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STATE-OF-THE-ART REVIEW

Cardiometabolic Comorbidities in Cancer Survivors

JACC: CardioOncology State-of-the-Art Review

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ABSTRACT

There are nearly 17 million cancer survivors in the United States, including those who are currently receiving cancer therapy with curative intent and expected to be long-term survivors, as well as those with chronic cancers such as metastatic disease or chronic lymphocytic leukemia, who will receive cancer therapy for many years. Current clinical practice guidelines focus on lifestyle interventions, such as exercise and healthy eating habits, but generally do not address management strategies for clinicians or strategies to increase adherence to medications. We discuss 3 cardiometabolic comorbidities among cancer survivors and present the prevalence of comorbidities prior to a cancer diagnosis, treatment of comorbidities during cancer therapy, and management considerations of comorbidities in long-term cancer survivors or those on chronic cancer therapy. Approaches to support medication adherence and potential methods to enhance a team approach to optimize care of the individual with cancer across the continuum of disease are discussed. (J Am Coll Cardiol CardioOnc 2022;4:149–165) Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

There are nearly 17 million individuals in the United States who are cancer survivors—including those who are currently receiving therapy with curative intent, those with chronic cancer such as chronic lymphocytic cancer (CLL) or metastatic disease who will receive cancer therapy for many years, and long-term survivors.[1] The National Cancer Institute defines a cancer survivor from the time of cancer diagnosis through the continuum of life,[2] encompassing each of these distinctly different subgroups. Hereafter, we use the term *cancer survivor* to represent individuals across this continuum.

At the time of diagnosis, many cancer survivors have pre-existing comorbidities, such as hypertension, dyslipidemia, and diabetes, that increase their risk of both cancer and non-cancer-related morbidity

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

CVD = cardiovascular disease

LDL-C = low-density lipoprotein cholesterol

and mortality (**Central Illustration**).[3-7] This is due in part to aging, and the fact that the development of many cancers have shared risk factors (eg, obesity and sedentary lifestyles) with cardiovascular disease (CVD). Many individuals will survive their cancer only to have a preventable cardiac death. Management of cardiometabolic comorbidities associated with CVD is essential during and after cancer therapy.

This point is best illustrated in women with breast cancer.[8,9] With advances in screening, early detection, and cancer therapy, the 5-year survival rate for breast cancer now exceeds 90%, with the survival rate for localized disease nearly 99%.[10] Population-based data suggest that breast cancer survivors are at a greater risk for CVD mortality compared with women without breast cancer, and the increase in risk manifests approximately 7 years after cancer diagnosis.[6] While research has focused on the risk of heart failure due to the administration of anthracyclines and anti-HER2 therapy,[11-15] or coronary artery disease due to left-sided breast irradiation,[16,17] the majority of CVD is due to aging, obesity, and sedentary lifestyles.[6,8,18-20] With a median age of 63 years at the time of breast cancer diagnosis, most women will have at least 1 cardiometabolic comorbidity, such as hypertension, diabetes, or dyslipidemia.[14,20-22] Appropriate pharmacotherapy for these comorbidities is often overlooked. Among women with early-stage breast cancer who were prescribed a statin prior to their breast cancer diagnosis, adherence significantly decreased from 1-year pre-diagnosis (67%) to 2 years post-diagnosis (35%).[23] Compared with the pre-cancer rate, by 3 years post-diagnosis the adherence rate (50%) was still substantially lower, even for women who were treated with surgery and radiation without adjuvant or neoadjuvant systemic therapy. This decrease in adherence was not confined to statin therapy; a similar trend was seen with antihypertensive and oral diabetes medications.[24] Not surprisingly, women who are nonadherent with their noncancer medications are also more likely to be nonadherent with their adjuvant endocrine therapy.[6] Nonadherence, combined with the weight gain and diminishing cardiorespiratory reserve, creates a perfect storm.[18,19,25-29] While this pattern of lifestyle changes and suboptimal adherence to noncancer medications has been best elucidated among women with breast cancer, there is a growing recognition that this cycle is common among both genders and other cancer populations.[3,4,30-39] Compared with individuals without a cancer history, individuals with cancer have disproportionately higher burdens of CVD comorbidities.[4,40-42]

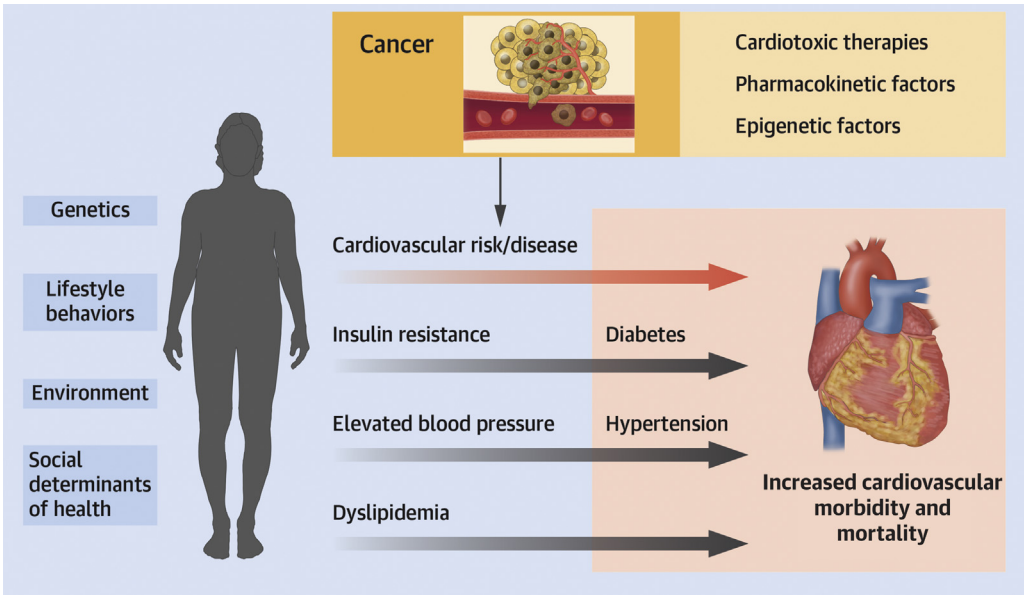
HIGHLIGHTS

- Cancer survivors are at increased risk for several chronic conditions, including hypertension, dyslipidemia, and diabetes.
- Determining optimal management of comorbidities for patients with cancer is critical.
- A multidisciplinary care approach is recommended throughout the continuum of active cancer treatment and survivorship.
- Survivorship research should focus on medication adherence and coordination of care.

