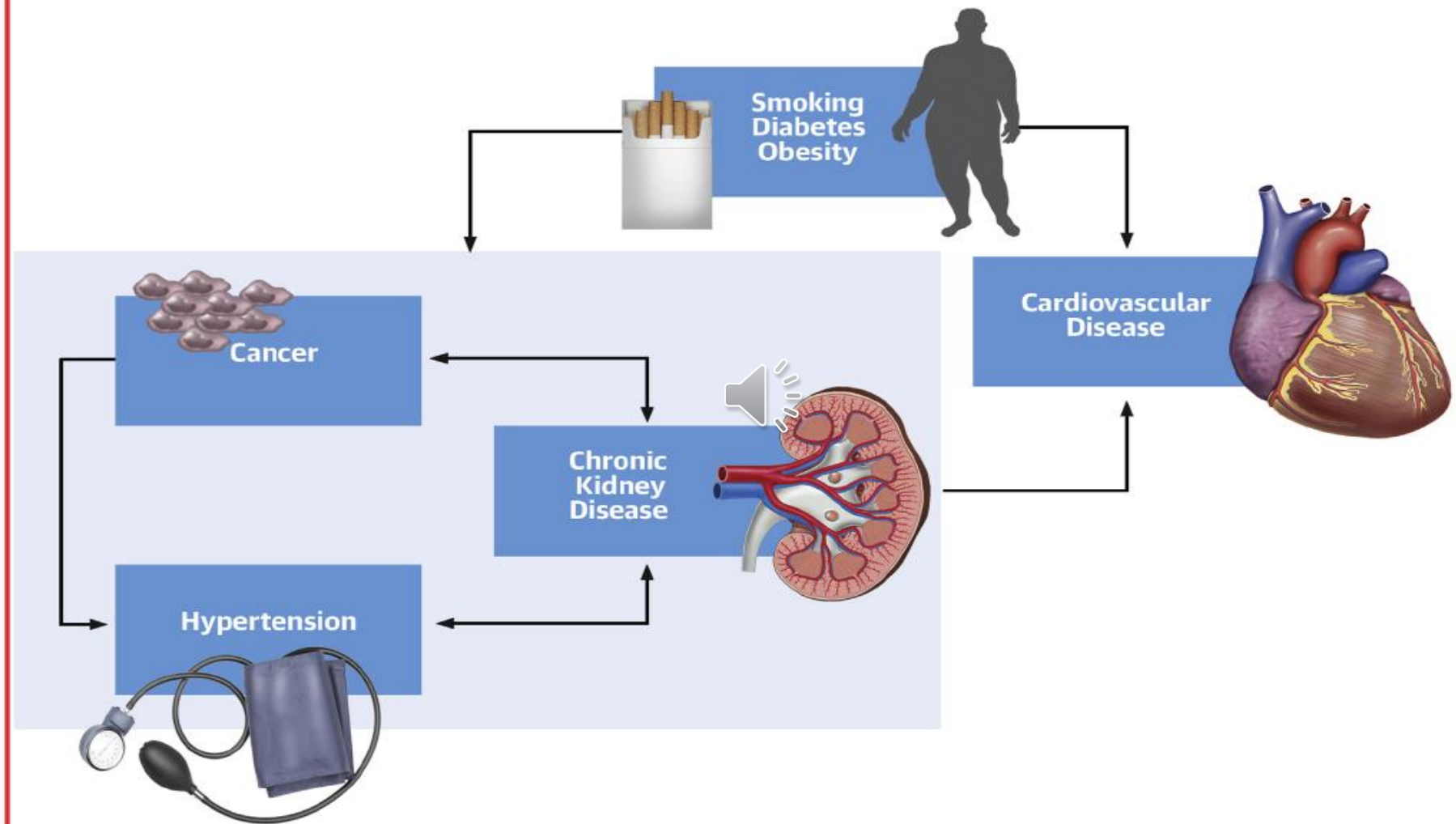
HTN….CANCER

- prevalence of hypertension is higher in patients with cancer and cancer survivors.
- Hypertension is associated with an increased risk of cancer….most clearly renal cell carcinoma.
- HTN is the most common comorbidity (38% prevalence).
- common risk factors and pathophysiological mechanisms, including smoking, diabetes, chronic kidney disease, physical inactivity, obesity, oxidative stress, and inflammation.
- Chemotherapy: independent risk factor for hypertension.
- Hypertension has been reported in over one-half of patients treated with anti-VEGF therapy.

