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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Clinical Approach to Cardiovascular Toxicity of Oral Antineoplastic Agents

JACC State-of-the-Art Review

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ABSTRACT

Precision medicine has ushered in a new era of targeted treatments for numerous malignancies, leading to improvements in overall survival. Unlike traditional chemotherapy, many molecular targeted antineoplastic agents are available in oral formulation, leading to enhanced patient convenience and a perception of reduced risk of adverse effects. Although oral antineoplastic agents are generally well-tolerated, cardiovascular toxicities are being reported with increasing frequency in part due to U.S. Food and Drug Administration and manufacturer recommended cardiac monitoring. Monitoring strategies have focused on left ventricular dysfunction, hypertension, and QT prolongation/arrhythmias. Given the rapid pace of development and availability of new oral antineoplastic agents, the purpose of this review is to provide clinicians with an up-to-date practical approach to monitoring and management of cardiovascular toxicities with the aim of improving overall outcomes for patients with cancer. (J Am Coll Cardiol 2021;77:2693–716) © 2021 The Authors. 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/).

Historically, the first chemotherapeutic agents demonstrating serious cardiovascular (CV) side effects were anthracyclines. Left ventricular (LV) dysfunction and heart failure (HF) were observed in a dose-response relationship (1). The introduction of trastuzumab for the treatment of breast cancer, although a paradigm shift in cancer care, was associated with LV dysfunction and HF, particularly in patients treated with concomitant anthracyclines (2). As a result, oncologists modified chemotherapy regimens and expanded care for patients by establishing CV monitoring algorithms to prevent cardiotoxicity. The current landscape of oncological care has been revolutionized with the ability to routinely perform tumor typing, thus identifying key cellular signaling pathways responsible for oncological transformation. Drugs specifically targeting these pathways, such as tyrosine kinase inhibitors (TKIs), have dramatically improved overall cancer survival rates. However, these same pathways are vital for normal physiological function of many organs, including the cardiovascular system.

Despite increased recognition of CV side effects from cancer therapy, clinical care for patients remains

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ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional

AF = atrial fibrillation

ARB = angiotensin receptor blocker

BP = blood pressure

CMR = cardiac magnetic resonance

CTRCD = cancer therapy-related cardiac dysfunction

CV = cardiovascular

DCCB = dihydropyridine calcium channel blocker

ECG = electrocardiogram

FDA = U.S. Food and Drug Administration

GLS = global longitudinal strain

HF = heart failure

LV = left ventricular

LVEF = left ventricular ejection fraction

mRCC = metastatic renal cell carcinoma

TdP = torsade de pointes

TKI = tyrosine kinase inhibitor

WCH = white coat hypertension

a challenge resulting from a lack of accessible education/information and clear CV monitoring recommendations. Several new journals with a cardio-oncology focus recently launched and provide some guidance. However, in practical terms for clinicians, web searches are often the starting point for understanding what potential cardiotoxicities exist for a new antineoplastic agent. U.S. Food and Drug Administration (FDA) drug labels represent comprehensive analyses of existing data with respect to individual drug efficacy and safety, providing the framework for understanding and monitoring of CV toxicities.

Herein, we provide a synthesized and simplified approach to cardiovascular monitoring for FDA approved oral antineoplastic agents. We aim to address "what" CV monitoring should be conducted based upon FDA drug labeling, "how to" perform CV monitoring, as well as suggest management strategies when CV toxicity is encountered (**Central Illustration**).

METHODS/FDA DRUG LABELING

Given extensive vetting associated with FDA approval of drug labeling, we used these documents to compile monitoring recommendations for cardiac adverse effects associated with oral antineoplastic agents. FDA labeling for medications approved before July 2020 were reviewed for cardiac adverse effects and associated monitoring recommendations. Overall, 56 of 85 medications reviewed (66%) recommend some form of cardiac monitoring. **Table 1** presents a comprehensive list of oral agents grouped by drug target, cancer(s) treated, typical dosing, and CV toxicities based upon drug incidence. These agents are also grouped by specific CV toxicity in Supplemental Tables 1 to 5. **Table 2** summarizes reasonable recommendations for baseline testing and subsequent monitoring strategies based upon our synthesis of FDA label recommendations, protocols of phase III trials, and our own clinical experience. We attempted to balance the risk of over-testing, which may lead to inappropriate withholding of life-saving antineoplastic therapy, with missing identification of CV toxicity that can impact overall outcomes for patients with cancer.

Although several oral agents are associated with increased risk for myocardial infarction and venous and/or arterial thromboembolism (**Table 1**), there is a lack of FDA label monitoring recommendations beyond screening for signs/symptoms for these important adverse effects. Prophylaxis and treatment recommendations for venous/arterial thromboembolism have recently been published (3). We recommend a baseline fasting lipid panel and consideration of statin and aspirin therapy in those agents with potential to lead to progression of atherosclerosis such as: BCR-ABL inhibitors (nilotinib and ponatinib), as well as hormonal therapies (anastrozole, apalutamide, darolutamide, and enzalutamide). Lastly, clinically significant pulmonary arterial hypertension has been observed with dasatinib and is reviewed elsewhere (4).

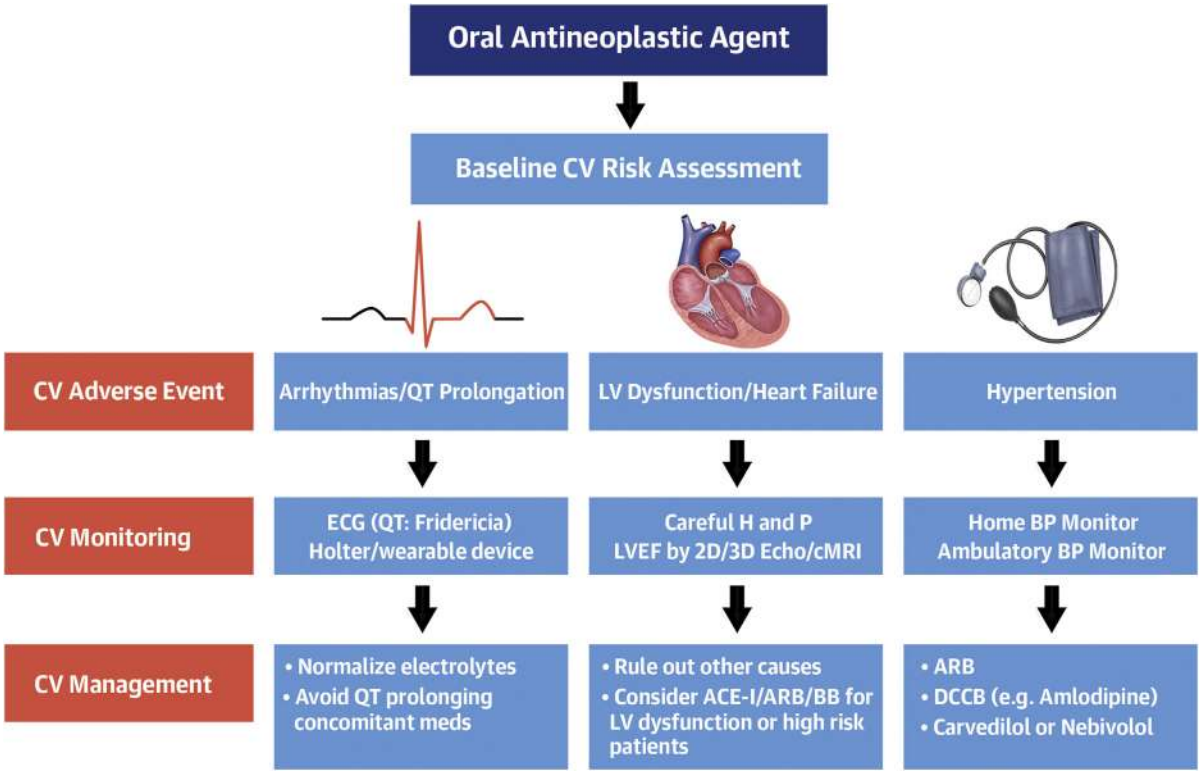
HIGHLIGHTS

- Early detection, management, and prevention of CV toxicities with oral molecular targeted antineoplastic agents are areas of unmet clinical need.
- Oral agents are associated with CV toxicities (LV dysfunction, hypertension, and arrhythmia/QT prolongation).
- Adjudication of CV adverse events in oncology trials and studies to demonstrate the overall benefit of a multidisciplinary CV monitoring approach is warranted.

ASSESSMENT OF BASELINE CV RISK

Initial evaluation of a patient receiving an oral antineoplastic agent with the potential for CV toxicity should include a complete assessment of baseline CV risk factors. Several reviews have specifically addressed the importance of defining the CV risk profile in this setting (5,6). Importantly, baseline CV risk factors include age >60 years, history of coronary artery disease or myocardial infarction, atrial fibrillation (AF), history of HF, tobacco use, hyperlipidemia, hypertension, diabetes, and obesity. Patients with any of these risk factors coupled with potential cardiotoxic oral cancer therapy places them in the American College of Cardiology (ACC)/American Heart Association (AHA) HF stage A, and steps should be taken to prevent progression to HF stage B (2,7). Optimization of CV risk factors is imperative at all stages of cancer treatment—before initiation of an oral antineoplastic agent, during cancer treatment, as well as in survivorship—to achieve best possible outcomes. Several models have been developed integrating baseline CV risk with chemotherapy-related

CENTRAL ILLUSTRATION **Oral Targeted Antineoplastic Agent Cardiovascular Toxicity, Monitoring, and Management Strategies**



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Graphical illustration of how to monitor and manage LV dysfunction, arrhythmia/QT prolongation, and HTN due to oral antineoplastic agents. 2D/3D = 2-dimensional/3-dimensional; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; BP = blood pressure; cMRI = cardiac magnetic resonance imaging; CV = cardiovascular; DCCB = dihydropyridine calcium-channel blocker; ECG = electrocardiogram; H and P = history and physical; LV = left ventricular; LVEF = left ventricular ejection fraction.

CV toxicity risk (8,9). For most oral agents with potential for CV toxicity, a reasonable approach includes obtaining a baseline electrocardiogram (ECG), as well as serum fasting lipid profile and hemoglobin A_{1C} (6). Finally, many patients with cancer have had thoracic imaging, which provides an opportunity to identify atherosclerosis, which can help establish indications for aspirin and/or statin therapies (10).

LV DYSFUNCTION: MONITORING AND MANAGEMENT

LV dysfunction in the setting of cancer therapy is referred to as cancer therapy-related cardiac dysfunction (CTRCD). The most widely accepted definition is a decline in left ventricular ejection fraction (LVEF) from baseline of >10% and/or a value of <53% (11). Multiple drugs used in oncology can lead to LV dysfunction, with the most common therapies being anthracyclines and trastuzumab. Although anthracyclines can cause irreversible LV dysfunction, including many years after treatment, there are no current data to suggest oral agents cause permanent LV dysfunction. The mechanisms of LV dysfunction observed with oral agents are not well characterized but potentially include direct effects (e.g., osimertinib through inhibition of the epidermal growth factor receptor [EGFR] and human epidermal growth factor receptor-2 [HER2] pathways [12]), as well as indirect effects such as hypertension and arrhythmias.