How the existing pattern of care and lack of adherence to medications for noncancer comorbidities evolved is understandable. Two to 3 decades ago, survival rates were lower and cancer care was less complex. Medical oncologists often served as the cancer patient's primary care provider.[43,44] Surgeons and radiation oncologists often felt more comfortable managing noncancer problems for their cancer survivors than primary care providers (PCPs), as the latter group became increasingly removed from active participation in cancer care.[45,46] At the same time, with a focus solely on treating the cancer, the message often interpreted by the patient was that the "noncancer stuff" was not particularly important. While there are exceptions to this pattern of care, it has been generally acknowledged by patients, cancer specialists, and PCPs. This time period in their patient's trajectory is often referred to by PCPs as a "black hole."[47]

To optimize both cancer and noncancer therapy with an aim of not only curing cancer (or controlling chronic cancer), but also maximizing long-term health and productivity, a team-based approach to health care delivery is essential. The following discussion is intended for health care providers or researchers who may be involved in this goal. The focus of the discussion is on the 3 aforementioned cardiometabolic comorbidities: hypertension, dyslipidemia, and diabetes, among cancer survivors. Because the prevalence or incidence of therapy-induced changes and the robustness of the literature varies among these 3 cardiometabolic comorbidities, subheadings for each outcome varies. Because CVD risk factors among childhood cancer survivors have

CENTRAL ILLUSTRATION **Predicting Risk in a Person-Centric Model (Lifetime Model)**



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We present a lifetime model predicting risk in a person-centric model. Individual traits including genetic factors, lifestyle behaviors, environment, and social determinants of health impact insulin resistance, elevated blood pressure, and dyslipidemia. This impacts the development of diabetes, hypertension, and ultimate cardiovascular disease risk. This coupled with the cancer diagnosis impacts increased cardiovascular morbidity and mortality.

recently been reviewed by Leerink et al,[48] our paper focuses solely on individuals diagnosed with cancer in adulthood.

A few caveats are important to understand with respect to this paper. First, some cancer therapy-induced comorbidities are short term and resolve upon cessation of the therapy (eg, steroid induced hypertension), and thus may not warrant long-term treatment. However, it must be remembered that most of the CVD risk arises not from these less common sequelae, but rather from the relative inattention given to management of "garden variety" hypertension, dyslipidemia, or diabetes after the cancer diagnosis. Providers should also avoid overtreatment of these comorbidities among patients with advanced disease with shortened life expectancies. Last, there is a paucity of evidence-based guidelines for the management of these 3 comorbidities among cancer survivors. We have extrapolated from existing guidelines intended for noncancer populations, recognizing that cancer survivors should have the same long-term benefits.

HYPERTENSION

Approximately 32% of U.S. adults 40 to 59 years of age have hypertension,[49] with a prevalence that increases with age.[50] Among older individuals, 70% of U.S. adults have hypertension.[49] Given that two-thirds of cancers are diagnosed among individuals 65 years of age and older, most patients have pre-existing hypertension at the time of their cancer diagnosis. However, for others, such as adolescents or young adults with cancer, it is rather uncommon to have pre-existing hypertension. The obesity epidemic in the United States may increase the number of younger cancer patients with pre-existing hypertension. This was illustrated by a recent retrospective cohort study by Chao et al[51] in which 11.8% of adolescent or young adult cancer survivors, 15 to 39 years of age at time of diagnosis, had pre-existing hypertension compared with 7.4% of a matched comparison group without cancer. In a large data linkage study from Kaiser Permanente Northern California, the investigators observed that breast cancer survivors had a higher

TABLE 1 Drug Class and Management Considerations for Anticancer Therapy Associated With Hypertension

Drug Class	Cancer Therapy	Frequency of Hypertension	Example Malignancies Treated	Management Strategies	Notes and Considerations
Alkylating agents	Cisplatin[157]	Very common	Bladder, breast, esophageal, head and neck, lung, testicular		
Antiandrogens	Bicalutamide	Common	Prostate	Spironolactone for abiraterone No specific first-line recommendation for lupron and degarelix	Spironolactone may decrease the therapeutic effect of abiraterone
	Flutamide	Uncommon	Prostate		
	Nilutamide	Uncommon	Prostate		
Aromatase inhibitors	Anastrozole[158]	Very common	Breast	No specific considerations among first-line agents	85% hepatic elimination via N-dealkylation, hydroxylation, glucuronidation
	Exemestane[159]	Common	Breast		
	Letrozole[159]	Common	Breast		
BRAF inhibitors	Vemurafenib[160]	Very common	Melanoma		
Chimeric antigen receptor T cell therapy	Tisagenlecleucel	Very common	Leukemia, lymphoma		
MEK inhibitors	Trametinib[161]	Very common	Melanoma		
Monoclonal antibodies	Ramucirumab[162]	Very common	Colorectal, gastric, lung		
	Rituximab	Common	Leukemia, lymphoma		
	Ofatumumab[163]	Uncommon	Leukemia, lymphoma		
	Alemtuzumab[164]	Rare	Leukemia, lymphoma		
mTOR inhibitors	Everolimus[165]	Very common	Breast, pancreas, renal	Dihydropyridine CCBs ACE inhibitor	Temsirolimus may enhance adverse/toxic effects of ACE inhibitor
	Temsirolimus[166]	Common	Renal		
Proteasome inhibitors	Bortezomib	Common	Multiple myeloma, lymphoma	No specific considerations among first-line agents	P450 3A4 inducers and inhibitors may alter serum concentration of bortezomib
	Carfilzomib	Very common	Multiple myeloma		
Tyrosine kinase inhibitors	Axitinib[167]	Very common	Renal, thyroid	Nifedipine shown to be effective first-line agent in a clinical trial Amlodipine ACE inhibitor/ARBs Dihydropyridine CCBs	ACE inhibitor/ARBs less effective than nifedipine ACE inhibitor may be effective against risk of proteinuria; though data are limited Nondihydropyridines contraindicated
	Cabozantinib	Very common	Renal, thyroid		
	Ibrutinib	Very common	Leukemia/lymphoma		
	Ponatinib[168]	Very common	Leukemia		
	Pazopanib[169]	Very common	Renal, sarcoma, thyroid		
	Regorafenib[25]	Very common	Colorectal, GIST, HCC		
	Sorafenib[170]	Very common	HCC, renal, thyroid		
	Sunitinib[171]	Very common	GIST, PNET, renal, sarcoma, thyroid		
	Vandetanib[172]	Very common	Thyroid		
VEGF inhibitors	Bevacizumab[78]	Very common	Breast, cervical, colorectal, endometrial, glioblastoma, ovarian, renal, sarcoma,	ACE inhibitor/ARB Dihydropyridine CCBs Beta-blocker Thiazide diuretic	Renal clearance Beta-blocker may have beneficial effect via interaction with endothelial NO pathway Thiazides may cause electrolyte imbalance ACE inhibitor may be effective against risk of proteinuria; though data are limited
	Ziv-aflibercept[172]	Very common	colorectal		