Definition of Hypertension

ACC/ AHA 2017[6]	Normal SBP <120 mm Hg DBP <80 mm Hg	Elevated SBP 120–129 mm Hg DBP <80 mm Hg	Stage 1 SBP 130–139 mm Hg DBP 80–90 mm Hg Drug therapy indicated if ASCVD risk >10%	Stage 2 SBP >140 mm Hg DBP >90 mm Hg Drug therapy goal BP <130/80 mm Hg	Hypertensive crisis SBP >180 mm Hg DBP >120 mm Hg Urgent BP drug therapy initiation

CENTRAL ILLUSTRATION Multidimensional Relationship Between Cancer, Hypertension, and Cardiovascular Disease



Cohen, J.B. et al. J Am Coll Cardiol CardioOnc. 2019;1(2):238-51.

Hypertension induced by anticancer drugs

Reversible after interruption of treatment.

Rebound hypotension after termination of cancer therapy.

National hypertension guidelines.

Mechanisms: reduced nitric oxide generation, oxidative stress, endothelin-1, prostaglandins, endothelial dysfunction, increased sympathetic outflow, and microvascular rarefaction

Table 2. Incidence of Hypertension Induced by Different Classes of Anticancer Drugs

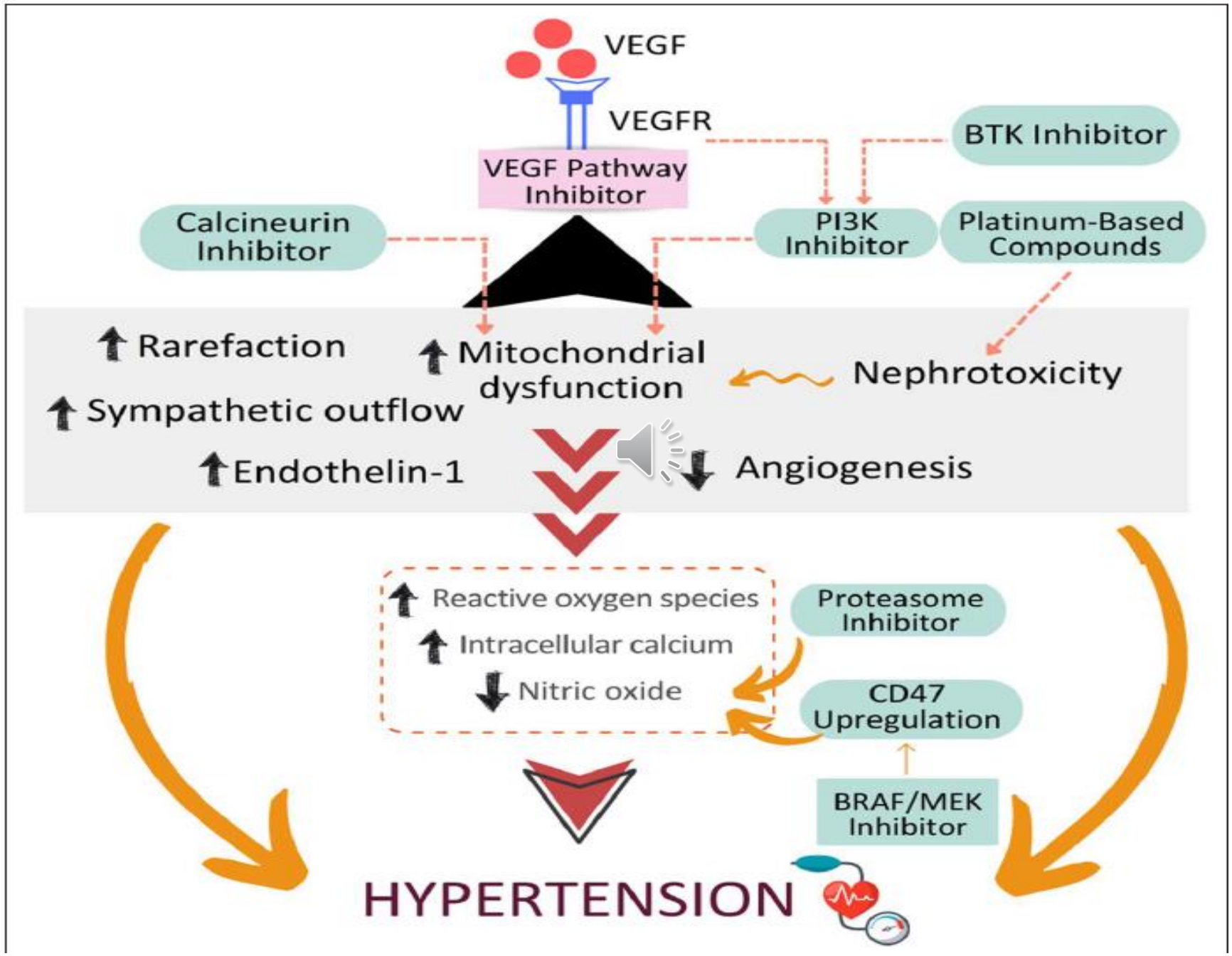
Drug class	Select example drugs	Select malignancies treated	Incidence of hypertension
VSPIs	Bevacizumab, Sorafenib, Sunitinib, Nilotinib, Pazopanib, Dasatinib, Regorafenib, Cabozantinib, Lenvatinib, Ponatinib, Axitinib, Tivozanib, Vandetanib, Ramucirumab	Renal, hepatocellular, thyroid, gastrointestinal stromal cancer	20%–90%[12]