Oral agents that can cause LV dysfunction are summarized in **Table 1** and Supplemental Table 1. FDA label monitoring recommendations for these agents are summarized in **Table 2**. For oral agents with a lower incidence of LV dysfunction (<10%), we recommend a baseline LVEF and repeat assessment if the patient develops signs or symptoms of HF. However, for oral agents with a high incidence

TABLE 1 Oral Antineoplastic Agent CV Adverse Effects

				Select Cardiac Adverse Effects						
Classification	Drug	Oncology Indication(s)	Usual Dosage	QT Prolongation	Hypertension	Bradycardia	Tachycardia	Atrial Fibrillation	Left Ventricular Dysfunction	Other
ALK										
	Alectinib (Alecensa)	NSCLC	600 mg BID			++				
	Brigatinib (Alunbrig)	NSCLC	90–180 mg daily		**+++**	++				
	Ceritinib (Zykadia)	NSCLC	450 mg daily	++		++				
	Crizotinib (Xalkori)	NSCLC	250 mg BID	++		**+++**				
	Lorlatinib (Lorbrena)	NSCLC	100 mg daily							AV block: ++
BCR-ABL										
	Bosutinib (Bosulif)	CML	400–600 mg daily	+					++	
	Dasatinib (Sprycel)	CML, ALL	100–140 mg daily	++					++	PAH: ++
	Imatinib (Gleevec)	CML, ALL, MDS, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, GIST	400–800 mg daily		+				++	PAH: +
	Nilotinib (Tasigna)	CML	300–400 mg daily	+						MI*/VAT: **+++**
	Ponatinib (Iclusig)	CML, ALL	45 mg daily	+	**+++**	+	+	++	**+++**	MI*/VAT: **+++**
BRAF										
	Dabrafenib (Tafinlar)	Melanoma, NSCLC, anaplastic thyroid cancer	150 mg BID	+					++	
	Encorafenib (Braftovi)	Melanoma, colorectal cancer	300–450 mg daily	+						
	Vemurafenib (Zelboraf)	Melanoma	960 mg BID	++	**+++**					
BTK										
	Acalabrutinib (Calquence)	Mantle cell lymphoma, CLL	100 mg BID					++		
	Ibrutinib (Imbruvica)	Mantle cell lymphoma, CLL, Waldenstrom's macroglobulinemia, marginal zone lymphoma	420–560 mg daily		**+++**			**+++**		Ventricular arrhythmia: +
	Zanubrutinib (Brukinsa)	Mantle cell lymphoma	160 mg BID or 320 mg daily					++		
EGFR/HER2										
	Lapatinib (Tykerb)	Breast cancer	1,250–1,500 mg daily	+					++	
	Osimertinib (Tagrisso)	NSCLC	80 mg daily	+					++	
FLT3										
	Gilteritinib (Xospata)	AML	120 mg daily	++						
	Midostaurin (Rydapt)	AML, mast cell leukemia	50–100 mg BID	++						

Continued on the next page

of LV dysfunction (>10%) (e.g., BRAF inhibitors in combination with MEK inhibitors), we recommend serial LVEF assessment every 3 months throughout duration of therapy. Monitoring algorithms for specific oral agents are still an area of active research, and therefore, these recommendations are subject to change as more real-world studies are completed.

TABLE 1 Continued

Classification	Drug	Oncology Indication(s)	Usual Dosage	Select Cardiac Adverse Effects						
				QT Prolongation	Hypertension	Bradycardia	Tachycardia	Atrial Fibrillation	Left Ventricular Dysfunction	Other
HDAC										
	Panobinostat (Farydak)	Multiple myeloma	20 mg 3 times/ week during weeks 1 and 2 of each 21-day cycle	++						MI: ++
	Vorinostat (Zolinza)	CTCL	400 mg daily	++						VAT: ++
Hormonal therapy										
	Abiraterone (Zytiga)	Prostate cancer	1,000 mg daily		**+++**					
	Anastrozole (Arimidex)	Breast cancer	1 mg daily							MI*: ++
	Apalutamide (Erleada)	Prostate cancer	240 mg daily		**+++**				++	MI*: +
	Bicalutamide (Casodex)	Prostate cancer	50 mg daily		++				++	MI*: ++
	Darolutamide (Nubeqa)	Prostate cancer	600 mg BID		+				++	MI*: ++
	Enzalutamide (Xtandi)	Prostate cancer	160 mg daily		++					MI*: ++
	Exemestane (Aromasin)	Breast cancer	25 mg daily							MI: ++
	Flutamide (Eulexin)	Prostate cancer	250 mg TID		++					MI*: +
	Letrozole (Femara)	Breast cancer	2.5 mg daily							MI*: ++
	Nilutamide (Nilandron)	Prostate cancer	150–300 mg daily		++				++	
Immuno-modulator										
	Lenalidomide (Revlimid)	Multiple myeloma, MDS, mantle cell lymphoma, follicular lymphoma, marginal zone lymphoma	10 mg daily or 20–25 mg daily for 21 days of each 28-day cycle						++	VAT: **+++**
	Pomalidomide (Pomalyst)	Multiple myeloma, Kaposi sarcoma	4–5 mg daily for 21 days of each 28-day cycle						+	VAT: ++
	Thalidomide (Thalomid)	Multiple myeloma	200 mg daily		**+++**	+			+	VAT/MI: **+++**
MEK										
	Binimetinib (Mektovi)	Melanoma	45 mg BID						++	VAT: ++
	Cobimetinib (Cotellic)	Melanoma	60 mg daily for 21 days of each 28-day cycle		**+++**				**+++**	
	Trametinib (Mekinist)	Melanoma, NSCLC, anaplastic thyroid cancer	2 mg daily						++	VAT: ++

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IMAGING

Currently, there is a lack of specific FDA drug label guidance regarding which modality to use to screen for LV dysfunction. Historically, multigated acquisition scans were used to evaluate LVEF due to high availability and ability to perform in patients with obesity and poor acoustic windows (13). However, limitations include uncertain reproducibility, radiation exposure (especially with serial testing), and limited visualization of nonventricular structures (14). Two-dimensional (2D) echocardiography is currently the most widely used imaging modality to evaluate LVEF (15) and has advantages over multigated acquisition, given the lack of radiation exposure and ability to evaluate valvular and pericardial

TABLE 1 Continued

Classification	Drug	Oncology Indication(s)	Usual Dosage	Select Cardiac Adverse Effects						
				QT Prolongation	Hypertension	Bradycardia	Tachycardia	Atrial Fibrillation	Left Ventricular Dysfunction	Other
VEGFR										
	Axitinib (Inlyta)	RCC	5 mg BID		+++				++	MI/VAT: ++
	Cabozantinib (Cabometyx)	RCC, HCC	60 mg daily		+++				++	MI/VAT: ++
	Lenvatinib (Lenvima)	Differentiated thyroid cancer, HCC, endometrial cancer, RCC	8–24 mg daily	++	+++				++	MI/VAT: ++
	Pazopanib (Votrient)	RCC, soft tissue sarcoma	800 mg daily	++	+++				+++	MI/VAT: ++
	Regorafenib (Stivarga)	Colorectal cancer, GIST, HCC	160 mg daily for 21 days of each 28-day cycle		+++					MI: +
	Sorafenib (Nexavar)	HCC, RCC, differentiated thyroid cancer	400 mg BID	+	+++				++	MI: ++
	Sunitinib (Sutent)	GIST, RCC, PNET	37.5 mg daily or 50 mg daily for 4 weeks of each 6-week cycle	+	+++				+++	MI: +
	Vandetanib (Caprelsa)	Medullary thyroid cancer	300 mg daily	++	+++				+	
Miscellaneous agents (drug target)										
	Entrectinib (Rozlytrek) *(TRK, ROS1)*	NSCLC, solid tumors with NTRK gene fusion	600 mg daily	+					++	
	Everolimus (Afinitor) *(mTOR)*	Breast cancer, PNET, RCC	10 mg daily		+++					
	Fedratinib (Inrebic) *(JAK2, FKT3)*	Myelofibrosis	400 mg daily						++	
	Glasdegib (Daurismo) *(Hedgehog Pathway)*	AML	100 mg daily	++						
	Ivosidenib (Tibsovo) *(IDH1)*	AML	500 mg daily	++						
	Niraparib (Zejula) *(PARP)*	Ovarian cancer	200–300 mg daily		+++		++			
	Ribociclib (Kisqali) *(CDK 4/6)*	Breast cancer	600 mg daily 21 days on/ 7 days off	++						
	Ripretinib (Qinlock) *(KIT, PDGFRA)*	GIST	150 mg daily		+++				++	
	Selpercatinib (Retevmo) *(RET)*	NSCLC, thyroid cancer	120–160 mg BID	++	+++					
	Tretinoin (Vesanoid) *(Retinoic Acid Derivative)*	APL	45 mg/m^2/day divided BID		+++	+++			++	VAT: ++

Incidence depiction represents all grade adverse effects for the listed toxicities, except for QT prolongation. Incidence depiction for QT prolongation represents the incidence of QT >500 ms. All data are abstracted from FDA-approved drug labeling. *Associated with progression of atherosclerosis which may lead to myocardial infarction.

+ = rare; incidence of adverse effect <1%; ++ = uncommon; incidence of adverse effect 1% to 10%; +++ = frequent; incidence of adverse effect >10%; ALK = anaplastic lymphoma kinase; ALL = acute lymphocytic leukemia; AML = acute myeloid leukemia; APL = acute promyelocytic leukemia; BID = twice daily; BTK = Bruton's tyrosine kinase; CDK = cyclin-dependent kinase; CLL = chronic lymphocytic leukemia; CML = chronic myelogenous leukemia; CTCL = cutaneous T-cell lymphoma; CV = cardiovascular; CYP = cytochrome P450; EGFR = epidermal growth factor receptor; FDA = U.S. Food and Drug Administration; FLT3 = fms-like tyrosine kinase 3; GIST = gastrointestinal stromal tumor; HCC = hepatocellular carcinoma; HDAC = histone deacetylase; HER2 = human epidermal growth factor receptor 2; IDH1 = isocitrate dehydrogenase 1; JAK2 = Janus kinase; KIT = stem cell factor receptor; MDS = myelodysplastic syndrome; MEK = mitogen-activated protein kinase; MET = hepatocyte growth factor receptor; MI = arterial thromboembolism/ischemic cardiovascular event; mTOR = mammalian target of rapamycin; NSCLC = non-small cell lung cancer; NTRK = neurotrophic receptor tyrosine kinase; PAH = pulmonary arterial hypertension; PARP = poly (ADP-ribose) polymerase; PDGFRA = platelet derived growth factor receptor alpha; PNET = primitive neuro-ectodermal tumors; RCC = renal cell carcinoma; Ret = rearranged during transfection; ROS1 = reactive oxygen species; TID = 3 times daily; TRK = tropomyosin receptor kinase; VAT = venous and/or arterial thrombosis; VEGFR = vascular endothelial growth factor receptor.

TABLE 2 Oral Antineoplastic Agent CV Toxicity Monitoring Recommendations

Drug Target	Drug	FDA-Approved Manufacturer Labeling Recommended Monitoring	Monitoring Conducted in Published Phase III Clinical Trials	Recommendations for Clinical Practice*	
				Baseline Cardiac Monitoring	Cardiac Monitoring During Treatment
ALK					
	Alectinib (Alecensa)	Bradycardia: monitor periodically	HR: weeks 0, 4, 8, then every 8 weeks	HR	HR: daily home monitoring, correlate with in-clinic visits
	Brigatinib (Alunbrig)	Hypertension: BP after 2 weeks then monthly Bradycardia: monitor regularly		BP/HR	BP/HR: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management
	Ceritinib (Zykadia)	Bradycardia: monitor periodically QT prolongation: ECG in patients at risk	HR: cycle 1 days 1, 2, 8, 15 then days 1, 15 during subsequent cycles ECG: cycle 1 day 1, then every cycle and end of therapy	HR ECG	HR: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Crizotinib (Xalkori)	Bradycardia: monitor periodically QT prolongation: ECG in patients at risk	HR: weeks 0, 4, 8, then every 8 weeks ECG: day 1 of cycles 1–3	HR ECG	HR: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Lorlatinib (Lorbrena)	AV block: ECG at baseline and periodically	ECG: cycle 1 days 1, 8, 15, then with each cycle up to cycle 5	ECG	ECG: after 14 days, then if patient develops symptoms of bradycardia (fatigue, dizziness, syncope, etc.)
BCR-ABL					
	Bosutinib (Bosulif)	One dose with ketoconazole did not increase QT, but demonstrated at low frequency in trials Monitor for s/sx of cardiac failure	ECG: baseline, then every 4 weeks × 3 (1.5% with QT prolongation in study) LVEF: baseline then as clinically indicated	ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Dasatinib (Sprycel)	May increase risk of prolongation of QTc Monitor patients for s/sx of cardiac dysfunction	ECG: baseline, week 4 and as clinically indicated	ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡ In patients with dyspnea, consider obtaining a chest x-ray to rule out a pleural effusion Pulmonary hypertension may contribute to dyspnea
	Imatinib (Gleevec)	Monitor for cardiac failure	LVEF: baseline, month 3, month 12 (optional)	BP LVEF	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡
	Nilotinib (Tasigna)	ECG: at baseline, day 8, then periodically	ECG: baseline, cycle 1 day 8, end of cycles 3, 6, 9, and 12	ECG Fasting lipid panel§	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation Fasting lipid panel: every 6 months§
	Ponatinib (Iclusig)	BP: monitor during therapy Monitor for s/sx consistent with heart failure	ECG: baseline, cycle 2 day 1, and cycle 3 day 28 LVEF: baseline and cycle 3, day 28	HR/BP ECG LVEF Fasting lipid panel§	HR/BP: daily home monitoring, correlate with in-clinic visits ECG: if s/sx of arrhythmias LVEF: if s/sx of heart failure‡ Fasting lipid panel: every 6 months§

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disease. However, disadvantages include poor image quality in those with challenging body habitus, significant interobserver variability, and insensitivity to detect small changes in LVEF (16), suboptimal reproducibility (17), and substantial influence of loading conditions on the LVEF measurement. The recommended method of LV volume and LVEF quantification in 2D echo is modified biplane Simpson's technique (method of disks) (15,18). Ultrasonic enhancing agents such as Definity (Lantheus, North Billerica, Massachusetts) can improve endocardial definition and should be used when 2 contiguous segments of the LV cannot be visualized from an apical view (19,20). High-quality 3-dimensional (3D) echocardiography provides better reproducibility (15,17,21) and intra- and interobserver and test-retest variability (22) because it does not suffer from geometric assumptions and minimizes foreshortening.