The frequency of hypertension was graded as: very common >10%; common > 5% to 10%; uncommon 1% to 5%; rare <1%. High normal: SBP 130 to 139 mm Hg and/or DBP 85 to 89 mm Hg. Grade 1: SBP 140 to 159 mm Hg and/or DBP 90 to 99 mm Hg. Grade 2: SBP 160 to 179 mm Hg and/or DBP 100 to 109 mm Hg. Grade 3: SBP ≥180 mm Hg and/or DBP ≥110 mm Hg. Isolated systolic hypertension: SBP ≥140 mm Hg and DBP <90 mm Hg.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; DBP = diastolic blood pressure; GIST = gastrointestinal stromal tumor; PNET = primitive neuroectodermal tumor; SBP = systolic blood pressure; VEGF = vascular endothelial growth factor.

cumulative incidence of hypertension after 2 years compared with matched control subjects (10.9% vs 8.9%). Hypertension risk was higher for cases receiving left-sided radiation or endocrine therapy.[52] In an analysis of data from the National Health Interview Survey, 2002 to 2018, Jiang et al[53] noted that the prevalence of hypertension among individuals with a history of cancer increased from 35.9% in 2002 to 40.6% in 2018.

Several guideline committees[54-57] have created algorithms for the management of hypertension in noncancer patients. The management of hypertension in patients with cancer prior to diagnosis should be consistent with current standard guidelines.[55]

CANCER THERAPY–INDUCED HYPERTENSION. A recent review by Cohen et al[58] provides a comprehensive review of hypertension during and after cancer therapy, with a special emphasis on therapy-

induced hypertension. The authors provided an excellent discussion on the prevalence of, and potential mechanisms for, therapy-induced hypertension, including therapy with vascular endothelial growth factor (VEGF) inhibitors (ie, bevacizumab), tyrosine kinase inhibitors (ie, ibrutinib), and proteasome inhibitors (ie, bortezomib, carfilzomib, and ixazomib) (**Table 1**). Relevant to this discussion, however, are preliminary results from a retrospective review of our institution's experience with ibrutinib among 219 consecutive patients with CLL (K. C. Oeffinger, personal communication, January 15, 2021). Prior to initiation of ibrutinib, 59.4% of CLL patients had pre-existing hypertension, of which most (78.5%) were considered controlled. Following initiation of ibrutinib, 74.5% of these patients with pre-existing hypertension were subsequently uncontrolled (eg, systolic blood pressure [BP] ≥140/90 mm Hg). Of the 89 patients who did not have pre-existing hypertension, almost half (47.2%) developed new onset hypertension following initiation of ibrutinib. In total, following initiation of ibrutinib, 64.8% of the 219 patients developed either uncontrolled or new onset HTN. These findings highlight the need for a team-based approach for the management of both cancer and noncancer conditions.

Antiandrogen agents (ie, abiraterone, enzalutamide, and apalutamide) have revolutionized the treatment of castrate-resistant prostate cancer. These agents have been associated with an increased incidence of hypertension. In a meta-analysis of abiraterone administered with prednisone the incidence of all grade and grade 3 to 4 hypertension was 21.9% (95% CI: 13.6%-33.2%) and 10.2% (95% CI: 6.9%-11.6%), respectively. Abiraterone was associated with significantly increased hypertension risk of all grades with a relative risk of 1.8 (95% CI: 1.5%-2.2%; $P < 0.001$) and high grade with a relative risk of 2.1 (95% CI: 1.7%-2.7%; $P < 0.001$) in comparison with control subjects.[59] While it would appear logical to use spironolactone to reverse some of these cardiovascular side effects associated with excess mineralocorticoid, there have been reports that this may cause progression of prostate cancer due to a potential selective antiandrogen effect.[60,61] Gonadotropin-releasing hormone analogs, such as Lupron, have reported a <5% risk of hypertension.[62] Gonadotropin-releasing hormone receptor antagonists, such as degarelix, have a 6% to 7% reported occurrence of hypertension.[63]

Estrogens have a protective effect on the cardiovascular system and regulate lipid homeostasis, coagulation system, and the production of vasoactive molecules such as nitrous oxide and prostaglandins, and thus increase vasodilation.[64] Aromatase inhibitors, which reduce breast cancer–related mortality in post-menopausal women with estrogen-positive breast cancer by inhibiting estrogen production have been implicated in increasing the risk of hypertension and CVD-related mortality; however, this association is controversial.[65-67] The incidence of hypertension with anastrozole is between 5% and 13%,[64] and the incidence with anastrozole was higher compared with placebo (risk ratio: 1.6; 95% CI: 1.2-2.3) in the IBIS-II (International Breast Cancer Intervention Study II) trial.[68]

HYPERTENSION IN LONG-TERM CANCER SURVIVORS. Most therapy-induced BP elevations are short term, resolving upon cessation of therapy. Few therapies used to treat cancer in adults directly result in new, long-term hypertension. An exception to this generalization is allogeneic hematopoietic cell transplant (HCT) survivors. Several studies have demonstrated increased prevalence of hypertension in HCT survivors. In a study of 1,089 HCT recipients (both allogeneic and autologous) at least 2 years post-treatment not currently taking immunosuppressants, patients were 2.1 times (95% CI: 1.4-3.0) more likely to develop hypertension than their siblings.[3] In a case-matched comparison study of 44 HCT patients and their donor siblings, rates of hypertension in survivors were increased as compared with siblings (50% vs 73%).[69] Additionally, allogeneic HCT survivors have an increased relative risk of hypertension (5.2) as compared with autologous HCT survivors.[70] The mechanism(s) by which this increased risk of hypertension occurs is not well understood.

