Circulation: Cardiovascular Quality and Outcomes

AHA SCIENTIFIC STATEMENT

Palliative Pharmacotherapy for Cardiovascular Disease: A Scientific Statement From the American Heart Association

Katherine E. Di Palo, PharmD, MBA, MS, FAHA, Chair; Shelli Feder, PhD, APRN, ACHPN, FPCN, FAHA, Vice Chair; Yleana T. Baggenstos, PharmD; Cyrille K. Cornelio, PharmD; Daniel E. Forman, MD; Parag Goyal, MD, MSc; Min Ji Kwak, MD, MS, DrPH; Colleen K. McIlvennan, PhD, DNP, FAHA; on behalf of the American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing

ABSTRACT: Cardiovascular disease exacts a heavy toll on health and quality of life and is the leading cause of death among people ≥65 years of age. Although medical, surgical, and device therapies can certainly prolong a life span, disease progression from chronic to advanced to end stage is temporally unpredictable, uncertain, and marked by worsening symptoms that result in recurrent hospitalizations and excessive health care use. Compared with other serious illnesses, medication management that incorporates a palliative approach is underused among individuals with cardiovascular disease. This scientific statement describes palliative pharmacotherapy inclusive of cardiovascular drugs and essential palliative medicines that work synergistically to control symptoms and enhance quality of life. We also summarize and clarify available evidence on the utility of guideline-directed and evidence-based medical therapies in individuals with end-stage heart failure, pulmonary arterial hypertension, coronary heart disease, and other cardiomyopathies while providing clinical considerations for de-escalating or deprescribing. Shared decision-making and goal-oriented care are emphasized and considered quintessential to the iterative process of patient-centered medication management across the spectrum of cardiovascular disease.

Key Words: AHA Scientific Statements ■ cardiovascular diseases ■ drug therapy ■ palliative care ■ patient-centered care ■ transitional care

Palliative care is the active holistic care of individuals with serious health-related suffering attributable to severe illness, including cardiovascular disease (CVD).[1] Palliative pharmacotherapy is an integral component of this care that can be deployed throughout the clinical course of CVD to treat symptoms, which include dyspnea, pain, and fatigue, in conjunction with disease-modifying therapies. Although guidelines provide a pharmacological framework to target underlying disease processes, there is a paucity of clear evidence and literature to elucidate which drugs should be continued or deprescribed, as well as when and how these drugs should be initiated or de-escalated, for palliation among individuals with CVD. As a result, there are missed opportunities to alleviate symptom burden, physical suffering, and emotional and spiritual distress.[2,3]

The intent of this scientific statement is to serve as a resource for clinicians caring for individuals with CVD and provide practical suggestions for incorporating palliative methods to medication management in contemporary clinical practice. Palliative pharmacotherapy, inclusive of cardiovascular and common palliative drugs, is described in detail, and strategies to implement across the continuum of care are highlighted. Clinicians can safely deprescribe or de-escalate cardiovascular drugs with limited benefit or increased risk of adverse drug events while still using guideline-directed medical therapy (GDMT) or evidence-based therapies to improve quality of life or reduce disease burden. Furthermore, these tactics can often be enhanced by prescribing palliative drugs to align with patient goals.

Supplemental Material is available at https://www.ahajournals.org/journal/doi/suppl/10.1161/HCQ.0000000000000131.

Circulation: Cardiovascular Quality and Outcomes is available at http://www.ahajournals.org/journal/circoutcomes

IMPORTANCE OF PALLIATIVE CARE IN PEOPLE WITH CVDs

Numerous guidelines and consensus statements have underscored the primacy of palliative care among people with heart failure (HF), pulmonary arterial hypertension (PAH), valvular heart disease, and coronary heart disease.[4–8] These chronic CVDs and conditions require sustained treatment, are usually progressive, and are associated with high 5-year mortality.[9] Palliative care complements cardiovascular care by (1) reducing physical symptom burden, (2) managing emotional and spiritual distress, (3) providing sufficient support for caregivers, and (4) assisting patients in making decisions that coincide with their goals of care.[10]