TABLE 2 Continued

Drug Target	Drug	FDA-Approved Manufacturer Labeling Recommended Monitoring	Monitoring Conducted in Published Phase III Clinical Trials	Recommendations for Clinical Practice*	
				Baseline Cardiac Monitoring	Cardiac Monitoring During Treatment
BRAF					
	Dabrafenib (Tafinlar)	LVEF: baseline, at 1 month, then every 2–3 months	ECG: baseline then months 1, 3, 6, 9, 12 LVEF: baseline then months 1, 3, 6, 9, 12	ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: after 1 month then every 3 months when used in combination with a MEK inhibitor
	Encorafenib (Braftovi)	QT prolongation: ECG in patients at risk	ECG: baseline, 1.5 h after combination with binimetinib, cycle 2 day 1, then every 12 weeks	ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: after 1 month then every 3 months when used in combination with a MEK inhibitor
	Vemurafenib (Zelboraf)	QT prolongation: ECG at baseline, day 15, then monthly × 3 months, then every 3 months		HR/BP ECG LVEF	HR/BP: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: after 1 month then every 3 months when used in combination with a MEK inhibitor
BTK					
	Acalabrutinib (Calquence)	Monitor for atrial fibrillation and atrial flutter		ECG	ECG: if s/sx of atrial arrhythmias HR: daily home monitoring, correlate with in-clinic visits
	Ibrutinib (Imbruvica)	BP: monitor throughout therapy Monitor patients clinically for cardiac arrhythmias		BP ECG	BP/HR: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management ECG: if s/sx of atrial arrhythmias
	Zanubrutinib (Brukinsa)	Monitor for atrial fibrillation and atrial flutter		ECG	ECG: if s/sx of atrial arrhythmias HR: daily home monitoring, correlate with in-clinic visits
EGFR/HER2					
	Lapatinib (Tykerb)	QT prolongation: consider ECG in patients at risk LVEF: baseline and during treatment—monitored at 8-week intervals in trials		ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Osimertinib (Tagrisso)	QT prolongation: ECG in patients at risk LVEF: at baseline and during treatment in patients with cardiac risk factors or if develops s/sx	ECG: cycle 1 days 1, 8, 15, day 1 of cycles 2–6, then every 6 weeks LVEF: cycle 1, day 1 then every 12 weeks	ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
FLT3					
	Gilteritinib (Xospata)	QT prolongation: ECG at baseline, days 1 and 8 of cycle 1, then day 1 of cycle 2 and 3		ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Midostaurin (Rydapt)	QT prolongation: ECG if taken concurrently with meds that can prolong QT interval	ECG: before drug on days 1, 3, and 14 of each cycle of induction and consolidation and day 1 of each cycle of continuation therapy	ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation

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However, there is a learning curve in acquiring and analyzing images (21), and 3D echo is more costly with less availability than 2D echo.

Multiple studies have found that echocardiographic LV global longitudinal strain (GLS) can detect subclinical LV dysfunction early in patients who received anthracyclines and/or trastuzumab (23,24). GLS has also been found to be superior in predicting all-cause mortality compared with LVEF (25) and provides better risk stratification in individuals with HF (26). However, GLS is dependent on image quality and vendor software, and is influenced by loading

TABLE 2 Continued

Drug Target	Drug	FDA-Approved Manufacturer Labeling Recommended Monitoring	Monitoring Conducted in Published Phase III Clinical Trials	Recommendations for Clinical Practice*	
				Baseline Cardiac Monitoring	Cardiac Monitoring During Treatment
HDAC					
	Panobinostat (Farydak)	QT prolongation: ECG at baseline then periodically	ECG: throughout the first 8 cycles	ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Vorinostat (Zolinza)	QT prolongation: QT increases demonstrated in clinical studies Canadian PI: ECG at baseline then periodically	ECG: baseline and cycle 1 day 15; perform more routinely as clinically indicated	ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
Hormonal therapy					
	Abiraterone (Zytiga)	Mineralocorticoid excess: monitor blood pressure at least monthly		BP Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management Fasting lipid panel every 6 months§
	Apalutamide (Erleada)	Cardiac effects described; no monitoring recommendations provided		BP LVEF Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡ Fasting lipid panel every 6 months§
	Bicalutamide (Casodex)	Cardiac effects described; no monitoring recommendations provided		BP LVEF Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡ Fasting lipid panel every 6 months§
	Darolutamide (Nubeqa)	Cardiac effects described; no monitoring recommendations provided		BP LVEF Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡ Fasting lipid panel every 6 months§
	Enzalutamide (Xtandi)	Cardiac effects described; no monitoring recommendations provided		BP Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management Fasting lipid panel every 6 months§
	Flutamide (Eulexin)	Cardiac effects described; no monitoring recommendations provided		BP Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF if hypertension develops to assist with management Fasting lipid panel every 6 months§
	Nilutamide (Nilandron)	Cardiac effects described; no monitoring recommendations provided		BP LVEF Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡ Fasting lipid panel every 6 months§
Immuno-modulators					
	Lenalidomide (Revlimid)	Cardiac effects described; no monitoring recommendations provided	LVEF: according to clinician decision	LVEF	LVEF: if s/sx of heart failure‡ Monitor for s/sx of venous/arterial thrombosis
	Pomalidomide (Pomalyst)	Cardiac effects described, but no monitoring recommendations		LVEF	LVEF: if s/sx of heart failure‡ Monitor for s/sx of venous/arterial thrombosis
	Thalidomide (Thalomid)	Cardiac effects described, but no monitoring recommendations		HR/BP LVEF	HR/BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡ Monitor for s/sx of venous/arterial thrombosis
MEK					
	Binimetinib (Mektovi)	LVEF: baseline, after 1 month then every 2-3 months		LVEF	LVEF: after 1 month then every 3 months
	Cobimetinib (Cotellic)	LVEF: before treatment, after 1 month, then every 3 months thereafter; after a dose reduction or interruption at 2, 4, 10, 16 weeks, then as clinically indicated		BP LVEF	BP: daily home monitoring, correlate with in-clinic visits LVEF: after 1 month then every 3 months
	Trametinib (Mekinist)	LVEF: baseline, at 1 month, then every 2-3 months		LVEF	LVEF: after 1 month then every 3 months

Continued on the next page

TABLE 2 Continued

Drug Target	Drug	FDA-Approved Manufacturer Labeling Recommended Monitoring	Monitoring Conducted in Published Phase III Clinical Trials	Recommendations for Clinical Practice*	
				Baseline Cardiac Monitoring	Cardiac Monitoring During Treatment
VEGFR					
	Axitinib (Inlyta)	Hypertension: monitor as needed Monitor for s/sx of cardiac failure	BP: baseline, weeks 2 and 4, then every 4 weeks	BP LVEF	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡
	Cabozantinib (Cabometyx)	Hypertension: monitor regularly	VS: baseline, weeks 3, 5, 7, 9 then every 4 weeks	BP LVEF	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡
	Lenvatinib (Lenvima)	Hypertension: monitor at 1 week, then every 2 weeks × 2 months, then monthly QT prolongation: ECG in patients at risk Monitor for s/sx of cardiac dysfunction	ECG: day 1 of each cycle LVEF: at baseline then every 16 weeks or sooner if clinically indicated	BP ECG LVEF	BP: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Pazopanib (Votrient)	Hypertension: monitor at baseline and within 1 week after start, then frequently QT prolongation: ECG at baseline and periodic monitoring LVEF: baseline and periodic evaluation in patients at risk	BP: days 1, 14, 28, and 42 of cycles 1–4 (6-week cycles); cycle 5+ days 28 and 42 ECG: cycle 1 day 1, then day 28 of every even-numbered cycle (6-week cycles) LVEF: cycle 1 day 1, then day 28 of cycle 3 then as clinically indicated	BP ECG LVEF	BP: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Regorafenib (Stivarga)	Hypertension: monitor weekly for the 1st 6 weeks then every cycle		BP	BP: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management
	Sorafenib (Nexavar)	Hypertension: monitor weekly for first 6 weeks then periodically QT prolongation: ECG in patients at risk	ECG as needed at baseline and day 1 of each cycle	BP ECG LVEF	BP: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Sunitinib (Sutent)	Hypertension: monitor Baseline and periodic evaluations of QT prolongation: consider periodic ECG monitoring in all patients; recommend monitoring if at risk LVEF should be considered at baseline and periodically as clinically indicated during therapy	BP: day 1 of all cycles ECG: baseline and cycle 1 day 28, day 1 of subsequent cycles LVEF: baseline, day 1 of subsequent cycles	BP ECG LVEF	BP: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Vandetanib (Caprelsa)	Hypertension: monitor QT prolongation: ECG at baseline, after 2–4 weeks, after 8–12 weeks, then every 3 months Monitor for s/sx of heart failure		BP ECG LVEF	BP: daily home monitoring, correlate with in-clinic visits ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡

Continued on the next page

conditions (15). A recent review by Liu et al. (27) details when and how to use GLS in cardio-oncology.

Cardiac magnetic resonance (CMR) is considered the gold standard when measuring LVEF (28), with significantly better spatial resolution compared with 2D echo (29) that leads to highly accurate and reproducible measurement of LVEF, ventricular volumes and mass (30,31). It allows scanning from multiple planes and does not make geometric assumptions like 2D echo, nor does it depend on optimal acoustic windows. Given these advantages, the American Society of Echocardiography/European Association of Cardiovascular Imaging expert consensus document recommends that CMR be considered if the calculated LVEF is near the threshold of 53%, discontinuation of chemotherapy is being considered, or echo image

TABLE 2 Continued

Drug Target	Drug	FDA-Approved Manufacturer Labeling Recommended Monitoring	Monitoring Conducted in Published Phase III Clinical Trials	Recommendations for Clinical Practice*	
				Baseline Cardiac Monitoring	Cardiac Monitoring During Treatment
Miscellaneous therapies					
	Entrectinib (Rozlytrek)	QT prolongation: ECG at baseline and periodically if at risk LVEF: baseline in patients at risk then if patient develops s/sx		ECG LVEF	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation LVEF: if s/sx of heart failure‡
	Everolimus (Afinitor)	Hypertension: no monitoring recommendations		BP Fasting lipid panel§	BP: daily home monitoring, correlate with in-clinic visits LVEF if hypertension develops to assist with management Fasting lipid panel every 6 months§
	Fedratinib (Inrebic)	Cardiac failure incidence 5%, but no monitoring recommendations		LVEF	LVEF: if s/sx of heart failure‡
	Glasdegib (Daurismo)	QT prolongation: ECG at baseline, at 1 week, then monthly × 2 months; consider monitoring more frequently in patients at risk		ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Ivosidenib (Tibsovo)	QT prolongation: ECG weekly for the first 3 weeks, then monthly		ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Niraparib (Zejula)	Monitor HR/BP monthly × 1 year and periodically thereafter		HR/BP	HR/BP: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management
	Ribociclib (Kisqali)	QT prolongation: ECG at baseline and approximately day 14 of the first cycle, then at the beginning of the second cycle		ECG	ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Ripretinib (Qinlock)	BP: monitor regularly during treatment LVEF: baseline and as clinically indicated	LVEF: baseline and every third cycle	BP LVEF	BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡
	Selpercatinib (Retevmo)	BP: baseline, after 1 week, then at least monthly QT prolongation: ECG at baseline and periodically in patients at risk for QT prolongation; more frequent monitoring with concomitant CYP3A inhibitors	Not available	BP ECG	BP: daily home monitoring, correlate with in-clinic visits LVEF: if hypertension develops to assist with management ECG: after 14 days, then as clinically indicated in those at risk† for QT prolongation
	Tretinoin (Vesanoid)	Heart failure described, but no monitoring recommendations		HR/BP LVEF	HR/BP: daily home monitoring, correlate with in-clinic visits LVEF: if s/sx of heart failure‡

*Recommendations felt to be reasonable based upon assessment of FDA labeling, monitoring in published phase III clinical trials, and clinical experience. †Patients at risk for QT prolongation include those with congenital long QT syndrome or QT ≥480 ms in females or 470 ms in males at baseline, congestive heart failure, bradyarrhythmias, electrolyte abnormalities, or those on concomitant medications known to prolong the QT interval. ‡LVEF monitoring recommended in any patient developing symptoms of heart failure such as dyspnea, edema, worsening fatigue, jugular venous distention, etc. §Aspirin use is reasonable, unless contraindicated, in patients with atherosclerosis.