Another group of interest are those patients receiving long-term or intermittent cancer therapies that are known to cause hypertension. As noted previously, this includes patients with CLL, men receiving androgen deprivation therapy, and possibly women on an aromatase inhibitor. Because each of these groups can do well on cancer therapy, it is essential to monitor their BP and treat appropriately.

Last, there is an extended period of nonadherence to noncancer medications, even among patients treated only with cancer surgery. This problem was highlighted by Calip et al[24] in a cohort of 4,216 women of which, approximately 2 years after a diagnosis of early-stage breast cancer diagnosis, 37% were nonadherent to their antihypertensive medications. Thus, even among long-term survivors who were treated with curative intent, there are frequently patients who may have inadequately controlled hypertension several years after their cancer diagnosis. This, again, is in part due to the fragmentation of the

health care of survivors and the lack of coordination between oncology and PCPs.

BP MANAGEMENT DURING AND AFTER CANCER THERAPY. Cohen et al[58] provide an excellent set of algorithms for measuring and managing elevated BP among cancer survivors during and following cancer therapy.

We fully agree that it is essential to monitor the BP of patients throughout cancer management and align BP goals with current Joint National Committee guidelines.[71,72] For patients receiving cancer therapy, other than endocrine therapy, we recommend following the standard hypertension target of <140/90 mm Hg. Notably, many patients may have problems with eating, nausea, etc., and so we do not advocate aggressive management of the BP. Agents commonly used for BP management include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and beta-blockers, recognizing that all 3 of these classes of agents are preferred options for patients receiving cardiotoxic therapies such as an anthracycline-based regimen. Because of the frequent electrolyte abnormalities among patients receiving chemotherapy, we tend to avoid or be very cautious with the use of thiazide-type diuretics.

For patients who have completed chemotherapy, we advocate a stratified approach to hypertension management. For those patients who have not received a potentially cardiotoxic cancer therapy, a goal <140/90 mm Hg, consistent with current position statements[73] and societal cardio-oncology guidelines is recommended.[74] In this scenario, the major pharmacologic agents for hypertension management are the same as those for the general population, including the thiazide-type diuretics, ACE inhibitors, beta-blockers, or dihydropyridine calcium-channel blockers. However, for patients treated with a potentially cardiotoxic cancer therapy, we recommend the goal set by the American College of Cardiology/American Heart Association (ACC/AHA) of <130/80 mm Hg.[55] Similarly, these antihypertensive agents are also used in the prevention and treatment of left ventricular dysfunction (eg, ACE inhibitors, ARBs, and/or beta-blockers).

Noncancer patient guidelines recommend that patients with hypertension undergo routine monitoring for other CVD risk factors and target organ damage, which can be minimized with optimal BP control.[55] Concomitant use of excessive alcohol, steroids, or nonsteroidal anti-inflammatory drugs may cause additional BP-increasing effects, and pain alleviation and stress management are important treatment goals. Lifestyle recommendations remain applicable and include weight loss or weight control, physical activity, alcohol moderation, and a Dietary Approaches to Stop Hypertension eating plan, which includes sodium reduction.[55]

There are a few caveats to BP management with specific chemotherapeutic exposures (**Table 1**). Prior to initiation of therapy with VEGF inhibitors (eg, bevacizumab), screening for high BP and other cardiovascular risk factors should be performed. Hypertension diagnosed prior to cancer therapy should be treated with appropriate pharmacotherapy.[55] However, some specific modifications of hypertension management are important to consider during bevacizumab therapy. The occurrence of hypertension on anti-VEGF therapy has been associated with better oncologic response to therapy[75,76]; therefore, hypertension should be managed appropriately and interruption in cancer therapy avoided unless severe, uncontrolled hypertension occurs. Second, VEGF inhibitors can cause renal thrombotic microangiopathy and glomerular injury,[77] and therefore renal function, proteinuria, and blood counts should be monitored. Some guidelines recommend dihydropyridine calcium-channel blockers, ACE inhibitors, or ARBs as first-line therapies for management of bevacizumab-induced hypertension.[78] There are no significant interactions reported between bevacizumab and antihypertensive drugs. However, diuretics may exacerbate already volatile electrolyte homeostasis during cancer treatment and result in hypokalemia, hyponatremia, hyperuricemia, or magnesium depletion. The selective beta-blocker, nebivolol, has vasodilatory effects by serving as a B3 receptor agonist and releasing endothelial nitrous oxide thereby targeting BP in 2 ways: a nitric oxide (NO) pathway and beta agonist pathway. Nitrates, which work mainly by the NO release pathway, could be considered for BP management, however there is a theoretical risk that concurrent use with VEGF inhibitors could counteract the antitumor effect, given that they work solely on the NO pathway.[75]

For reducing hypertension induced by cediranib, a hypertension management protocol with nifedipine as a first-line agent, has been shown to be effective, and early treatment resulted in fewer cases of severe hypertension, although this did not translate into reduction in cancer treatment dose interruptions or discontinuations.[79] In preclinical studies, nifedipine did not affect antitumor activity of cediranib.[80] Other treatment options include ACE inhibitors, ARBs, or beta-blockers, and like treatment of bevacizumab-associated hypertension, there may be potential concerns with the use of nitrates and diuretics.

We are currently piloting an approach to integrate continuous BP monitoring by leveraging a blue tooth enabled BP monitor in an on-going study in cancer patients at our institution (NCT03919214). Cancer survivors on active cancer therapy, being treated with curative intent, monitor their BP at home and send values directly into the electronic health record using SMART on FHIR (Fast Healthcare Interoperability Resources). An automated electronic health system messaging algorithm then sends alerts for abnormal weekly average pressures to the cancer survivors' primary care team, with copies to the patient and the oncologist. The goal of the study is to determine the proportion of PCPs who received and acted on the automated message, as well as the proportion of patients with cancer who completed 3 weekly BP measurements.

For long-term cancer survivors, there are no evidence-based recommendations for specific agents. However, we and others[58] favor the use of ACE inhibitors or ARBs among patients treated with anthracyclines or at risk for heart failure or renal dysfunction. Lifestyle modifications including exercise and dietary changes should be tailored to meet an individual patient's needs.

HYPERTENSION HIGHLIGHTS.