Bruton TKIs	Ibrutinib Acalabrutinib	Chronic lymphocytic leukemia, mantle cell lymphoma	71%[16]
Proteasome inhibitors	Carfilzomib Bortezomib	Multiple myeloma	32%[17] 10%[17]
Platinum-based compounds	Cisplatin Carboplatin Oxaliplatin	Mesothelioma, testicular, bladder, gynecological, colorectal, and lung cancers	53%[18]
Alkylating agents	Cyclophosphamide Busulfan Ifosfamide	Hematologic and solid organ malignancies	36% in adults[14] 58% in children[14] 15% in children[19]

Incidence of Hypertension Induced by Different Classes of Anticancer Drugs

Calcineurin inhibitors	Tacrolimus Cyclosporin	After stem cell transplantation	30%–60%[20]
BRAF/MEK inhibitors	Vemurafenib, Dabrafenib, Encorafenib, Trametinib, Binimetinib, Cobimetinib	Melanoma, colorectal cancer	19.5%*[21]
RET kinase inhibitors	Selpercatinib Pralsetinib	Thyroid, non–small cell lung cancer	43%[22] 21%[22]
Poly(ADP-ribose) polymerase inhibitors	Niraparib	Breast, ovarian cancer	19%[23]
Androgen receptor blockers	Enzalutamide	Metastatic prostate cancer	11 (5%)[24]
Androgen synthesis inhibitors	Abiraterone Leuprolide	Metastatic prostate cancer Prostate cancer	26 (7%)[24] 15%[12]
Aromatase inhibitors	Anastrozole	Breast cancer	13%[25]
	Letrozole	Breast cancer	8%[25]
	Exemestane	Breast cancer	10%[25]
mTOR inhibitors	Everolimus Sirolimus	Renal cell, breast, PNET cancer	13% (PNET)[12]

TABLE 1 Cancer Treatments Associated With the Development and Exacerbation of Hypertension