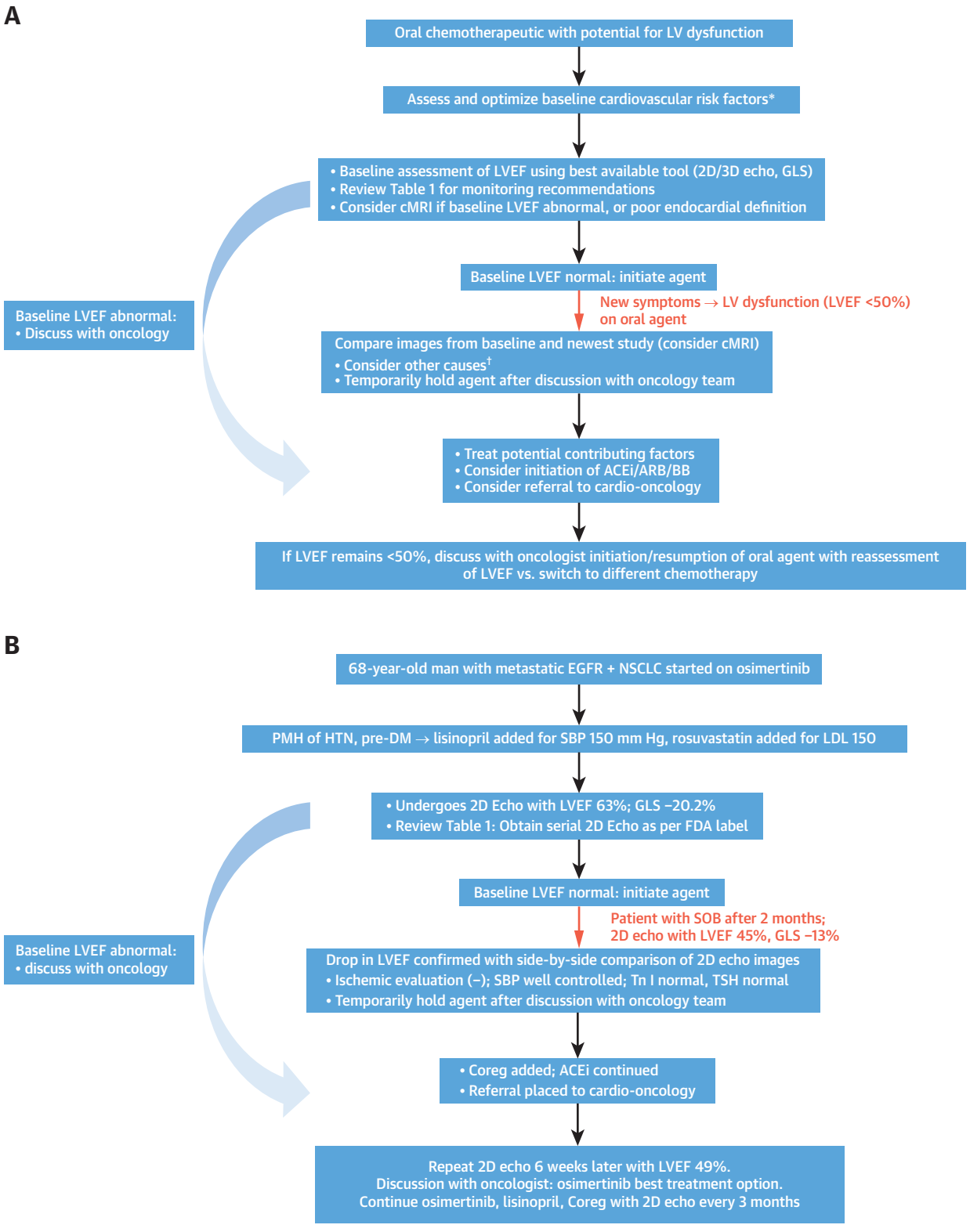
AV = atrioventricular; BP = blood pressure; ECG = electrocardiogram; HR = heart rate; LVEF = left ventricular ejection fraction; PI = package insert; s/sx = signs or symptoms; VS = vital signs; other abbreviations as in Table 1.

quality is suboptimal (15). CMR also offers information on tissue characterization such as presence of myocardial fibrosis via T1 and T2 mapping techniques, calculation of extracellular volume fraction, or serial changes in myocardial strain that may aid in detection of subclinical CTRCD (32-34). Disadvantages to CMR include decreased availability, patient claustrophobia, and contraindication in patients with ferromagnetic hardware such as breast tissue expanders (15).

CARDIAC BIOMARKERS

Biomarkers have the potential to identify subclinical cardiotoxicity before the onset of HF. Troponin I is sensitive and specific for myocardial injury (35), and

FIGURE 1 **LV Dysfunction Due to Oral Antineoplastic Agents**



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has been shown to be elevated in individuals receiving traditional chemotherapy such as anthracyclines and trastuzumab, as well as newer agents such as TKIs (36–40). High-sensitivity troponin has a high negative predictive value for LVEF decline, thus identifying patients who may be at low risk for CTRCD (15). One study suggested that GLS coupled with ultrasensitive troponin increased the sensitivity in detecting CTRCD (38). More research is needed with regard to timing of troponin draw, optimal cutoff values to enhance diagnostic performance, and ways to increase specificity of a positive troponin value. Although FDA labels do not specifically mention measurement of cardiac biomarkers in the setting of oral agents that can cause LV dysfunction, growing number of published reports supports their use in patients with high baseline CV risk, as well as serial monitoring in patients requiring long-term chemotherapy to reduce the burden/cost of cardiac imaging in this setting (41).

MANAGEMENT OF LV DYSFUNCTION

Recognition of a decreased LVEF, even asymptomatic, is important because treatment with beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers (ARBs) have been shown to improve both LVEF and symptoms of HF, as well as prevent the onset of symptoms before they occur (42). In the setting of LV dysfunction, implementation of these therapies is a Class I indication according to the ACC/AHA guidelines (42). A few smaller studies have also demonstrated the benefit of these medications, including sacubitril/valsartan, in the setting of anthracycline and/or trastuzumab exposure (43–45). Although data are lacking with oral agents, utilization of these cardioprotective therapies may also have a role in the prevention and treatment of LV dysfunction in this setting.

Figure 1 shows a proposed LV function monitoring algorithm and a clinical case highlighting management strategies. Clinical pearls for LV dysfunction are presented in **Table 3**. In addition to providing appropriate HF care, ongoing multidisciplinary collaboration between the oncology and CV team is important to determine the risk/benefit of continuing cancer therapy. Discontinuation of oncological therapy can have significant implications on cancer mortality as a recent study demonstrated increased risk of breast cancer recurrence with trastuzumab interruption (46). However, continuation of trastuzumab was also recently shown to be safe in patients with asymptomatic LV dysfunction as long as they were being treated with appropriate cardioprotective medications and closely monitored by a cardiologist (47,48). Lastly, when initiating oral agents, recent guidelines recommend a similar approach to initiation of anthracyclines or trastuzumab, including aggressive risk factor modification and consideration of switching baseline antihypertensive therapy to potentially cardioprotective medications such as beta-blockers and neurohormonal modulators, until more data become available (6,49).

TABLE 3 Clinical Pearls: LV Dysfunction Due to Oral Antineoplastic Agents

Obtain baseline LVEF with best available technique (for most, 2D echo with volumetric measurement by Simpson's biplane) before initiation of cardiotoxic oral therapy. Repeat imaging using the same modality with new patient symptoms or change in clinical status. Study images should be reviewed and compared with baseline images to ensure that LVEF variations are truly present.
Consider CMR if discrepancies in sequential LVEF are present, borderline LVEF is noted, or echocardiogram imaging windows are poor despite contrast administration.
When LV dysfunction is noted (at baseline or after initiation of therapy), recommend ruling out ischemic and reversible non-ischemic causes. Consider referring to cardio-oncology at onset of LV dysfunction, or sooner.
ACE inhibitor/ARB/BB used to treat other forms of heart failure with reduced LVEF should also be initiated in the setting of LV dysfunction with oral agents.
Multidisciplinary approach is essential when LV dysfunction occurs, weighing the risk versus benefit of continuing with oral chemotherapy.

2D = 2-dimensional; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BB = beta-blocker; CMR = cardiac magnetic resonance; LV = left ventricular; LVEF = left ventricular ejection fraction.

ARRHYTHMIAS AND QT PROLONGATION: MONITORING AND MANAGEMENT

ATRIAL AND VENTRICULAR TACHYARRHYTHMIAS.

Patients with cancer frequently exhibit tachycardia due to multiple factors. Often, this is sinus

FIGURE 1 Continued

(A) Algorithm for LV dysfunction monitoring and management for oral antineoplastic agents. **(B)** Clinical scenario for LV dysfunction due to an oral antineoplastic agent. *Baseline risk factors: family history of cardiovascular disease, exercise tolerance, hypertension, lipids, glucose, tobacco, obesity. †Causes: ischemia, hypertension, arrhythmia, myocarditis, thyroid abnormalities, genetic. 2D/3D = 2-dimensional/3-dimensional; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; BB = beta-blocker; cMRI = cardiac magnetic resonance imaging; DM = diabetes mellitus; EGFR = epidermal growth factor receptor; FDA = U.S. Food and Drug Administration; GLS = global longitudinal strain; HTN = hypertension; LDL = low-density lipoprotein; LV = left ventricular; LVEF = left ventricular ejection fraction; NSCLC = non-small cell lung cancer; PMH = past medical history; SBP = systolic blood pressure; SOB = shortness of breath; Tn I = troponin I; TSH = thyroid stimulating hormone.

TABLE 4 Drugs to Avoid (if Possible) in Patients Taking Oral Antineoplastic Agents With QT-Prolonging Potential

Anti-Infective Agents	Antiemetics	Antidepressants	Antipsychotic Agents	Antiarrhythmic Agents	Other
Fluoroquinolones	Domperidone	SSRIs	Clozapine	Amiodarone	Fosphenytoin
Ciprofloxacin	Droperidol	Citalopram	Thioridazine	Disopyramide	Methadone
Levofloxacin	Ondansetron	Escitalopram	Haloperidol	Dofetilide	Methylphenidate
Moxifloxacin		Fluoxetine	Quetiapine	Dronedarone	Phenytoin
Macrolide antibiotics		Paroxetine	Risperidone	Ibutilide	
Azithromycin		Sertraline	Ziprasidone	Procainamide	
Clarithromycin		Trazodone		Quinidine	
Erythromycin		SNRIs		Sotalol	
Azole antifungals		Venlafaxine			
Fluconazole		TCAs			
Itraconazole		Amitriptyline			
Ketoconazole		Clomipramine			
Voriconazole		Desipramine			
Antimalarials		Doxepin			
Chloroquine		Imipramine			
Hydroxychloroquine		Nortriptyline			
Mefloquine					

SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

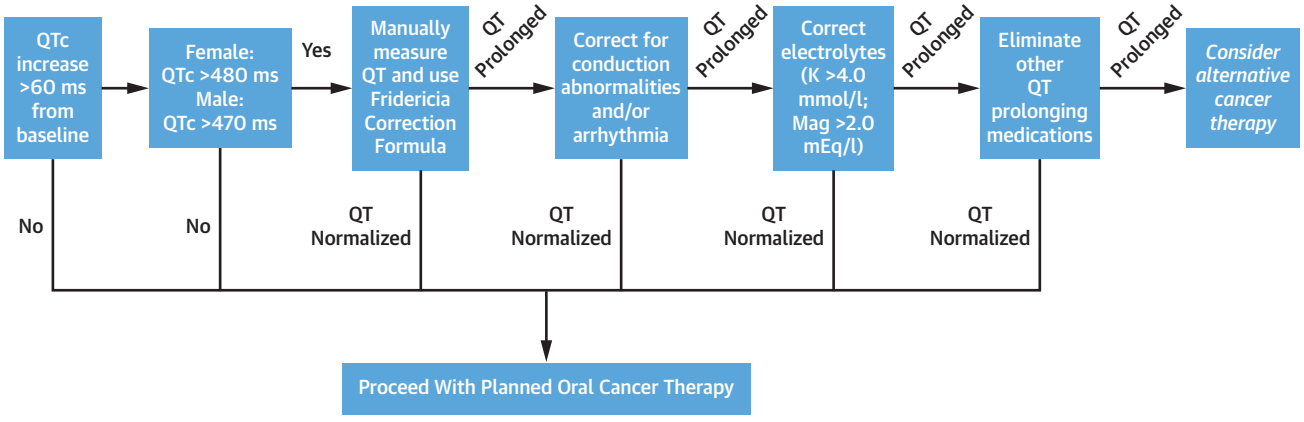
tachycardia, which can either be a manifestation of autonomic dysfunction from cancer therapeutics or a consequence of another medical issue (i.e., pulmonary embolus, dehydration, pain, or infection). Various oral agents have been associated with both atrial and ventricular tachyarrhythmias, although the exact incidence for many of these treatments is not known (**Table 1,** Supplemental Table 2) (50). A more systematic approach to arrhythmia evaluation is necessary to better quantitate the burden and to help develop appropriate treatment and prevention strategies. In general, cancer patients with tachycardia should be referred for an ECG.