- Most patients have pre-existing hypertension at the time of their cancer diagnosis.
- The management of hypertension in patients with cancer prior to diagnosis should be consistent with current standard guidelines.
- Many therapy-induced BP elevations can be short term, resolving upon cessation of therapy.

DYSLIPIDEMIA

Elevated total cholesterol and low-density lipoprotein cholesterol (LDL-C) are present in 11.9% and 30.3% of the general population, respectively, and low high-density lipoprotein cholesterol is present in 18.7% of the general population.[81] Among patients with active or remitted cancer, dyslipidemia prevalence ranges from 28% to 58%.[82,83] Dyslipidemia in the general population is associated with CVD and mortality.[84-87] In populations with active cancer, dyslipidemia is associated with increased tumor growth and increased cancer-related mortality.[88-90]

In contrast with cancer therapy-induced hypertension, there are few cancer therapies that cause dyslipidemia. Survivors who have undergone hormone therapy for prostate and breast cancer often develop dyslipidemia.[91] This outcome is likely multifactorial and may be related to changes in body composition and relative increases in fat mass concurrent with decreases in lean muscle mass.

MANAGEMENT OF DYSLIPIDEMIA IN PATIENTS RECEIVING ACTIVE CANCER THERAPY. Regarding tumor progression in patients with active cancer, it is well established that cholesterol is concentrated in cancerous tissue, and increased dietary cholesterol is associated with increased cancer progression.[92] Higher dietary cholesterol intake is associated with increased tumor progression across many cancers; similarly, cholesterol-lowering diets are associated with a decreased cancer risk.[93-95] As noted in the recommendations by the ACC/AHA Task Force, lifestyle modification through diet and exercise are the first-line recommendations to avoid or manage dyslipidemia.[96]

The use of statins for patients on active cancer therapy remains less clear. Some early observational studies demonstrated an association between lower or declining cholesterol levels and an increased risk of cancer-specific mortality.[97-99] This literature base even began to call into question treatment guidelines for cholesterol in the 1990s.[100] Studies have long demonstrated that cholesterol-lowering diets, a key recommended lifestyle modification strategy for dyslipidemia management, do not increase cancer risk or cancer-specific mortality.[101] More recently, evidence on the impact of statins on cancer-specific mortality continues to offer mixed conclusions. While most of the meta-analytic evidence suggests statins have no effect on cancer-specific mortality,[102,103] large studies suggest small effects of statins reducing cancer-specific mortality in various populations.[104,105] In contrast to studies in the general population, in which overall and CVD-specific mortality are the primary outcomes, among cancer populations, CVD-specific mortality is rarely examined. Statin therapy has several benefits for patients on active cancer therapy. Statins may impact cancer-specific mortality; however, the primary goal for prescribing statins among cancer survivors is the reduction of CVD mortality. Prevailing evidence suggests that statin use is not associated with decreased cancer-specific mortality. In a meta-analysis of 26 separate randomized controlled trials comprising almost 87,000 patients, 6,662 incidences of cancer, and 2,407 cancer-related deaths, statin use was unrelated to cancer-specific mortality, with point estimate odds ratios very close to 1 on both accounts.[102] In a more recent meta-analysis, 27 separate trials comprising 175,000 patients, 10,431 incidences of cancer, and 3,651 cancer-related deaths, both the presence and intensity of statin use was again unrelated to cancer incidence or cancer-specific

mortality.[103] These meta-analyses alleviate some concerns of the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) and CARE (Cholesterol and Recurrent Events) statin trials, which found increased incidence of gastrointestinal cancer and breast cancer among statin users, respectively.[106,107] Any evidence suggesting an association between statin use and cancer incidence or cancer-specific mortality should be interpreted cautiously. Nevertheless, this unclear and sometimes conflicting evidence on statins and their association with cancer-related outcomes has caused confusion among patients and their providers regarding statin adherence.[23] The role of statins in reducing CVD-mortality is clear. Thus, among cancer survivors treated with curative intent, the reduction of CVD risk is essential.

Recognizing that many patients treated for a solid tumor will experience weight gain, an increase in fat mass, a decrease in lean muscle mass during therapy due to a decrease in physical activity, frequent use of corticosteroids in antinausea regimens, and changes in diet, we advocate for continued monitoring of the lipid profile as per ACC/AHA guidelines. For patients with pre-existing dyslipidemia, statin, or other pharmacologic therapy should be continued, with the caveat of being aware of potential drug interactions by other agents metabolized by cytochrome P450. Pravastatin, with an alternate route of clearance compared with most cancer drugs, may have a lower risk of drug interactions. For patients with new onset dyslipidemia, diet and lifestyle modifications should be offered as initial treatment.

MANAGEMENT OF DYSLIPIDEMIA IN LONG-TERM SURVIVORS. Poor dyslipidemia management can persist among patients with cancer.[23,24] Consistent with other severe comorbidities, reasons for poor management include focusing self-management, health care, and other sources of support on the more severe comorbidity (ie, cancer) at the expense of other underlying chronic conditions (ie, dyslipidemia) and the asymptomatic nature of dyslipidemia. The lack of adherence to statin therapy among 4,221 women with early-stage breast cancer who were on statin therapy at least 1 year prior to cancer diagnosis was well illustrated by Calip et al.[23] At 3 years post-diagnosis, the adherence rate was only 50%, even for women who were treated with surgery and radiation without adjuvant or neoadjuvant therapy. Adherence to noncancer medications has also been observed in other studies.[24,39,108]

Specific cholesterol management goals for long-term cancer survivors and those on chronic cancer therapy should be the same as for the general population, driven largely by their 10-year atherosclerotic CVD risk and cardiovascular comorbidities, including hypertension and diabetes mellitus. Meta-analytic results support these cholesterol management goals as adequate in cancer populations as well.[109] Of the 10 primary recommendations by the ACC/AHA Task Force, 2 are consistent irrespective of patient status: 1) emphasize a heart-healthy lifestyle across the life course; and 2) assess adherence and response to LDL-C-lowering medications and lifestyle changes.[96] These 2 recommendations underscore the need to manage cholesterol specifically through patient self-management. It is well documented that additional comorbidities can impair patients' abilities to self-manage their chronic conditions, and dyslipidemia in populations with active or remitted cancer is no different.[23,24]

Management of dyslipidemia through statins and lifestyle modification are recommended in most cancer survivors.[110] While various forms of cancer do not have specific statin recommendations, dyslipidemia management benefits cancer survivors' overall chronic disease risk, quality of life, and cancer recurrence outcomes.[83,111] Statin therapy is associated with decreased recurrence across breast, prostate, lung, colorectal, liver, and other cancers.[112] Additionally, exercise in cancer survivors is strongly recommended due to its multiple benefits from reduced fatigue to decreased cardiovascular risk.[113-115] Specifically, exercise increases high-density lipoprotein cholesterol with beneficial effects on the cardiovascular profile or prognosis. The combination of increased risk for other chronic conditions, poorer prognosis with those conditions, and additional cancer-related benefits that dyslipidemia management portends strongly supports the need to maintain a focus on these dyslipidemia management behaviors (ie, medication adherence, diet, and exercise) in cancer survivors.

