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VIEWPOINT

A Cardio-Oncology Cardiovascular Prevention Framework*

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Cardiovascular disease (CVD) is a leading cause of death among >15 million cancer survivors in the United States (1). Oncology patients and survivors have an increased risk of CVD, hypothesized to be due to cancer therapies and an increased burden of CVD risk factors. In this issue of *JACC: CardioOncology*, Cohen et al. (2) focus their excellent review on hypertension, the foremost modifiable risk factor of adverse cardiovascular outcomes among oncology patients (3). This viewpoint provides a summary of its key points, a cardio-oncology CVD prevention framework, and highlights innovations in CVD prevention.

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KEY POINTS

1. ONCOLOGICAL THERAPEUTICS ARE SIGNIFICANT RISK FACTORS FOR INCIDENT OR WORSENING HYPERTENSION. The cardiovascular toxicity of select anticancer therapeutics causes the accelerated development of hypertension. Antivascular endothelial growth factor (VEGF) pathway inhibitors, including tyrosine kinase inhibitors, cause hypertension through a decrease in nitric oxide production by endothelial cells, a decrease in the number of small arteries and arterioles (rarefaction), and an increase in the potent vasoconstrictor endothelin-1 (4,5). Clinical trials demonstrate newer VEGF-inhibitors cause hypertension in nearly 70% of patients (6). Moreover, alkylating agents (e.g., cyclophosphamide) promote endothelial injury and nephrotoxicity; antimicrotubule agents prevent microtubule polymerization and are hypothesized to affect endothelial cell gene expression; and antimetabolite therapy is linked to thrombotic microangiopathy and hypertension. Oncological interventions associated with hypertension development include abdominal radiation (i.e., renal artery stenosis), head/neck radiation (i.e., baroreflex failure), and nephrectomy. Additional therapies, including erythropoietin-stimulating agents, nonsteroidal anti-inflammatory drugs, corticosteroids, calcineurin inhibitors, may cause or worsen hypertension.

2. OUT-OF-OFFICE BLOOD PRESSURE MEASUREMENT IS RECOMMENDED FOR THE DIAGNOSIS AND TREATMENT OF HYPERTENSION IN CANCER PATIENTS. The advantage of out-of-office blood pressure (BP) measurement is it addresses the limitations of clinic measurements. Among cancer patients, there is a higher rate of white coat hypertension (hypertensive in office and normotensive out-of-office) and masked hypertension (normotensive in clinic and hypertensive out-of-office). Patients on anti-VEGF therapy, tyrosine kinase inhibitors, alkylating agents, or high-dose corticosteroids may warrant closer BP monitoring. Hypertension guidelines emphasize out-of-office BP measurement for the diagnosis and treatment of hypertension in cancer patients, which is particularly important because they may have more labile BPs and an increased risk for masked or white coat hypertension.

3. GIVEN LIMITED EVIDENCE FOR A CANCER-SPECIFIC GOAL BP, ACC/AHA GUIDELINES ARE A REASONABLE THERAPEUTIC TARGET. The traditional target BP goal for cancer patients is to lower BP below 140/90 mm Hg, and patients with additional cardiovascular risk factors may benefit from more intensive BP control below 130/80 mm Hg. However, limited data

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exist to support these thresholds because cancer patients were excluded from randomized clinical trials. First-line management is lifestyle modification, sodium restriction, weight loss, and exercise as emphasized in recent American College of Cardiology/American Heart Association (ACC/AHA) 2019 Primary Prevention Guidelines (7) (Table 1).

4. ANTIHYPERTENSIVE THERAPY NEEDS TO BE INDIVIDUALIZED IN CANCER PATIENTS, GIVEN CONSIDERATIONS FOR THE EFFECTS OF CANCER AND CANCER THERAPIES. In addition to adhering to ACC/AHA guidelines, clinicians should be aware that cancer patients are at higher risk for orthostatic hypotension after initiation of antihypertensive medications and may warrant short-interval assessment of symptoms and orthostatic vitals. One can tailor antihypertensive therapy to cancer patients allowing for "sick-day protocol": withholding these medications for 24 to 48 h during symptomatic episodes to prevent risk of volume depletion. Consideration of medication interactions from oncology therapeutics is necessary, including the avoidance of hypertensive agents that are metabolized by cytochrome p450 3A4 (i.e., verapamil and diltiazem) given many cancer therapies also interact with this pathway. The investigators recommend an individualized discussion of goals of care, prognosis, comorbidities, and pain control before antihypertensive therapy initiation and/or modification.