Ibrutinib is a small molecule inhibitor of the Bruton's tyrosine kinase used in the treatment of various B-cell malignancies and has been linked to both atrial and ventricular arrhythmias. Rates of AF associated with ibrutinib range from 5% to 15%, with several systematic reviews and meta-analyses reporting the relative risk to be between 3.5 and 8.8 (51–53). Management of ibrutinib-associated AF can be challenging. In general, non-dihydropyridine calcium-channel blockers (NDCCB) should be avoided, given interactions with cytochrome P450 (CYP3A4), which can lead to increased concentrations of ibrutinib. Similarly, digoxin should also be used with caution because levels can increase in the setting of ibrutinib due to the latter drug's inhibition of p-glycoprotein. The majority of antiarrhythmic drugs have similar interactions with these metabolic pathways. Overall, beta-blockers are considered relatively safe. Moreover, the use of anticoagulation to minimize the risk of thromboembolism in the setting of AF is challenging, because ibrutinib increases the risk of bleeding due to its inhibitory effects on platelet function. Vitamin K antagonists should not be used due to increased rates of subdural hematomas reported in mantle cell lymphoma trials. The direct oral anticoagulant agents appear to be relatively safe, though dedicated studies in this population are lacking and interactions with both CYP3A4 and p-glycoprotein can lead to increased drug concentrations and bleeding. Pharmacy involvement can be especially helpful in determining the optimal treatment (54,55).

More recently, ventricular arrhythmias have also been reported with ibrutinib, though the incidence is significantly lower than AF (56). The incidence of ventricular arrhythmias has been estimated at 596 per 100,000 person-years (57). The ventricular arrhythmias are not related to QT prolongation, and in fact, data suggest QT shortening with ibrutinib (58). The mechanism of ibrutinib-associated arrhythmogenesis is not well-established but may be related to on-target inhibition of cardiac BTK, off-target inhibition of the phosphoinositide 3-kinase (PI3K) pathway or C-terminal SRC kinase, or enhanced automaticity from effects on calcium-channel handling (59,60).

BRADYARRHYTHMIAS. Although bradycardia can occur with oral agents, severe or symptomatic conduction disease necessitating pacemaker placement is rare. Bradycardia is most associated with the anaplastic lymphoma kinase (ALK) inhibitors, crizotinib and ceritinib, which are used to treat non-small cell lung cancer. In most cases, patients are asymptomatic; however, in rare cases, dose reduction is necessary (61). More commonly, bradycardia results from drug-drug interactions such as NDCCB and chemotherapeutic agents that have an impact on the

FIGURE 2 **Algorithm for QT-Interval Monitoring in Patients Receiving Oral Antineoplastic Agents**



If baseline QT interval is prolonged, manual measurement and Fridericia correction should be completed. If QT increases by more than 60 ms from baseline to a level beyond 480 ms for females and 470 ms for males, QT should be corrected for conduction abnormalities/arrhythmias, electrolytes addressed, and concomitant QT-prolonging medications changed before proceeding with oral chemotherapy.

CYP3A4 system. Similarly, imatinib (used to treat chronic myeloid leukemia) and abiraterone (anti-androgen for metastatic prostate cancer) both have an impact on CYP2D6 metabolism, which can increase concentrations of beta-blockers leading to bradycardia (62,63). It should also be recognized that medical conditions such as hypothyroidism, obstructive sleep apnea, and increased vagal tone from vomiting can lead to bradycardia and should be considered in the differential of a patient with a low heart rate (64).

QT PROLONGATION. Other electrophysiological abnormalities such as QT prolongation are also frequently encountered with oral antineoplastic agents (**Table 1,** Supplemental Table 3) (50). Heterogeneity in ventricular repolarization can predispose to the life-threatening ventricular arrhythmia torsade de pointes (TdP). It is well recognized that the QT interval is a relatively poor surrogate for identifying this phenomenon. However, there are few other easily measured alternatives, and therefore, the QT interval has been widely adopted to assess risk.

Accurate assessment of the QT interval can be challenging, and over-reliance on the electronic QTc reported by the ECG machine can lead to inaccurate values and adversely affect patient care (Supplemental Table 6) (65). For these reasons, it is recommended that oncologists partner with a cardiologist/cardio-oncologist to help with the appropriate measurement and management of the QT interval. The Bazett (QTcB) formula is the most frequently used algorithm for electronic ECG assessment of the QT interval and is therefore familiar to the majority of clinicians. Unfortunately, the QTcB is also the correction formula most prone to error as it significantly overcorrects at faster heart rates and undercorrects at slower heart rates. Alternatively, the Fridericia (QTcF) formula provides more accurate values during tachycardia or bradycardia. Although these methods have not been compared directly to determine which is most accurate for predicting TdP, it is generally recommended to use the QTcF when evaluating patients with cancer (66,67).

QT prolongation frequently results from the on-target or off-target effects of various oncological and nononcological pharmaceuticals. Most commonly this is due to direct inhibition of the IK_r potassium channels; however, effects on sodium channels or intracellular signaling pathways such as the PI3K pathway can also lead to prolongation of repolarization (68). Arsenic is the cancer therapy most associated with QT prolongation although many oral agents can also affect cardiac repolarization (69). Among the oral agents, nilotinib, vandetanib, and ribociclib are notable for their QT-prolonging effects. Nilotinib, a TKI used to treat chronic myeloid leukemia, carries an FDA black box warning for QT prolongation and sudden cardiac death, though the actual event rate is

TABLE 5 Clinical Pearls: Impact of Oral Antineoplastic Agents on QT Interval and Arrhythmias

The Fridericia (QTcF) formula is recommended when evaluating the QT interval in patients with cancer.
Although several oral antineoplastic agents can prolong the QT interval, the risk of torsade de pointes is low.
Variable definitions for QT prolongation in oncology trials remain a barrier to implementation of standardized monitoring protocols.
Tachycardia in a patient with cancer should prompt an electrocardiogram because this may represent sinus or a true atrial or ventricular arrhythmia.
Atrial fibrillation and ventricular tachycardia are known arrhythmic complications of ibrutinib and require a nuanced (or individualized) management approach.

approximately 0.3% with a mean prolongation of the QTc of only 5 to 15 ms (70). QT prolongation occurs more often with vandetanib (16% to 18%) with a weighted incidence of QT interval >500 ms at 2.6% (71). Despite their potential to prolong the QT interval, a recent meta-analysis of chemotherapeutics demonstrated these QT-prolonging effects were not predictive of an increased risk of ventricular arrhythmias (71).

Patients with cancer are at particular risk for the additive effects of multiple QT-prolonging medications given concurrently, including oral chemotherapeutic agents, antibiotics, antifungals, psychiatric medications, and antiemetics. Because the oncological agents are essential and cannot be easily changed, alternative treatments that do not prolong the QT interval should be considered for other concurrent conditions (**Table 4**). If these agents are essential, then close monitoring for QT-interval prolongation is essential (67).

Management of QT prolongation requires a nuanced approach, focusing on both treatment modification as well as addressing comorbid conditions (**Figure 2**). Clinical pearls for QT prolongation are presented in **Table 5**. Collaboration with cardiologists, oncologists, and pharmacists is essential to minimize the risk of serious adverse events and to avoid unnecessary drug-drug interactions. Electrolyte abnormalities should be corrected: magnesium should be maintained at a level >2.0 mEq/l and potassium at >4.0 mmol/l. If a patient develops sustained TdP, advanced cardiac life support should be quickly initiated with prompt defibrillation. Moreover, magnesium should be infused, and mechanisms to increase the heart rate should be initiated (i.e., chronotropic agents such as dopamine or overdrive pacing).

The lack of a standardized definition of QT prolongation for cancer therapeutics makes the implementation of screening and monitoring programs challenging. At this point, relying on FDA drug label recommendations is necessary. For oral agents that can prolong the QT, we recommend a baseline ECG, ECG at 14 days, and repeat ECG as clinically indicated in those at risk (**Table 2**). Programming the ECG machines to calculate the Fridericia formula, if possible, would be an important first step. Finally, if the QT remains prolonged, the patient should be referred to a cardio-oncologist or electrophysiologist for further evaluation and management.

ARRHYTHMIA AND QT MONITORING. Traditionally, arrhythmia and QT monitoring has required the use of 12-lead ECG at specified time points or when symptoms necessitate evaluation. In the current COVID environment in which social distancing and minimizing direct interactions are often necessary, it is prudent to establish monitoring algorithms that maintain patient safety while minimizing overtesting. Moreover, leveraging novel technology, including the use of patch monitors, implantable loop recorders, and wearable devices, is becoming increasingly attractive to monitor for arrhythmic complications, including QT interval prolongation. The Apple Watch (Apple, Cupertino, California) can provide single-lead ECG data with excellent fidelity, and the KardiaMobile 6L developed by AliveCor (Mountain View, California) for AF detection recently received emergency clearance from the FDA for QT monitoring of COVID-19 patients. Application of these devices could prove useful for cardio-oncology patients requiring arrhythmia and QT monitoring; however, dedicated studies in this population are thus far lacking (72,73).

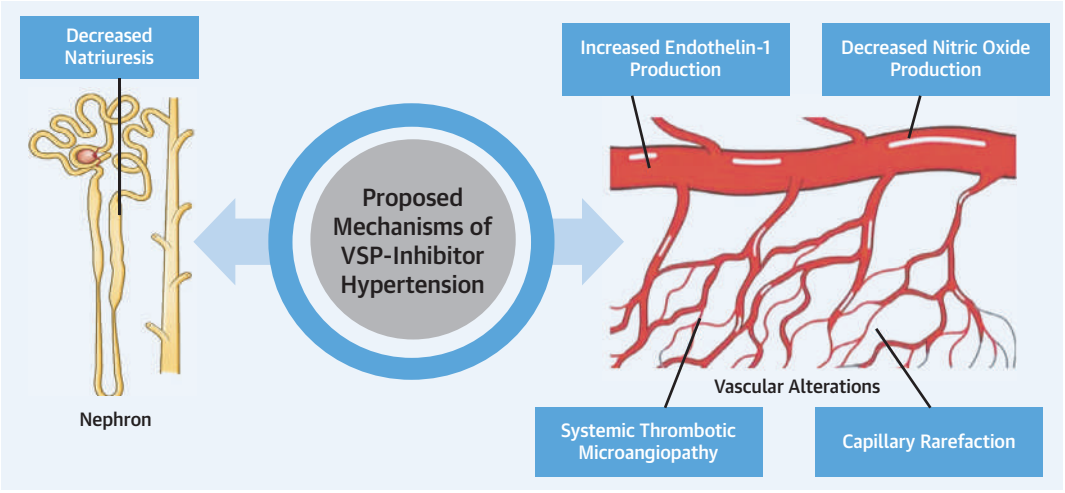
HYPERTENSION: MONITORING AND MANAGEMENT

Vascular signaling pathway (VSP) inhibitors, including vascular endothelial growth factor (VEGF) inhibitors, have been associated with the development and/or worsening of hypertension (**Table 1**, Supplemental Table 4). In addition, commonly used therapies such as alkylating agents (e.g., cyclophosphamide) and adjuvant oral therapies also accentuate hypertension. This side effect can negatively affect cancer efficacy outcomes as clinicians decrease antineoplastic agent dosing or remove these agents from regimens (74).