DYSLIPIDEMIA HIGHLIGHTS.

- Dyslipidemia is common among patients with cancer.[82,83]
- In populations with active cancer, dyslipidemia is associated with increased tumor growth and increased cancer-related mortality.[88-90]
- There are few cancer therapies that cause dyslipidemia.
- Management of dyslipidemia through statins and lifestyle modification are recommended in most cancer survivors.[110]

DIABETES

In the United States, 13% of adults, and 27% of those 65 years of age and older, have diabetes mellitus.[116] Diabetes is more common in cancer survivors than

the general population and likely contributes to the observed excess risk of CVD morbidity and mortality in survivorship. Among 1,582 survivors of breast, prostate, colorectal, and gynecological cancer, diabetes was more prevalent (21%) than among age-matched control subjects ($P < 0.0001$).[20] In a pooled analysis of 13 cohort studies, cancer survivors were 1.4 times as likely to have diabetes than noncancer individuals (95% CI: 1.3-1.5).[117] Recently, Ose et al[118] observed an increase in the prevalence of diabetes among 5,865 adults from 12% at the time of cancer diagnosis to 25% at 1 year post-diagnosis. In a large administrative data linkage study from Ontario, the investigators observed that cancer survivors with diabetes were less likely to receive recommended cardiovascular risk-reducing therapies compared with people with diabetes without cancer of similar age, sex, and diabetes duration.[119]

In cancer patients, several factors are likely to contribute to the association of diabetes with increased cardiovascular morbidity[120] and all-cause mortality.[121,122] First, diabetes may inherently limit access to life-saving cancer therapies; for instance, registry data from 194 Hodgkin's lymphoma patients found that those with diabetes received less chemotherapy.[123] Second, diabetes may potentiate treatment-related cardiovascular risks, such as left ventricular dysfunction in patients treated with anthracyclines or trastuzumab.[11]

CANCER THERAPY–INDUCED HYPERGLYCEMIA. Several conventional and novel oncologic treatments can potentiate the development of diabetes. For instance, PEG-L-asparaginase, a cytotoxic chemotherapeutic agent, can induce hyperglycemia through direct (inhibition of insulin production and release) and indirect toxicity (pancreatitis) mechanisms.[124] Corticosteroid-containing regimens commonly induce hyperglycemia. As examples, 39% of patients hospitalized with hematologic malignancies[125] and 59% of patients with central nervous system tumors or hematologic malignancy[126] developed hyperglycemia. Traditional diabetes risk factors (eg, body mass index, personal or family history) were not predictive.[126] Targeted therapies can affect molecular pathways important to glucose homeostasis; hyperglycemia is an increasingly recognized side effect, particularly with agents that inhibit insulin growth factor receptor 1 and mTOR.[127] Immune checkpoint inhibitors, such as programmed cell death-1 inhibitors, can trigger immune-related adverse events, including development of type 1 diabetes,[128] which, although rare (<1%), requires prompt recognition and management.[128,129] Beyond direct treatment effects, "indirect" lifestyle perturbations (eg, weight gain, physical inactivity) during cancer can synergistically increase long-term risk for diabetes and impair cardiovascular reserve.[25]

MANAGEMENT OF HYPERGLYCEMIA AND DIABETES IN PATIENTS RECEIVING ACTIVE CANCER THERAPY. The current diagnostic paradigm for diabetes has limitations during active oncologic treatment. The American Diabetes Association criteria for the diagnosis of diabetes includes: 1) hemoglobin A1c (HbA1c) ≥6.5%; 2) fasting plasma glucose of ≥126 mg/dL; or 3) 2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test.[130] Glycemic monitoring during active oncologic treatment can be challenging. Dependence on blood product transfusions for some patients may undermine HbA1c measurement reliability, and oral glucose tolerance testing is not routinely available in the oncology clinic setting. Diabetic patients often need frequent regimen modifications in the setting of weight loss or poor oral intake.

Diabetes has the potential to complicate active oncologic treatment with important consequences for morbidity and mortality in cancer patients throughout the cancer continuum of active treatment and survivorship. For example, a common adverse effect of alpelisib, a PIK3CA inhibitor approved for treatment of hormone receptor positive metastatic breast cancer, is grade 3 to 4 hyperglycemia, which in severe cases can lead to cessation of treatment.[131] Accordingly, awareness and prompt diagnosis of diabetes is necessary to inform oncologic treatment decisions. Because diabetes is also an integral driver of CVD, facilitation of early cardiovascular interventions that reduce the risk of downstream morbidity and mortality is necessary. Partnerships among oncologists and diabetic care providers familiar with cancer treatments can facilitate risk-based, exposure-driven approaches to overcome these diagnostic challenges[132] and have previously demonstrated success in cancer survivors.[133]

MANAGEMENT OF DIABETES IN LONG-TERM SURVIVORS. The optimal treatment of diabetes in long-term survivors is necessary to minimize the potential for cardiovascular morbidity and mortality in the setting of gains in cancer survival. Guidance on diabetes management in long-term survivors should be extrapolated from American Diabetes Association guidelines.[130] This guideline recommends comprehensive lifestyle modifications followed by metformin as first-line therapy for patients with type 2 diabetes, with additional therapies considered based on clinical context. For type 1 diabetes, insulin

remains the first-line therapy based on insufficient endogenous insulin. In general, HbA1c goals are <7% (class A), with stringency of goals based on patient-specific factors, such as life expectancy or hypoglycemia risk (classes C and B, respectively).[130] Data from the United Kingdom Prospective Diabetes Study revealed that, over a 10-year study period in patients with newly diagnosed type 2 diabetes, intensive glycemic control with either sulfonylurea or insulin significantly reduced diabetic microvascular complications, such as renal failure or retinal disease, but not macrovascular complications, such as myocardial infarction or stroke.[134] However, there was a statistically significant increase in hypoglycemia in the intensive control arm,[134] and similar adverse outcomes with intense glycemic lowering were seen in later clinical trials.[135-137] Accordingly, current evidence suggests that less intense glycemic targets may be advantageous but should be balanced carefully against the well-established, graded relationship between glycemic control and cardiovascular complications.[138] Novel sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide 1 receptor agonist agents have revolutionized secondary and tertiary prevention of CVD and may emerge alongside metformin in the primary prevention of diabetes.[139] Sodium-glucose cotransporter 2 inhibitors have additional promise in heart failure treatment, and future studies may consider whether these benefits extend to cancer therapy–related cardiac dysfunction and heart failure management in certain populations with active cancer.