TABLE 1 Adapted ACC/AHA Guidelines for Adults With High BP

COR	Recommendations
I	In adults with elevated BP, nonpharmacological interventions are recommended: • Weight loss • Heart-healthy dietary pattern • Sodium reduction • Dietary potassium supplementation • Increased physical activity with structured exercise program • Limited alcohol
I	In adults with an estimated 10-yr ASCVD risk of ≥10% and an average systolic BP ≥130 mm Hg or a diastolic BP ≥80 mm Hg, use of BP-lowering medications is recommended.
I	If confirmed hypertension and a 10-yr ASCVD risk of ≥10%, a BP target of <130/80 mm Hg is recommended.
I	If hypertension and chronic kidney disease, treat to a BP goal of <130/80 mm Hg.
I	If T2DM and hypertension, antihypertensive drug treatment should be initiated at a BP of ≥130/80 mm Hg, with a goal of <130/80 mm Hg
I	If an estimated 10-yr ASCVD risk <10% and a systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg, initiate BP-lowering medication
IIb	If confirmed hypertension without additional markers of increased ASCVD risk, a target of <130/80 mm Hg may be reasonable.

Data from Arnett et al. (7).

ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic vascular disease; BP = blood pressure; COR = Class of Recommendation; T2DM = type 2 diabetes mellitus.

CARDIO-ONCOLOGY CARDIOVASCULAR PREVENTION FRAMEWORK

In addition to BP management, clinicians should incorporate a broader ABCDE (8) cardio-oncology framework for cancer patients and management of the CVD risk factors: assessment of risk, antiplatelet/anticoagulant therapy, blood pressure, cholesterol, cigarette/tobacco cessation, diet and weight management, diabetes prevention and treatment, and exercise.

RISK ASSESSMENT. The first step is to identify cancer patients with established atherosclerotic vascular disease (ASCVD), diabetes mellitus, and chronic kidney disease (stage II or worse), and traditional cardiovascular risk factors. Risk-enhancing factors should be discussed which include family history of premature ASCVD, persistently elevated low-density lipoprotein cholesterol levels ≥160 mg/dl (≥4.1 mmol/l), metabolic syndrome; chronic kidney disease, history of preeclampsia or premature menopause (age <40 years), chronic inflammatory disorders (e.g., rheumatoid arthritis, psoriasis, or chronic HIV), high-risk ethnic groups (e.g., South Asian), persistent elevations of nonfasting triglycerides ≥175 mg/dl (≥1.97 mmol/l), and if measured in selected individuals, apolipoprotein B ≥130 mg/dl, high-sensitivity C-reactive protein ≥2.0 mg/l, ankle-brachial index <0.9, and lipoprotein(a) ≥50 mg/dl or 125 nmol/l. In the future, cancer may be recognized as a "risk-enhancing factor," given the inflammatory state produced by cancer and increased ASCVD risk observed with cancer therapies.

Clinicians should also review the cardiotoxic effects of cancer therapies and assess any limitations in cardiopulmonary fitness (lymphedema, bony metastasis) that might have a further impact on cardiovascular health. The ASCVD Risk Calculator can be used to estimate 10-year ASCVD risk for patients not on statin therapy. The selective use of a noninvasive coronary artery calcium assessment can be considered for a more precise estimate of the patient's individual CVD risk, if the need for statin therapy remains unclear.

BLOOD PRESSURE. Hypertension control reduces risk for coronary heart disease, stroke, atrial fibrillation, heart failure, and chronic kidney disease. Although there are limited data for specific BP goals in cancer patients, the ACC/AHA guidelines provide a reasonable approach for the diagnosis and treatment thresholds for cancer patients, although those receiving cardiotoxic chemotherapeutic agents should aim for a goal BP of <130/<80 mm Hg. For cancer survivors, lifestyle modifications are first-line, and weight loss is recommended if overweight (body

mass index >25 kg/m^2), as is increased moderate-intensity physical activity, reduction in alcohol consumption, reduced dietary sodium (<2 g daily), and adherence to a high-fiber diet consisting mainly of fruits, vegetables, lean protein.