INCIDENCE OF HYPERTENSION WITH ORAL VSP INHIBITORS

The incidence and prevalence of hypertension with VSP inhibitors, specifically TKIs, may be inaccurate due to a lack of standardization of hypertension classification and concrete definitions in clinical trials

FIGURE 3 VSP-Inhibitor Hypertension



Proposed mechanisms include decreased nitric oxide production leading to increased oxidative stress and subsequent capillary rarefaction and possible systemic thrombotic microangiopathy that partly eliminates an important resistance reduction mechanism. In the nephron, these cellular mechanisms lead to impaired natriuresis. VSP = vascular signaling pathway.

(75). Nonetheless, VSP inhibitor-induced hypertension was noted in 30% to 80% of patients (76). A meta-analysis of 77 studies reported a number needed to harm of 6 for the development of hypertension and 17 for severe hypertension (77). Higher incidence rates have been noted in metastatic renal cell carcinoma (mRCC) trials (78) and with more potent agents such as axitinib (79). The hypertensive effect is not necessarily dose-related in all cases (80). In a study of normotensive patients receiving sorafenib for advanced solid tumors, dose escalations of sorafenib were not associated with elevations in blood pressure (BP) uniformly, but rather showed that some patients had a hypertensive response, whereas others did not, independent of sorafenib plasma concentrations. Complicating our ability to make concrete associations, the method of BP measurement varies significantly across trials. This inconsistency is of great importance, given the incidence of white coat hypertension (WCH) noted in patients with cancer. In a retrospective study comparing BP measurements completed by physicians versus nurses in breast cancer patients, WCH was found in 59% of patients, with a greater propensity for diastolic WCH (81). More studies are warranted regarding the incidence, clinical significance and management of WCH in patients with cancer. Moreover, this observation emphasizes the need for out-of-clinic BP measurements rather than total dependence on in-clinic BP values.

The wide range of reported incidence of hypertension with these agents may largely be due to the differences in measurement methods which included in-office, home measurements, and 24-h ambulatory BP monitoring. Of these, 24-h ambulatory BP monitoring gives us the most detailed glimpse of the effect of these agents. In patients with mRCC on sunitinib, there was an average increase in systolic/diastolic blood pressure of 14/11 mm Hg, respectively. This study demonstrated that some patients' BPs never returned to baseline after completion of therapy. Rather, a new baseline was noted similar to BPs recorded after the first cycle of sunitinib (82). This points toward a more durable change in vascular biology in certain patients following exposure to VSP inhibition.

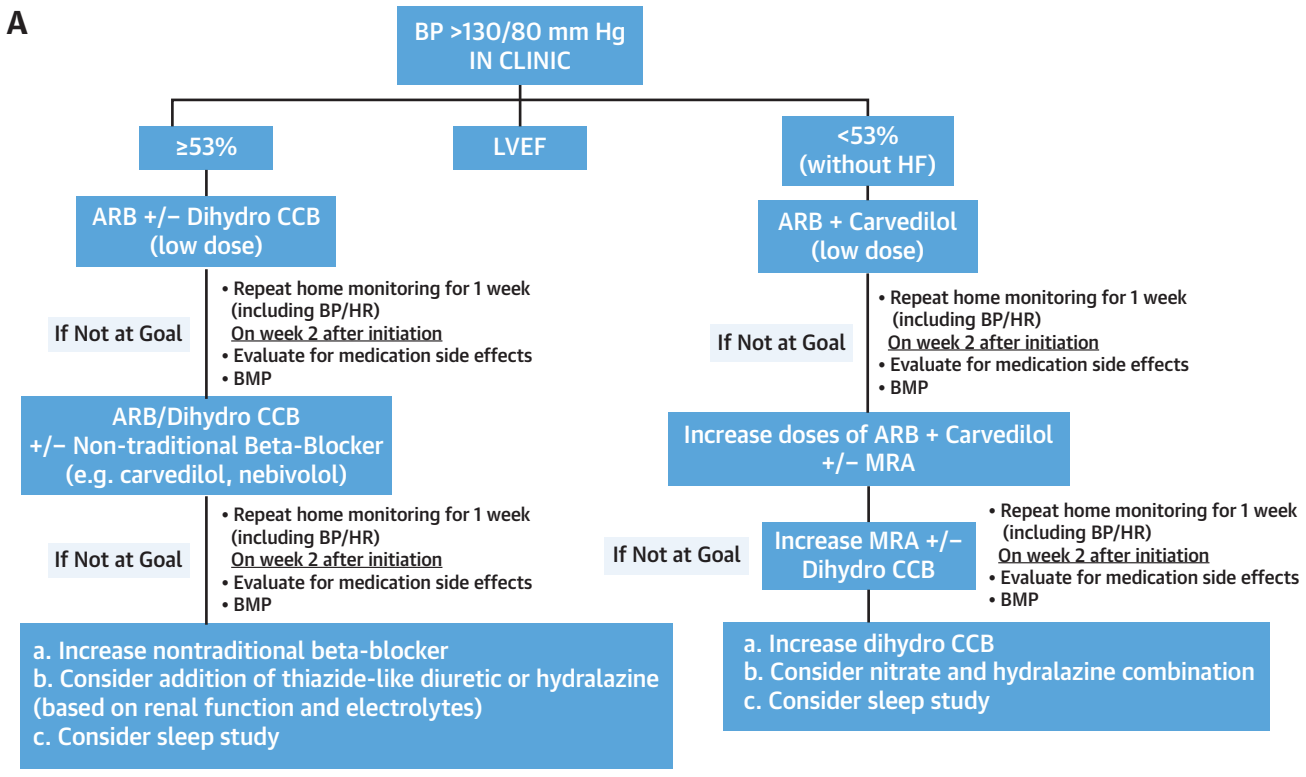
MECHANISMS OF HYPERTENSION

Certain patient characteristics have been associated with the development of hypertension with oral agents. These include pre-existing hypertension, higher body mass index (≥25 kg/m^2), higher age (≥60 years), and presence of mRCC (83). VSP inhibitory agents increase BP through multiple mechanisms that are summarized in **Figure 3** (84–88).

HYPERTENSION: A SIGNAL FOR EFFICACY?

Because the mechanisms of hypertension are a direct result of the therapeutic pathways of VSP inhibitors,

FIGURE 4 Oral Antineoplastic Agent–Induced Hypertension



B

67-year-old male on sorafenib for treatment of metastatic renal cell carcinoma has blood pressures that are consistently higher than 160/100 mm Hg in various clinic settings. Echocardiogram reveals an ejection fraction of 50-55%. Resting heart rate is 78 beats/min. He is on amlodipine 5 mg daily.

Home blood pressures are checked twice a day using an automated blood pressure monitor. Average blood pressure is 162/98 mm Hg.

Patient was placed on carvedilol 6.25 mg twice a day and losartan 50 mg daily. A BMP is checked 2 weeks later which is normal with a potassium of 3.9.

1 week later, a home blood pressure log is obtained which reveals a reduction in average pressures to 145/83 mm Hg. Average heart rate is 56 beats/min. An increase in losartan to 100 mg daily is made while the amlodipine is increased to 10 mg.

2 weeks later, a home blood pressure log shows the average blood pressure at 128/76 mm Hg. Repeat BMP reveals a normal creatinine and potassium of 4.4 mEq/l. The patient complains of some mild lower extremity edema since going on the higher dose of amlodipine.

(A) Treatment algorithm for oral antineoplastic agent-induced hypertension based upon LVEF. For LVEF ≥53%, initiate ARB in combination with Dihydro CCB. For LVEF <53% without signs of symptoms of HF, initiate ARB in combination with carvedilol. **(B)** Clinical scenario: Management of antineoplastic agent-induced hypertension. BMP = basic metabolic panel; bpm = beats/minute; Dihydro CCB = dihydropyridine calcium-channel blocker (e.g., amlodipine); HF = heart failure; HR = heart rate; MRA = mineralocorticoid receptor antagonist (e.g., spironolactone); other abbreviations as in Figure 1.

the notion that the presence of hypertension itself being a biomarker of efficacy can be postulated (89). In 1 study using pooled data from multiple trials, an association between longer overall survival and the presence of hypertension was noted in patients undergoing treatment with sunitinib for mRCC (90). In this study, median overall survival was 30.9 months in patients who developed therapy-induced hypertension versus 7.2 months in patients who did not. Of the 544 patients included in the efficacy analysis, 58% of patients had systolic-defined hypertension, and 48% had diastolic-defined hypertension by the end of cycle 1, whereas 80% had systolic-defined hypertension and 68% had diastolic-defined hypertension by the end of cycle 2. Although overall survival was noted to be higher in patients with a hypertensive response, more renal side effects were noted. By contrast, in a smaller study, no significant association was noted between the development of new/worsening hypertension and worsening renal function 30 days after initiation of any TKI for mRCC (91).

Although there is no clear-cut evidence that the treatment of TKI-induced hypertension will worsen antitumor response, there is, however, a signal toward ARBs playing a synergistic role in efficacy leading to survival benefits. The rationale for this lies within the mounting evidence that angiotensin II may play a critical role in VEGF-dependent angiogenesis. Preclinical data suggest that angiotensin II regulates VEGF and VEGF receptors after binding to angiotensin II type 1 and type II receptors (92). In a large pooled analysis from phase II and phase III studies involving axitinib, sorafenib, and sunitinib, the use of antihypertensive agents was examined for an association with survival and objective response rates (93). Overall survival was longer in patients receiving ARB therapy compared with those using other antihypertensive agents. Moreover, progression-free survival was longer in ARB users in comparison to those on non-ARB antihypertensive agents. Multivariate analyses highlighted the lack of ARB use, failure to develop treatment-associated hypertension, and individual cancer risk factors as independent predictors of worse overall survival.

MANAGEMENT OF VSP-INDUCED HYPERTENSION

DIAGNOSIS. The first indication of VSP-induced hypertension is often an elevated BP in the clinic. Tips to ensure an accurate BP is obtained are reviewed in Supplemental Table 7. Understandably, these rigorous steps are not undertaken at most busy clinics, leading to spuriously high in-office BPs.

TABLE 6 Clinical Pearls: Hypertension Due to Oral Antineoplastic Agents

Hypertension is a common adverse effect of oral antineoplastic agents owing to common molecular pathways.
The rates of white coat hypertension may be higher in the cancer population, and hence, greater attention must be placed on at-home blood pressure measurements.
Identification of secondary causes of hypertension should be addressed, including untreated obstructive sleep apnea, which may be under-recognized in this population.
The use of lower-dose, antihypertensive combination therapy may have inherent advantages including greater efficacy with lower side-effect profile.

Moreover, rates of WCH have been proposed to be higher in the cancer population (94). A greater reliance on nonclinic BPs may lead to a better understanding of whether a patient is truly hypertensive. A special population worth mentioning includes patients who have undergone unilateral or bilateral mastectomy in which axillary lymph node dissection was performed. Although guidelines have called for avoidance of BP measurements on the ipsilateral arm of the axillary lymph node dissection (95), these measurements have not been shown to prolong lymphedema or increase rates of infection (96,97). Lymphedema also does not compromise accuracy of BP measurement so long as an appropriately sized cuff is used. Some clinics have opted for the use of wrist or finger cuff techniques for BP monitoring. Several limitations of these cuffs include: internal sensors must be placed directly over the radial artery to obtain an accurate reading, the monitor may shift with pressure inflation causing the sensor to deviate from its target spot, and they have been noted to provide lower values than those obtained by more conventional methods (98).

Given the myriad issues confounding accurate in-clinic BP measurement, greater importance has been placed on home BP values. Patients should be instructed to take their BP twice a day, once upon getting up before taking morning medications and once before bedtime. Patients are also encouraged to purchase a BP monitor that can record heart rate to aid in detection of arrhythmias and ectopy that can be seen in this population. An average daytime home BP ≥130/80 mm Hg would be considered hypertensive (99). The daily exposure of oral antineoplastic agents versus cyclical exposure to parenteral agents further highlights the importance of home BP monitoring. The addition of nonsteroidal anti-inflammatory drugs and corticosteroids, as well as pain, can also cause BP elevation. In some cases, the lack of hypertension may speak toward issues with adherence to both antineoplastic and/or antihypertensive agents.