	Mechanism(s) of Blood Pressure Elevation
Chemotherapeutic agents	
Anti-VEGF therapy and tyrosine kinase inhibitors	Increased vascular resistance Reduced nitric oxide production (14) Reduced angiogenesis (15) Impaired natriuresis (16) Endothelin-1–mediated vasoconstriction (17) Thrombotic microangiopathy (18)
Alkylating and alkyl-like agents	
Cyclophosphamide	Vascular endothelial injury (24)
Ifosfamide	Nephrotoxicity (31,32)
Cisplatin	Nephrotoxicity (33) and vascular endothelial injury (34)
Vinblastine	Vascular endothelial injury (in vitro) (35)
Gemcitabine	Thrombotic microangiopathy (37) Vascular endothelial injury (in vitro) (38)
Radiation	
Abdominal radiation	Renal artery stenosis (41)
Head and neck radiation	Baroreflex failure (42,43)
Adjuvant therapies	
Erythropoietin stimulating agents	Increased erythrocyte mass Altered response to endogenous vasodilators and vasopressors (44)
Nonsteroidal anti-inflammatory drugs	Impaired natriuresis due to reduction in prostaglandin synthesis (45)
Corticosteroids	Sodium retention due to mineralocorticoid receptor stimulation (46)
Calcineurin inhibitors	Systemic and renal vasoconstriction (47)


VEGF
VEGFR
VEGF Pathway Inhibitor
BTK Inhibitor
PI3K Inhibitor
Calcineurin Inhibitor
Platinum-Based Compounds
Rarefaction
Mitochondrial dysfunction
Nephrotoxicity
Sympathetic outflow
Endothelin-1
Angiogenesis
Reactive oxygen species
Intracellular calcium
Nitric oxide
Proteasome Inhibitor
CD47 Upregulation
BRAF/MEK Inhibitor
HYPERTENSION

Vascular endothelial growth factor (VEGF) signaling pathway inhibitors (VSPIs)

- inhibition of VEGF-mediated tumor angiogenesis.
- directly or by inhibition of tyrosine kinase receptors.
- VSPI-induced hypertension has been suggested as a predictor or biomarker of therapeutic efficacy.