A multidisciplinary care approach is advised throughout the continuum of active oncologic treatment and cancer survivorship with regard to identification and management of cancer therapy–related diabetes.

DIABETES HIGHLIGHTS.

- Diabetes is more common in cancer survivors than the general population.
- Blood glucose monitoring and control during active oncologic treatment can be challenging.
- Less intense glycemic targets may be advantageous but should be balanced carefully with a well-established, graded relationship between glycemic control and cardiovascular complications.[138]

PROMOTING ADHERENCE TO LIFESTYLE INTERVENTIONS, ORAL CANCER THERAPIES, AND MEDICATIONS FOR CVD COMORBIDITIES

A multimodality approach is needed to offset the impact of cancer therapies on cardiovascular morbidity and mortality particularly in the setting of pre-existing CVD or risk factors. In a recent AHA Scientific Statement, Gilchrist et al[140] highlight the need for cardio-oncology rehabilitation to mitigate the CVD consequences of cancer therapy. The provision of comprehensive long-term services involving medical evaluation, prescriptive exercise, cardiac risk factor modification, and education, counseling, and behavioral interventions to facilitate cardiovascular risk reduction would hopefully lead to improve psychosocial well-being and reduce recurrent hospitalizations and the associated CVD morbidity and mortality. There currently is no reimbursement strategy in the United States to provide access to a multimodality cardiac rehabilitation program for patients with cancer.

Cancer survivors may be prescribed oral medications to treat their cancer, manage side effects, and reduce the likelihood of cancer recurrence. Although medication adherence is critical for achieving optimal clinical outcomes, many adults struggle with taking long-term medications, and only 50% of prescribed chronic cancer medications are taken as indicated.[141,142] Medication adherence is multifaceted and composed of 3 distinct phases: 1) initiation, which is when a patient takes the first dose of a prescribed medication; 2) implementation, the extent to which a patient's actual dosing corresponds with the prescribed regimen from initiation until the last dose; and 3) persistence, which is the time period between initiation and when a patient stops taking a prescribed medication (discontinuation).[143-147] Each of these phases warrants specific attention and support to ensure optimal benefit from the prescribed medication (**Table 2**).

For individuals with pre-existing chronic conditions, a cancer diagnosis often results in challenges with coordination of care across multiple providers and management of numerous medications for the treatment of comorbid conditions and cancer.[4] In such cases, treatment may transition from strategies focused on chronic disease management to strategies focused on reducing the burden of or delaying the progression of cancer.[4] For example, a cancer diagnosis has been associated with significant declines in adherence to evidence-based treatments for diabetes, hypertension, and lipid disorders.[4,38,148,149] Specifically, in a retrospective study, adherence to orally administered hypoglycemic agents, renin-angiotensin-aldosterone system inhibitors, and statins decreased 3.7%, 5.3%, and 3.2%, respectively, following an incident cancer diagnosis.[38]

Changes in medication adherence following a cancer diagnosis vary by cancer type, patient

TABLE 2 Phases of Adherence and Adherence-Promoting Strategies

Phase of Adherence	Initiation	Implementation	Persistence
Definition	When a patient takes the first dose of a prescribed medication	Extent to which a patient's actual dosing corresponds with the prescribed regimen from initiation until the last dose	Time between initiation and when a patient stops taking a prescribed medication (discontinuation)
Strategies to support adherence	Promote patient participation in decision making Offer choices Reduce stigma and fear of medication Cultivate understanding of illness Build trust in provider Ensure access to affordable medication	Make regimens as simple as possible Provide dosing reminder systems Pair taking medication with a daily habit (eg, brushing teeth) Increase social support (eg, peer support) Monitor for adverse drug reactions Plan for changes in routine (eg, travel, holidays) Provide concrete support (eg, medication delivery to home)	Provide refill reminder systems Maintain trust in provider Maintain access to affordable medication Synchronize medication refills Provide concrete support (eg, medication delivery to home)

demographic, and clinical characteristics. Research has demonstrated that significant decreases in adherence to orally administered antidiabetic medications and statins occurred in patients with a lung or colorectal cancer diagnosis[148-150]; however, declines in medication adherence for pre-existing diabetes, dyslipidemia, and hypertension were similar between breast and prostate cancer patients and matched noncancer cohorts.[150] In addition, larger declines in medication adherence were observed in older adults, multiracial patients, and those diagnosed with advanced cancer.[4,148,149] One study found that patients with stage IV cancer experienced a 10.7% decline in adherence to glucose-lowering mediations (compared with a 3.2% and 5.8% decrease in patients with stage II and III cancer, respectively)[4,148,149]; another study only observed significant decreases in statin adherence among non-Hispanic Whites and multiracial patients.[4,148,149]