TREATMENT. For the treatment of VSP-induced hypertension, action algorithms have been proposed by

experts and medical societies (94,100). **Figure 4** shows an algorithm and a clinical scenario outlining steps that can be taken to ensure optimal management in the cardio-oncology patient. It is important to recognize that there is lack of specific trial data examining optimal agents for therapy and that much of the treatment of VSP-induced hypertension has relied upon relatively theoretical benefits. As a result, ARBs, due to their proposed efficacy signal (93,101) and renal benefits in attenuating the progression of proteinuria and renal dysfunction, have been considered first-line agents (102). Although most clinicians in the United States use generic ARBs (losartan or valsartan) as their agents of choice (103), there are significant intraclass differences in BP reduction, hence, choosing nongeneric ARBs (irbesartan or olmesartan) may have benefits in selected patients (104) (Supplemental Table 8). Dihydropyridine calcium-channel blockers (DCCB) (e.g., amlodipine, felodipine) have also been espoused as first-line agents due to direct vasodilatory effects via arteriolar smooth muscle (105). Despite their efficacy, these agents can have a bothersome side effect of lower extremity edema. This is a particularly cumbersome feature, given that many oral chemotherapeutic agents (specifically TKIs) will leave patients at a higher risk of developing lower extremity edema (106). Independently, DCCB edema frequency is dose-dependent and has been noted to occur in 5% to 70% of recipients (107,108). Hence, the strategy of using an ARB alongside a DCCB as upfront therapy may have certain advantages. The practice of initiating lower doses of both agents (preferably in fixed-dose formulations) could minimize dose-dependent side effects and possibly minimize lower extremity edema as the venodilatory effect of ARBs may improve blood flow throughput through the lower extremity circulatory system (109,110). In addition, nocturnal administration of the DCCB may also minimize edema (111). Diuretic agents have had limited effect on this edema due to the vasodilatory etiology and can additively worsen renal dysfunction and electrolyte abnormalities.

Conversely, the use of NDCCB (e.g., verapamil, diltiazem) is to be avoided secondary to high CYP450 interactions (most commonly 3A4) with multiple oral agents, thereby increasing VSP inhibitor toxicity potential (112). Nontraditional beta-blockers may have a role in the treatment of VSP-related hypertension. Carvedilol, both an alpha- and beta-blocker, has the benefit of having free-radical binding properties (113). It is this effect that has been postulated as its rationale for efficacy for protection against the cardiotoxic effects of other chemotherapeutic agents such as anthracyclines (114). Similarly, nebivolol, a cardioselective beta-blocker, possesses nitric oxide-mediated vasodilatory effects (115). This latter effect may be conveniently attractive against the nitric oxide-depleting effects of VSP inhibitory agents. Prospective studies to understand whether these theoretical advantages translate to improved clinical responses are warranted. Clinical pearls for VSP hypertension are presented in **Table 6**.

ONCOLOGIST PERSPECTIVE

Patients receiving intravenous cancer therapy are closely monitored (e.g., heart rate and BP) in an infusion center for potential acute cancer treatment-related toxicity. However, familiarity with and monitoring of cardiovascular toxicities associated with oral targeted therapies is more challenging. The American Society of Clinical Oncology published guidelines for prevention and monitoring of cardiac dysfunction in patients undergoing cancer therapy (49). The National Comprehensive Cancer Network guideline also recommends monitoring for CV complications as an important part of survivorship (116). However, these guidelines focused mainly on parental chemotherapeutics such as anthracyclines and HER2 targeted therapies. A multidisciplinary effort is needed to provide guidance on CV monitoring strategies for patients prescribed oral targeted agents, given the number of new drugs with potential for CV toxicity being introduced into clinical practice each year.

To the CV health professionals looking to establish CV monitoring algorithms for oral agents, we recommend they: 1) emphasize to the oncologist that the goal of CV monitoring is not to stop anticancer therapy but rather to continue it safely; 2) engage the oncology pharmacist and/or oncology nurse navigator to help set up QT/arrhythmia, LV dysfunction, and hypertension monitoring algorithms/treatment plans, ideally embedded within the electronic medical record; 3) have an action plan when CV toxicity occurs and communicate promptly with the oncologist; 4) establish a rapid referral process and/or e-consult to allow for more seamless care and prevent delays in treatment; 5) attend oncology tumor boards to show the value that the cardiologist brings to the treatment team; and 6) use telemedicine when appropriate to treat vulnerable oncology patients during the COVID-19 pandemic. Following these steps will enable a care continuum and risk minimization strategy, allow for immediate interventions in the event of complications, and provide the best care for patients with cancer.

CONCLUSIONS/FUTURE DIRECTIONS

Oral molecular targeted antineoplastic agents are increasingly being used in the treatment of cancers. These agents target a variety of molecular pathways, and their CV side effects are heterogeneous, spanning from hypertension, LV dysfunction, to AF and QT prolongation. Given their outpatient administration and often prolonged use, in particular in the setting of advanced cancer, health care providers are increasingly likely to encounter patients receiving these agents in their daily practice. Although the number of cardio-oncology statements and guideline documents have significantly increased over the past few years, the exponential growth of approved novel oral targeted agents continues to create unique challenges.

First, very few of these agents had prospectively defined CV endpoints included in the clinical trials that led to their approval (117). This is not surprising, given that early-phase trials of new therapeutics often enroll patients with late-stage cancer who have relatively short survival expectations. Even in registration trials that are longer, there are multiple challenges with preexisting CV disease and exposure to multiple cancer agents, not only the trial drug (117). Finally, there are challenges with definition and adjudication of adverse effects using the National Cancer Institute Common Terminology Criteria for Adverse Events, which do not follow contemporary CV disease definitions. Together, these challenges have resulted in discrepancies between interpretation of incidence of CV events and professional society recommendations for assessment and monitoring (2).

In our paper, we have aimed to provide easy access to FDA recommendations for CV monitoring of oral cancer therapeutics that are not readily available in previously published documents, as well as to provide a practical approach to management of CV adverse events, including LV dysfunction, hypertension, and QT prolongation/arrhythmias. As survival in patients with cancer continues to improve, the relevance of early detection, management, and/or prevention of CV effects will continue to increase. Involvement of cardio-oncologists in oncology clinical trial design will be important for prospective definitions of clinically relevant CV effects and endpoints and more accurate adverse effect adjudication. We look forward to further research that will guide regulatory and clinical practice recommendations and confirm the overall benefit to clinical outcomes with this multidisciplinary approach.

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REFERENCES

1. Saleh Y, Abdelkarim O, Herzallah K, Abela GS. Anthracycline-induced cardiotoxicity: mechanisms of action, incidence, risk factors, prevention, and treatment. Heart Fail Rev 2020 May 14 [E-pub ahead of print].

2. Kenigsberg B, Wellstein A, Barac A. Left ventricular dysfunction in cancer treatment: is it relevant? J Am Coll Cardiol HF 2018;6:87–95.

3. Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline update. J Clin Oncol 2020;38:496–520.

4. El-Dabh A, Acharya D. EXPRESS: pulmonary hypertension with dasatinib and other tyrosine kinase inhibitors. Pulm Circ 2019 Jul 5 [E-pub ahead of print].

5. Lyon AR, Dent S, Stanway S, et al. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. Eur J Heart Fail 2020;22:1945–60.

6. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol 2020;31:171–90.

7. Jones DN, Jordan JH, Melendez GC, et al. Frequency of transition from stage A to stage B heart failure after initiating potentially cardiotoxic chemotherapy. J Am Coll Cardiol HF 2018;6:1023–32.

8. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc 2014;89:1287–306.

9. Alexandre J, Cautela J, Ederhy S, et al. Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European Cardio-Oncology guidelines. J Am Heart Assoc 2020;9:e018403.

10. Cuddy S, Payne DL, Murphy DJ, et al. Incidental coronary artery calcification in cancer imaging. J Am Coll Cardiol CardioOnc 2019;1:135–7.

11. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011–9.

12. Cross DA, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046–61.

13. Gottdiener JS, Mathisen DJ, Borer JS, et al. Doxorubicin cardiotoxicity: assessment of late left ventricular dysfunction by radionuclide cineangiography. Ann Intern Med 1981;94:430–5.

14. Huang H, Nijjar PS, Misialek JR, et al. Accuracy of left ventricular ejection fraction by contemporary multiple gated acquisition scanning in patients with cancer: comparison with cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2017;19:34.

15. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2014;27:911–39.

16. Ewer MS, Herson J. False positive cardiotoxicity events in cancer-related clinical trials: risks related to imperfect noninvasive parameters. Chemotherapy 2018;63:324–9.

17. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovic ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol 2013;61:77–84.

18. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group. J Am Soc Echocardiogr 2005;18:1440–63.

19. Mulvagh SL, Rakowski H, Vannan MA, et al. American Society of Echocardiography consensus statement on the clinical applications of ultrasonic contrast agents in echocardiography. J Am Soc Echocardiogr 2008;21:1179–201.

20. Senior R, Becher H, Monaghan M, et al. Contrast echocardiography: evidence-based recommendations by European Association of Echocardiography. Eur J Echocardiogr 2009;10:194–212.

21. Walker J, Bhullar N, Fallah-Rad N, et al. Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. J Clin Oncol 2010;28:3429–36.

22. Jenkins C, Moir S, Chan J, Rakhit D, Haluska B, Marwick TH. Left ventricular volume measurement with echocardiography: a comparison of left ventricular opacification, three-dimensional echocardiography, or both with magnetic resonance imaging. Eur Heart J 2009;30:98–106.

23. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol 2014;63:2751–68.

24. Negishi K, Negishi T, Hare JL, Haluska BA, Plana JC, Marwick TH. Independent and incremental value of deformation indices for prediction of trastuzumab-induced cardiotoxicity. J Am Soc Echocardiogr 2013;26:493–8.

25. Stanton T, Leano R, Marwick TH. Prediction of all-cause mortality from global longitudinal speckle strain: comparison with ejection fraction and wall motion scoring. Circ Cardiovasc Imaging 2009;2:356–64.

26. Cho GY, Marwick TH, Kim HS, Kim MK, Hong KS, Oh DJ. Global 2-dimensional strain as a new prognosticator in patients with heart failure. J Am Coll Cardiol 2009;54:618–24.

27. Liu JE, Barac A, Thavendiranathan P, Scherrer-Crosbie M. Strain imaging in cardio-oncology. J Am Coll Cardiol CardioOnc 2020;2:677–89.

28. Task Force of the European Society of Cardiology. The clinical role of magnetic resonance in cardiovascular disease. Eur Heart J 1998;19:19–39.

29. Cranney GB, Lotan CS, Dean L, Baxley W, Bouchard A, Pohost GM. Left ventricular volume measurement using cardiac axis nuclear magnetic resonance imaging. Validation by calibrated ventricular angiography. Circulation 1990;82:154–63.

30. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ. Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2000;2:271–8.

31. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol 2002;90:29–34.

32. Haslbauer JD, Lindner S, Valbuena-Lopez S, et al. CMR imaging biosignature of cardiac involvement due to cancer-related treatment by T1 and T2 mapping. Int J Cardiol 2019;275:179–86.

33. Thavendiranathan P, Amir E, Bedard P, et al. Regional myocardial edema detected by T2 mapping is a feature of cardiotoxicity in breast cancer patients receiving sequential therapy with anthracyclines and trastuzumab. J Cardiovasc Magn Reson 2014;16 Suppl 1:P273.

34. Houbois CP, Nolan M, Somerset E, et al. Serial cardiovascular magnetic resonance strain measurements to identify cardiotoxicity in breast cancer: comparison with echocardiography. J Am Coll Cardiol Img 2021;14:962–74.

35. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med 2009;361:858–67.

36. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004;109:2749–54.

37. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 2010;28:3910–6.

38. Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging 2012;5:596–603.

39. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. J Clin Oncol 2008;26:5204–12.

40. Michel L, Mincu RI, Mahabadi AA, et al. Troponins and brain natriuretic peptides for the prediction of cardiotoxicity in cancer patients: a meta-analysis. Eur J Heart Fail 2020;22:350–61.

41. Cardinale DM, Barac A, Torbicki A, Khandheria BK, Lenihan D, Minotti G. Cardio-oncological management of patients. Semin Oncol 2019;46:408–13.

42. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.

43. Gregorietti V, Fernandez TL, Costa D, Chahla EO, Daniele AJ. Use of sacubitril/valsartan in patients with cardio toxicity and heart failure due to chemotherapy. Cardiooncology 2020;6:24.

44. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. J Clin Oncol 2005;23:7820–6.

45. Martin-Garcia A, Lopez-Fernandez T, Mitroi C, et al. Effectiveness of sacubitril-valsartan in cancer patients with heart failure. ESC Heart Fail 2020;7:763–7.

46. Gibson J, Ren JY, Davis M, Simmons CE. The impact of mild left ventricular dysfunction on trastuzumab use and oncologic outcomes in early stage breast cancer therapy. J Clin Oncol 2017;35 Suppl:e18148.

47. Barron CC, Alhussein MM, Kaur U, et al. An evaluation of the safety of continuing trastuzumab despite overt left ventricular dysfunction. Curr Oncol 2019;26:240–6.