Out-of-office monitoring of BP is recommended to reassess progress with aggressive lifestyle modification. If lifestyle modifications do not achieve BP targets, and chemotherapy and adjunctive treatments are optimized, then initiation of antihypertensive medications is recommended.

CIGARETTE/TOBACCO CESSATION. Cigarette smoking increases exposure to known carcinogens and stimulates the sympathetic nervous system and contributes to arterial stiffness, which places smokers at increased risk for renovascular hypertension. In addition to providing counseling for tobacco cessation, cancer patients who are actively smoking should be offered behavioral counseling, telephone resources (e.g., 1-800-QUIT-NOW), nicotine replacement therapy, and either bupropion or varenicline based on safety of side-effect profiles.

DIET/DIABETES/WEIGHT MANAGEMENT. Cancer patients at times may have a diminished appetite and symptoms of nausea, particularly if undergoing active treatment. When cancer patients are able to resume their normal diet, it is important to recommend the Dietary Approaches to Stop Hypertension (DASH) eating plan, which has been shown to effectively lower BP. It is rich in vegetables, fruits, legumes, whole grains, and low saturated fat dairy, and emphasizes reduced processed foods high in refined sugar, cholesterol, and saturated fat. Patients should aim for a reduction in excess sodium intake <2 g daily, which can be achieved from avoiding deli meats, processed foods, canned goods, and prepared foods at fast food chains and restaurants. They should be encouraged to maintain a healthy weight with body mass index <25 kg/m^2. If considerably overweight and not currently on active treatment, weight loss should be recommended because even a weight loss of 5% has been shown to reduce BP. Cancer patients should be screened for diabetes mellitus, particularly if on long-term or high-dose steroids.

EXERCISE. Aerobic exercise is a cardioprotective factor and reduces BP by 5 to 7 mm Hg. Resistance exercise has a similar positive effect by reducing BP by 4 to 5 mm Hg (9). Cancer patients need to be carefully screened for exercise readiness and offered opportunities to participate in supervised exercise programs.

FUTURE DIRECTIONS

To improve quality of life, new solutions are addressing cancer-specific cardiovascular risk reduction. Supervised CORE (Cardio-Oncology REhabilitation) (10) is based on traditional cardiac rehabilitation. CORE offers a multimodal cardiac rehabilitation program of exercise plus nutritional counseling and risk assessment to prevent cardiovascular events. Mobile health interventions, including smartphone applications (apps), wearables (smartwatches), and wireless sensors (Bluetooth BP cuff), are emerging as patient-centered strategies to assist in the self-management of hypertension.

Over the last 4 years, we have collaborated with Apple and developed Corrie Health (11) for patients to improve adherence to guideline-directed management. Key features of Corrie CVD includes 5 modules relevant for cancer patients: 1) tracking and reminders for cardiac medications; 2) monitoring BP with an Food and Drug Administration-approved wireless BP cuff; 3) providing peer-reviewed educational videos and articles on diet, medications, and how to prevent hypertension/dyslipidemia/glucose intolerance through lifestyle modification; 4) reminders and scheduling help for appointments; and 5) connecting with providers and addressing social determinants of health services to optimize guideline-directed evidence-based care. Future trial investigating these mobile health interventions specifically among cancer patients are needed.

Cohen et al. (2) provide a call for action for improved hypertension identification, treatment, and control among cancer patients to reduce cardiovascular risk. It is critical to individualize hypertension management for cancer patients by accurately estimating their cardiovascular risk, type of cancer, oncological therapies, adjuvant medications, and pain level when initiating lifestyle modification and antihypertensive medications. Home BP monitoring with an accurate measurement collection protocol is an especially important tool for cancer patients. In the future, cardio-oncology-focused cardiac rehabilitation and mobile health tools may be a new approach to improving cardiovascular risk management with the ABCDE framework.

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