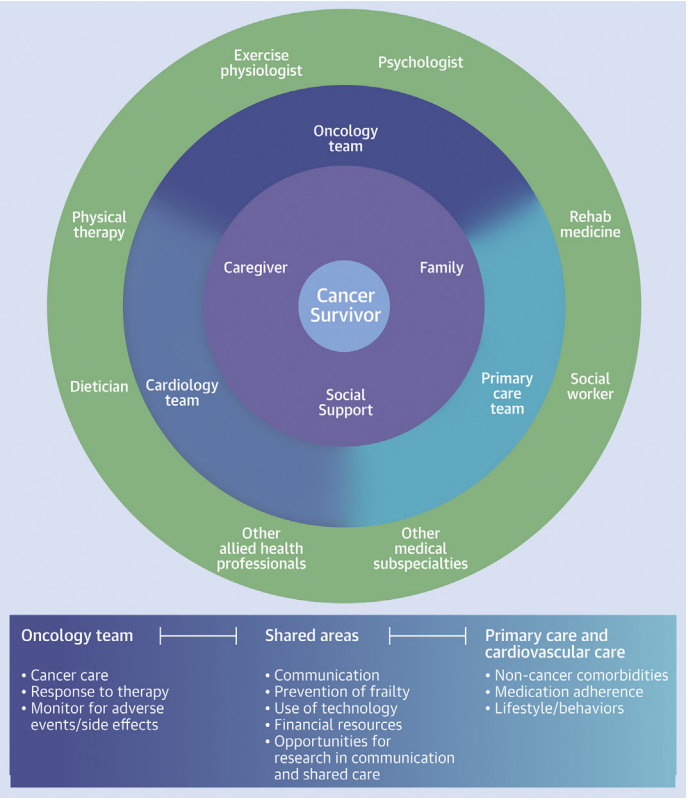
Despite the increased risk of CVD associated with potentially cardiotoxic chemotherapies and the reduced risk of CVD events and cancer recurrence associated with some long-term medications (eg, statins),[23,24,151] declines in medication adherence for comorbid chronic conditions persist during, and following, a patient's active cancer treatment. For example, in the year prior to a breast cancer diagnosis, adherence to statins and orally administered antidiabetic medications was 78% and 86%, respectively; however, during cancer treatment, adherence to statins and antidiabetic medications significantly decreased to 68% and 49%, respectively.[23,24] Moreover, declines in medication adherence for lipid disorders and diabetes continued in the years following breast cancer treatment (eg, in the second year following cancer therapy, statin adherence was 63% and antidiabetic medication adherence was 48%).[23,24]

TEAM-BASED APPROACH

To move beyond "curing" cancer to promoting a long, productive life for cancer survivors and those living with a chronic cancer, requires a team-based approach (**Figure 1**). Too often patient care is siloed, and efficient and timely communication is lacking. As noted previously, depending on the level of complexity of the comorbidities and the cancer therapy, different providers may be needed, including oncology, primary care, cardiology, and endocrinology providers, with the patient at the center of the picture. Importantly, the team should consider factors that likely impact access to care and medication adherence, including sociodemographics and factors associated with inequity.

Current ACC/AHA hypertension guidelines for noncancer patients stress the importance of involving each member of the interdisciplinary care team to enhance the adoption of positive lifestyle behaviors and promote medication adherence.[55] The efficacy of such an approach has also been indicated across different types of medication adherence barriers, especially to reconcile medication lists for patients during transitions of care, such as initiation or completion of cancer therapy.[152] Incorporation of current technologies that improve information sharing, such as electronic health record systems and other medical record sharing applications, have also been highlighted to improve communication and information sharing among patients and health care team members.[153] Despite a general call to action for such an approach, concrete literature on the efficacy of a team-based approach is lacking. We are currently conducting a National Cancer Institute–supported randomized controlled trial aimed at promoting a "one-team" approach aimed at improving CVD comorbidity management and adherence to

FIGURE 1 Medical Home for Cancer Survivors



We present a medical home for cancer survivors. The cancer survivor is at the center, surrounded by their social support including caregivers and family members. The next layer is the care team including oncology, primary care, and cardiology clinical teams, among others. Each team manages care in their respective clinical area, plus shared areas including prevention of frailty, financial resources, and research opportunities, among others. This group is supported by additional professionals.

medications for hypertension, diabetes, or dyslipidemia among patients with newly diagnosed solid tumors being treated with curative intent (NCT04258813). It is our goal to engage PCPs in the management of pre-existing cardiometabolic comorbidities for their patients during cancer therapy.[154] Enhancing PCP engagement early in the trajectory will provide the oncology team more time to focus on their area of expertise—achieving a durable cure for the patient. It will also familiarize the PCP with the patient's cancer journey and hopefully improve the subsequent transition to survivorship health care. Cardiologists, endocrinologists, exercise physiologists, pharmacists, nurses, and other allied health care providers are also integral with such a plan, particularly for the patient with complex health care needs.

Finally, many of the studies we described focused on prevalent users of medications for comorbid chronic conditions; however, future research should assess if and how active cancer treatment delays the initiation of medication for CVD or other chronic conditions. Indeed, most studies have used a cancer-centric approach whereby the assessment starts at the time of cancer diagnosis. For example, in reporting adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events for patients on active cancer therapy, one simply denotes whether a patient has hypertension and then grades the hypertension based on specific cutpoints.[155] However, this approach results only in a prevalence estimate and does not provide a perspective of changes from the pre-cancer status. We instead advocate using a more person-centric model (**Central Illustration**) that incorporates pre-cancer data to better understand how cancer and cancer therapy impact long-term outcomes, such as CVD.

CONCLUSION

Cancer survivorship is often marked by intensive and prolonged surveillance for cancer recurrence. However, cancer survivors are also at increased risk for a number of other chronic conditions, including dyslipidemia, hypertension, and diabetes.[156] With prolonged oncologic survival, determining optimal management for cancer patients with comorbidities is becoming critical. The management of chronic, but less salient, comorbid conditions in patients with active and remitted cancer is understandably difficult. A focus on screening could identify at-risk patients at cancer diagnosis, lending to a multidisciplinary care approach, which is advised throughout the continuum of active oncologic treatment and cancer survivorship.

The historical solution to continued care was to provide a survivorship care plan at the end of cancer treatment that includes what to expect, side effects, and which clinicians to see at what interval; however, lack of communication, combined with the timing of the plan, has rendered these plans inadequate at best. Thus, increased collaboration and communication between the oncology and cardiology care team, PCPs, and allied health care providers is required to adequately manage comorbid risk factors in cancer survivors. Coordination of care and treatment of comorbidities should remain a priority of treatment from the time of diagnosis.

Additionally, to improve medication adherence for comorbid chronic conditions, we recommend that future research be targeted toward all 3 phases of

medication adherence (initiation, implementation, and persistence) and consider adherence as a patient-reported outcome, particularly at critical time points across the cancer care continuum (eg, diagnosis, treatment initiation) that might impact medication adherence or chronic disease management. As the number of cancer survivors increases, addressing cardiovascular comorbidities and CVD among cancer survivors is paramount.

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