48. Lynce F, Barac A, Geng X, et al. Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study. Breast Cancer Res Treat 2019;175:595–603.

49. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:893–911.

50. Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias: focus on chemotherapy and targeted therapies. Circ Arrhythm Electrophysiol 2017;10:e005443.

51. Fradley MG, Gliksman M, Emole J, et al. Rates and risk of atrial arrhythmias in patients treated with ibrutinib compared with cytotoxic chemotherapy. Am J Cardiol 2019;124:539–44.

52. Caldeira D, Alves D, Costa J, Ferreira JJ, Pinto FJ. Ibrutinib increases the risk of

hypertension and atrial fibrillation: systematic review and meta-analysis. PLoS One 2019;14:e0211228.

53. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-associated atrial fibrillation. J Am Coll Cardiol EP 2018;4:1491–500.

54. Alomar M, Fradley MG. Electrophysiology translational considerations in cardio-oncology: QT and beyond. J Cardiovasc Transl Res 2020;13:390–401.

55. Rhea IB, Lyon AR, Fradley MG. Anticoagulation of cardiovascular conditions in the cancer patient: review of old and new therapies. Curr Oncol Rep 2019;21:45.

56. Salem J-E, Manouchehri A, Bretagne M, et al. Cardiovascular toxicities associated with ibrutinib. J Am Coll Cardiol 2019;74:1667–78.

57. Guha A, Derbala MH, Zhao Q, et al. Ventricular arrhythmias following ibrutinib initiation for lymphoid malignancies. J Am Coll Cardiol 2018;72:697–8.

58. Fradley MG, Welter-Frost A, Gliksman M, et al. Electrocardiographic changes associated with ibrutinib exposure. Cancer Control 2020;27:1073274820931808.

59. Chang PC, Wo HT, Lee HL, et al. Role of sarcoplasmic reticulum calcium in development of secondary calcium rise and early afterdepolarizations in long QT syndrome rabbit model. PLoS One 2015;10:e0123868.

60. Jiang L, Li L, Ruan Y, et al. Ibrutinib promotes atrial fibrillation by inducing structural remodeling and calcium dysregulation in the atrium. Heart Rhythm 2019;16:1374–82.

61. Ou SH, Tang Y, Polli A, Wilner KD, Schnell P. Factors associated with sinus bradycardia during crizotinib treatment: a retrospective analysis of two large-scale multinational trials (PROFILE 1005 and 1007). Cancer Med 2016;5:617–22.

62. Jamani R, Lee EK, Berry SR, et al. High prevalence of potential drug-drug interactions in patients with castration-resistant prostate cancer treated with abiraterone acetate. Eur J Clin Pharmacol 2016;72:1391–9.

63. Rhea I, Burgos PH, Fradley MG. Arrhythmogenic anticancer drugs in cardio-oncology. Cardiol Clin 2019;37:459–68.

64. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. J Am Coll Cardiol 2019;74:932–87.

65. Rautaharju PM, Surawicz B, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part IV: the ST segment, T and U waves, and the QT interval: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. J Am Coll Cardiol 2009;53:982–91.

66. Curigliano G, Spitaleri G, de Braud F, et al. QTc prolongation assessment in anticancer drug development: clinical and methodological issues. Ecancermedicalscience 2009;3:130.

67. Fradley MG, Moslehi J. QT prolongation and oncology drug development. Card Electrophysiol Clin 2015;7:341–55.

68. Ballou LM, Lin RZ, Cohen IS. Control of cardiac repolarization by phosphoinositide 3-kinase signaling to ion channels. Circ Res 2015;116:127–37.

69. Roboz GJ, Ritchie EK, Carlin RF, et al. Prevalence, management, and clinical consequences of QT interval prolongation during treatment with arsenic trioxide. J Clin Oncol 2014;32:3723–8.

70. Chandrasekhar S, Fradley MG. QT interval prolongation associated with cytotoxic and targeted cancer therapeutics. Curr Treat Options Oncol 2019;20:55.

71. Porta-Sanchez A, Gilbert C, Spears D, et al. Incidence, diagnosis, and management of QT prolongation induced by cancer therapies: a systematic review. J Am Heart Assoc 2017;6:e007724.

72. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). Mayo Clin Proc 2020;95:1213–21.

73. Brown SA, Rhee JW, Guha A, Rao VU. Innovation in precision cardio-oncology during the coronavirus pandemic and into a post-pandemic world. Front Cardiovasc Med 2020;7:145.

74. Rimassa L, Danesi R, Pressiani T, Merle P. Management of adverse events associated with tyrosine kinase inhibitors: improving outcomes for patients with hepatocellular carcinoma. Cancer Treat Rev 2019;77:20–8.

75. Nazer B, Humphreys BD, Moslehi J. Effects of novel angiogenesis inhibitors for the treatment of cancer on the cardiovascular system: focus on hypertension. Circulation 2011;124:1687–91.

76. Robinson ES, Khankin EV, Karumanchi SA, Humphreys BD. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. Semin Nephrol 2010;30:591–601.

77. Abdel-Qadir H, Ethier JL, Lee DS, Thavendiranathan P, Amir E. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis. Cancer Treat Rev 2017;53:120–7.

78. Li Y, Li S, Zhu Y, et al. Incidence and risk of sorafenib-induced hypertension: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2014;16:177–85.

79. Qi WX, He AN, Shen Z, Yao Y. Incidence and risk of hypertension with a novel multi-targeted kinase inhibitor axitinib in cancer patients: a systematic review and meta-analysis. Br J Clin Pharmacol 2013;76:348–57.

80. Karovic S, Wen Y, Karrison TG, et al. Sorafenib dose escalation is not uniformly associated with blood pressure elevations in normotensive patients with advanced malignancies. Clin Pharmacol Ther 2014;96:27–35.

81. Costa LJ, Varella PC, Del Giglio A. White coat effect in breast cancer patients undergoing chemotherapy. Eur J Cancer Care (Engl) 2003;12:372–3.

82. Azizi M, Chedid A, Oudard S. Home blood-pressure monitoring in patients receiving sunitinib. N Engl J Med 2008;358:95–7.

83. Hamnvik OP, Choueiri TK, Turchin A, et al. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. Cancer 2015;121:311–9.

84. van den Meiracker AH, Danser AHJ. Mechanisms of hypertension and renal injury during vascular endothelial growth factor signaling inhibition. Hypertension 2016;68:17–23.

85. Lankhorst S, Baelde HJ, Clahsen-van Groningen MC, Smedts FMM, Danser AHJ, van den Meiracker AH. Effect of high salt diet on blood pressure and renal damage during vascular endothelial growth factor inhibition with sunitinib. Nephrol Dial Transplant 2015;31:914–21.

86. Chen D-D, Dong Y-G, Yuan H, Chen AF. Endothelin 1 activation of endothelin A receptor/NADPH oxidase pathway and diminished antioxidants critically contribute to endothelial progenitor cell reduction and dysfunction in salt-sensitive hypertension. Hypertension 2012;59:1037–43.

87. Bridges JP, Gilbert JS, Colson D, et al. Oxidative stress contributes to soluble fms-like tyrosine kinase-1 induced vascular dysfunction in pregnant rats. Am J Hypertens 2009;22:564–8.

88. Kappers MHW, van Esch JHM, Sluiter W, Sleijfer S, Danser AHJ, van den Meiracker AH. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. Hypertension 2010;56:675–81.

89. Budolfsen C, Faber J, Grimm D, et al. Tyrosine kinase inhibitor-induced hypertension: role of hypertension as a biomarker in cancer treatment. Curr Vasc Pharmacol 2019;17:618–34.

90. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. J Natl Cancer Inst 2011;103:763–73.

91. Boursiquot BC, Zabor EC, Glezerman IG, Jaimes EA. Hypertension and VEGF (vascular endothelial growth factor) receptor tyrosine kinase inhibition: effects on renal function. Hypertension 2017 Jul 24 [E-pub ahead of print].

92. Deshayes F, Nahmias C. Angiotensin receptors: a new role in cancer? Trends Endocrinol Metab 2005;16:293–9.

93. McKay RR, Rodriguez GE, Lin X, et al. Angiotensin system inhibitors and survival outcomes in patients with metastatic renal cell carcinoma. Clin Cancer Res 2015;21:2471–9.

94. Cohen JB, Geara AS, Hogan JJ, Townsend RR. Hypertension in cancer patients and survivors: epidemiology, diagnosis, and management. J Am Coll Cardiol CardioOnc 2019;1:238–51.

95. National Cancer Institute. Lymphedema (PDQ®)–Health Professional Version. 2019.

Available at: https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq. Accessed December 20, 2020.

96. Ferguson CM, Swaroop MN, Horick N, et al. Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer. J Clin Oncol 2016;34:691–8.

97. Showalter SL, Brown JC, Cheville AL, Fisher CS, Sataloff D, Schmitz KH. Lifestyle risk factors associated with arm swelling among women with breast cancer. Ann Surg Oncol 2013;20:842–9.

98. Muntner P, Shimbo D, Carey RM, et al. Measurement of blood pressure in humans: a Scientific Statement from the American Heart Association. Hypertension 2019;73:e35–66.

99. Whelton PK, Carey RM, Aronow WS, 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.

100. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Natl Cancer Inst 2010;102:596–604.

101. Izzedine H, Derosa L, Le Teuff G, Albiges L, Escudier B. Hypertension and angiotensin system inhibitors: impact on outcome in sunitinib-treated patients for metastatic renal cell carcinoma. Ann Oncol 2015;26:1128–33.

102. Izzedine H, Massard C, Spano JP, Goldwasser F, Khayat D, Soria JC. VEGF signalling inhibition-induced proteinuria: mechanisms, significance and management. Eur J Cancer 2010;46:439–48.

103. Vaduganathan M, van Meijgaard J, Mehra MR, Joseph J, O'Donnell CJ, Warraich HJ. Prescription fill patterns for commonly used drugs during the COVID-19 pandemic in the United States. JAMA 2020;323:2524–6.

104. Abraham HM, White CM, White WB. The comparative efficacy and safety of the angiotensin receptor blockers in the management of hypertension and other cardiovascular diseases. Drug Saf 2015;38:33–54.

105. Mir O, Coriat R, Ropert S, et al. Treatment of bevacizumab-induced hypertension by amlodipine. Invest New Drugs 2012;30:702–7.

106. Masiello D, Gorospe G 3rd., Yang AS. The occurrence and management of fluid retention associated with TKI therapy in CML, with a focus on dasatinib. J Hematol Oncol 2009;2:46.

107. Toal CB, Mahon WA, Barnes C, Burelle D. Nifedipine gastrointestinal therapeutic system (GITS) for hypertensive patients in a primary care setting: results of the Extended Release Adalat Canadian Trial (EXACT). Clin Ther 1997;19:924–35.

108. Kloner RA, Weinberger M, Pool JL, et al. Comparison of Candesartan and Amlodipine for Safety, Tolerability and Efficacy (CASTLE) Study Investigators. Comparative effects of candesartan cilexetil and amlodipine in patients with mild systemic hypertension. Am J Cardiol 2001;87:727–31.

109. Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. Am J Cardiol 2000;86:1182–7.

110. Pedrinelli R, Dell'Omo G, Melillo E, Mariani M. Amlodipine, enalapril, and dependent leg edema in essential hypertension. Hypertension 2000;35:621–5.

111. Neutel JM, Alderman M, Anders RJ, Weber MA. Novel delivery system for verapamil designed to achieve maximal blood pressure control during the early morning. Am Heart J 1996;132:1202–6.

112. van Erp NP, Gelderblom H, Karlsson MO, et al. Influence of CYP3A4 inhibition on the steady-state pharmacokinetics of imatinib. Clin Cancer Res 2007;13:7394–400.

113. Flesch M, Maack C, Cremers B, Baumer AT, Sudkamp M, Bohm M. Effect of beta-blockers on free radical-induced cardiac contractile dysfunction. Circulation 1999;100:346–53.

114. Avila MS, Ayub-Ferreira SM, de Barros Wanderley MR Jr., et al. Carvedilol for prevention of chemotherapy-related cardiotoxicity: the CECCY trial. J Am Coll Cardiol 2018;71:2281–90.

115. Hilas O, Ezzo D. Nebivolol (bystolic), a novel beta blocker for hypertension. P T 2009;34:188–92.

116. Denlinger CS, Sanft T, Moslehi JJ, et al. NCCN guidelines insights: survivorship, version 2.2020. J Natl Compr Canc Netw 2020;18:1016–23.

117. Seltzer JH, Gintant G, Amiri-Kordestani L, et al. Assessing cardiac safety in oncology drug development. Am Heart J 2019;214:125–33.

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

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