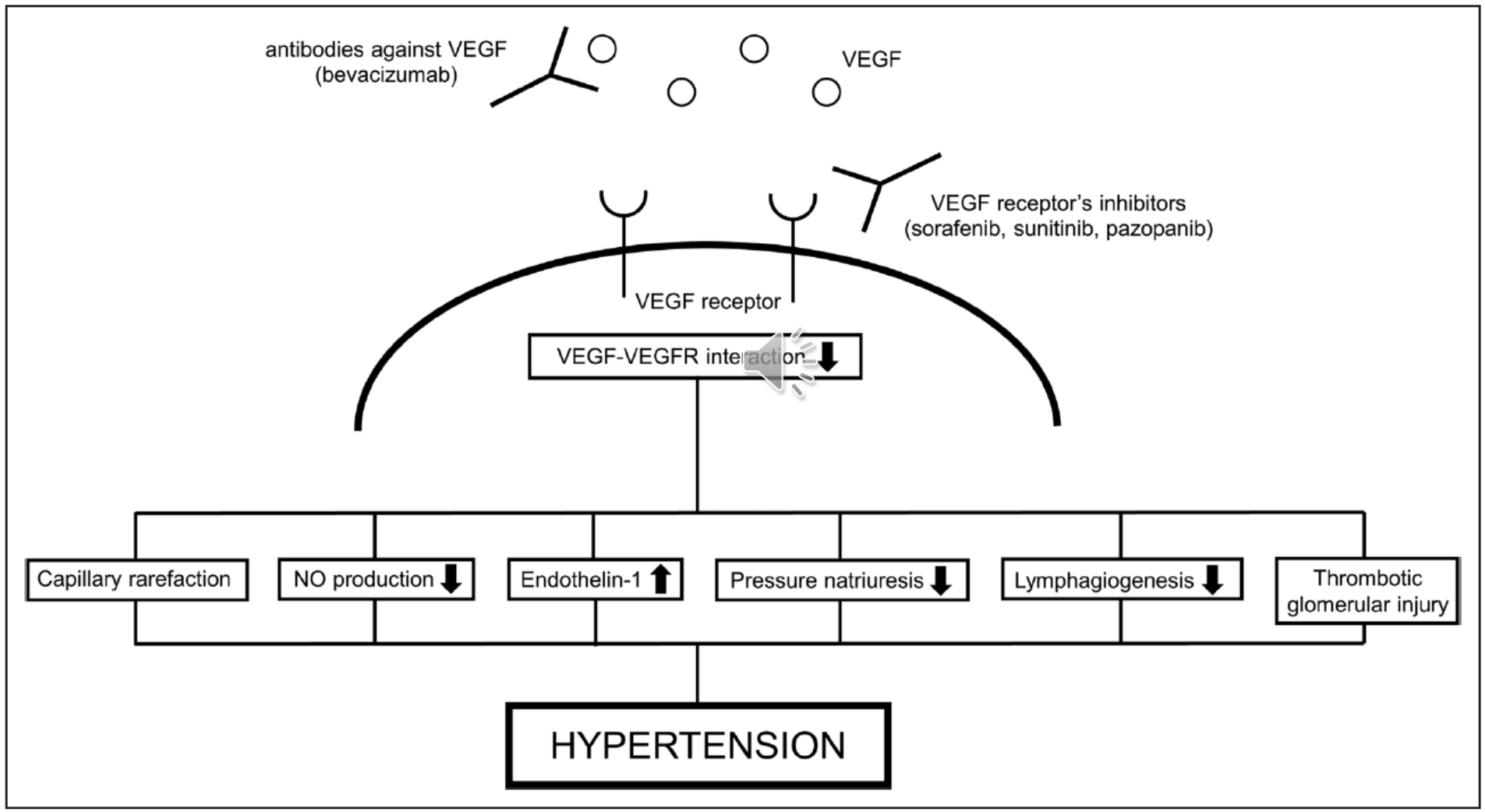
reduced bioavailability of NO

increased the potent vasoconstrictor endothelin-1,

increased reactive oxygen species,

vascular oxidative stress.

Rarefaction (reduced microvascular density)


antibodies against VEGF
(bevacizumab)
VEGF
VEGF receptor's inhibitors
(sorafenib, sunitinib, pazopanib)
VEGF receptor
VEGF-VEGFR interaction
Capillary rarefaction
NO production
Endothelin-1
Pressure natriuresis
Lymphagiogenesis
Thrombotic glomerular injury
HYPERTENSION

Chemotherapy….HTN

- **Rapidly Accelerated Fibrosarcoma B-Type (BRAF)/ and Mitogen-Activated Kinase Kinase (MEK) Inhibitors:**
- treatment of melanoma and colorectal Cancer (frequently prescribed in combination).
- BRAF gene mutation with subsequent dysregulation of the Raf-MEK–extracellular signal
- reduced NO bioavailability.
- **Proteasome inhibitors** (bortezomib, **carfilzomib,** ixazomib) For multiple myeloma.
- mediate oxidative stress by increasing reactive oxygen species production and suppressing antioxidant pathways. endothelial dysfunction and reduced NO bioavailability.
- **Platinum-Based Compounds** (cisplatin, carboplatin, oxaliplatin):uptake to DNA with consequent apoptotic cell death. late effect, in the circulation, chronic endothelial injury and dysfunction. Cisplatin nephrotoxicity is dose dependent and has been attributed to cellular mitochondrial damage, oxidative stress, apoptosis, and decreased NO bioavailability.

Chemotherapy….HTN

- Endocrine Therapy (Antiandrogens/Aromatase Inhibitors):
- Abiraterone: inhibits testosterone production through inhibition of the cytochrome P450 enzyme with consequent accumulation of mineralocorticoid precursors.
- mechanisms underlying enzalutamide-induced hypertension are unclear

Chemotherapy….HTN

- **Erythropoietin :**35% show increased peripheral vascular resistance and a mild decrease in cardiac output.
- . in patients with hemoglobin < 10 g/dl. 2 to 16 weeks after use...HTN

(1)increase in erythrocyte mass with increase in blood viscosity.

(2) change in production and sensitivity of endogenous vasopressor agents.

(3) change in the vascular smooth-muscle response to vasodilating factors.

(4) direct vasopressor effect of rhuEPO.

(5) remodeling through stimulation of vascular cell growth.

- calcium antagonists and alpha-adrenergic receptor blockers present good results.
- **Carotid baroreceptor injury by cervical radiation therapy** :increased sympathetic activity and reduction of parasympathetic activity.

CANCER….HTN

- hypertension is associated with a higher risk of RCC, colon cancer, esophageal (SCC), head and neck cancers, skin SCC, postmenopausal breast cancer, and uterine adenocarcinoma.
- Systolic blood pressure in the range of 130 to 139 mm Hg was associated with an increased risk for RCC.
- Mechanisms:

1- renal hypoxia induced by hypertension upregulated the transcription of HIFs (hypoxia-inducible factors) increased expression of HIF-responsive tumorigenesis genes, including VEGF and PDGF

2- overexpression of angiotensin receptors.

3- downregulation of ACE (angiotensin-converting enzyme).

CANCER….HTN

- **Antihypertensive Drugs and Cancer Risk**: thiazide ….skin cancer.

Thiazide is a photosensitizer that damages DNA and causes chronic subclinical skin inflammation.

A systematic review of 27 observational studies: diuretic … increase risk of kidney cancer.

- **Hypertension as a Consequence of Cancer:** in human RCC cell line… vasoactive peptides, including urotensin II, adrenomedullin, endothelin……HTN
- Hepatocellular carcinoma (Circulating angiotensin), paraneoplastic syndrome (HCC,RCC). Carcinoid tumors, and desmoplastic small round cell tumors.
- Certain types of cancers themselves can cause hypertension.

MANAGEMENT OF ANTICANCER THERAPY–INDUCED HYPERTENSION

- At least weekly BP monitoring is suggested for the first 4 to 8 weeks for patients on cancer drugs that increase BP .
- atherosclerotic CVD 10-year risk ≥10% or comorbidities such as chronic kidney disease and diabetes, treatment should be initiated in stage 1 hypertension.
- For others, treatment should be initiated in stage 2.
- The goal BP is <130/80 mm Hg for all individuals.
- withholding anticancer therapy is systolic BP ≥180 mm Hg or diastolic BP ≥110 mm Hg.

MANAGEMENT OF ANTICANCER THERAPY–INDUCED HYPERTENSION

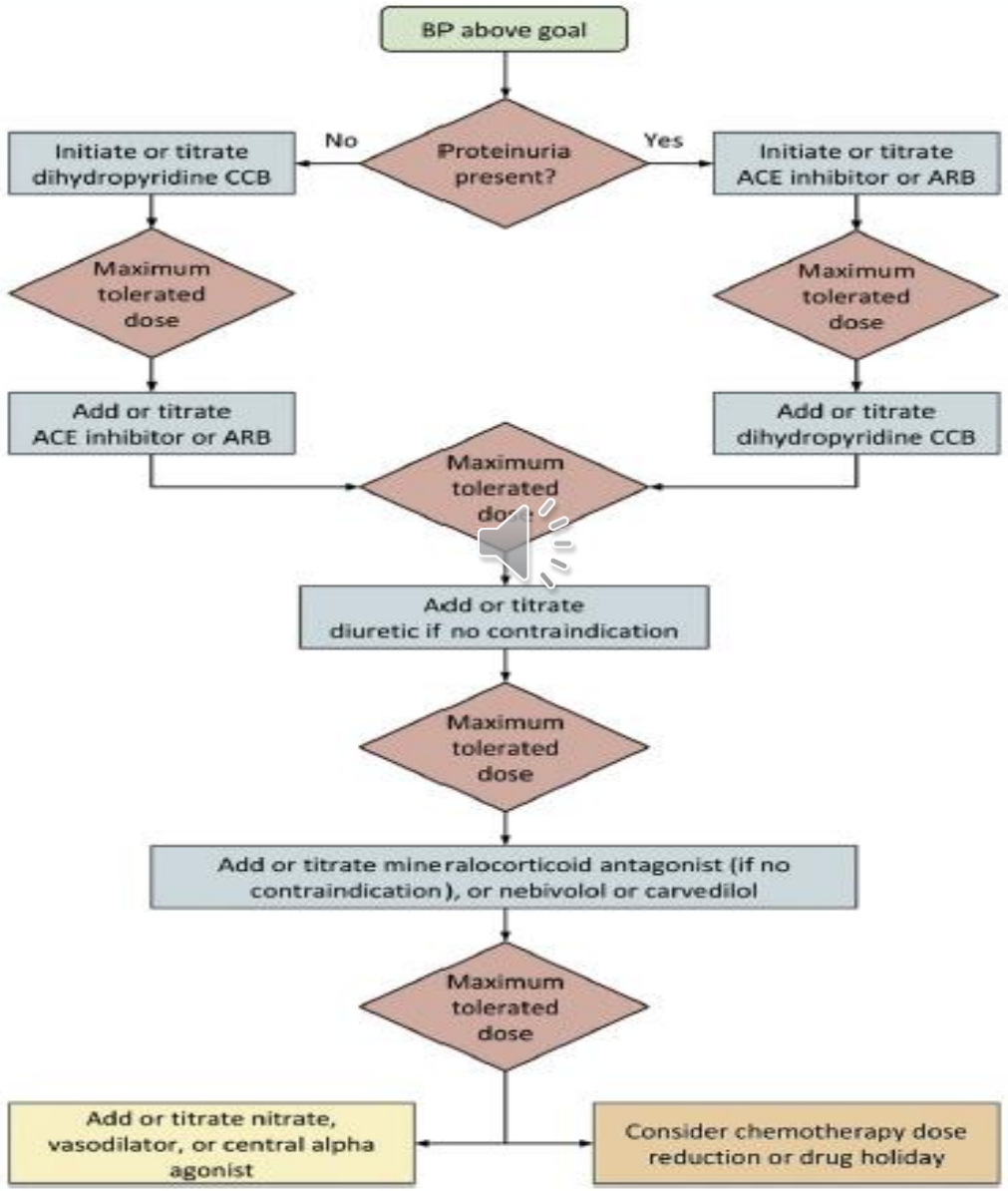
- medication strategy is not specific to patients with anticancer therapy–induced hypertension.
- **First-line** :ACE-I/ARB, dihydropyridine CCB, or thiazide or thiazide like diuretic.
- mineralocorticoid receptor antagonists :resistant hypertension.
- β-Blockers reserve for specific indication (eg, atrial fibrillation, recent MI, heart failure, reduced ejection fraction), already optimized on maximum tolerated doses of first-line antihypertensive agents.
- Nondihydropyridine CCB(eg, diltiazem, verapamil) with caution (**susceptible to interactions** with several anticancer therapies that are metabolized by P-glycoprotein and cytochrome P450 3A4)
- Lifestyle Modifications

MANAGEMENT OF ANTICANCER THERAPY–INDUCED HYPERTENSION

- **Dihydropyridine CCBs** may be the first-line choice in treating patients with cancer, because amlodipine lowers blood pressure among most patients with hypertension induced by bevacizumab.
- RAAS inhibitor: VSP inhibitors cause proteinuria,
- Patients with metastatic RCC …..revealed to live longer
- cancer who are using VEGF inhibitors because NO production is upregulated by RAAS inhibitors

- NO replacement with long-acting nitrate or phosphodiesterase inhibitors might improve VSP inhibitor-associated hypertension.

FIGURE 2 Approach to Treating Hypertension in Patients Receiving Cancer Therapy



MANAGEMENT OF ANTICANCER THERAPY–INDUCED HYPERTENSION

- **After completing anticancer therapy** :may need to reduce antihypertensive treatment to avoid rebound hypotension and ischemic events.
- daily home BP monitoring may be necessary.
- Over the long term, the prevalence of hypertension in cancer survivors is higher than in the general population……. benefit from closer monitoring .
- **Key gap**: timing and frequency of BP monitoring and cardiovascular risk assessment in patients with cancer.

With thanks