Although primary palliative care can be leveraged throughout the course of a serious illness as standard clinical practice by any health care professional, misperceptions and confusion between specialty palliative care and hospice care can result in referral delays. Specialty-aligned palliative care (SAPC) is a model of comanagement in which interprofessional subspecialty teams with extensive clinical experience partner with primary care or other specialty clinicians.[11] SAPC is distinct from hospice, which is restricted in the United States to end-of-life care for individuals with a life expectancy of ≤6 months.[10]

However, recognizing the right person at the right time to invoke a palliative approach is challenging. From a physiological perspective, HF is often the terminal consequence that results from the advancement of a multitude of chronic CVDs and conditions. Yet during this downward trajectory of persistent and worsening symptoms accompanied by increased frequency in hospitalizations, which are markers of severe illness and limited life expectancy,[4,8] HF may not be identified or perceived as the primary diagnosis given the complex nature of heart disease. Although GDMT and evidence-based therapies improve symptoms and prolong life, not all patients respond, or respond favorably.[12] Differentiating between patients with advanced CVD that is amendable to interventions (valve replacement, mechanical circulatory support, transplantation) and end-stage CVD (ESCVD), for which these interventions are unlikely to provide symptomatic benefit or are no longer indicated because of advanced frailty and noncardiovascular comorbidities, is also an important consideration. Patients may also choose to forgo life-sustaining therapies or invasive interventions on the basis of goals of care and perception of risks. To account for these complexities, it is imperative to apply a primary palliative approach across the spectrum of chronic CVDs and initiate a timely referral to SAPC for individuals with advanced CVD, especially among individuals with ESCVD that is refractory to further medical, surgical, or device intervention.

PALLIATIVE PHARMACOTHERAPY AS GOAL-ORIENTED PATIENT CARE

Ongoing discussions about goals of care are critical to ensure that preferences and priorities align with treatment plans. During earlier stages of CVD, goals of care typically center on initiating pharmacotherapy to prevent clinical events, improve cardiac function, and prolong life. Compared with other serious illnesses, ESCVD has less certainty in prognostication and less predictability in its decline.[13] Therefore, it is critical for patients to be fully informed about their diagnosis and how pharmacological focus may change throughout the disease management paradigm so that they have ample time to set and share their goals.[14] Palliative pharmacotherapy focuses on enhancing quality of life and minimizing symptom burden. Improved physical and cognitive function; reduced symptoms (pain, dyspnea, fatigue); and improved mood, sleep, and appetite are often goals of care that patients prioritize.[15] Appropriate drug regimens to address these goals may include cardiovascular drugs and common palliative medicines such as antidepressants and opioids. Regardless of the drug class, all medications that are prescribed or deprescribed should be individualized to the patient and complement their values and preferences. Supplemental Figure 1 provides additional details on this process.

Optimal effectiveness of palliative pharmacotherapy is attained when primary care clinicians, cardiovascular experts, and SAPC teams collaborate to deliver patient-centered care. Because adults with multiple chronic conditions are often on intricate and onerous drug regimens that may change frequently as a result of clinical instability, a multidisciplinary team approach is required to maneuver each patient's evolving circumstances and personal goals of care. The Figure indicates triggers for SAPC referral and illustrates how a palliative approach can be integrated into medication management in chronic, stable CVD, in addition to advanced CVD and ESCVD, as part of goal-oriented patient care.

DEPRESCRIBING AS AN APPROACH TO PALLIATIVE CARE

Deprescribing is the systematic, patient-centered process of tapering, withdrawing, or discontinuing a medication by a health care professional to improve outcomes. De-escalating is a type of deprescribing that focuses on dose reduction or therapeutic switch to deintensify a regimen according to patient-specific factors and drug response. Deprescribing and de-escalating are essential components of a palliative approach to medication management among adults with multiple chronic conditions and may be indicated at any time. Prompts for deprescribing include polypharmacy (taking ≥5 medications), which increases the risk of adverse drug reactions or

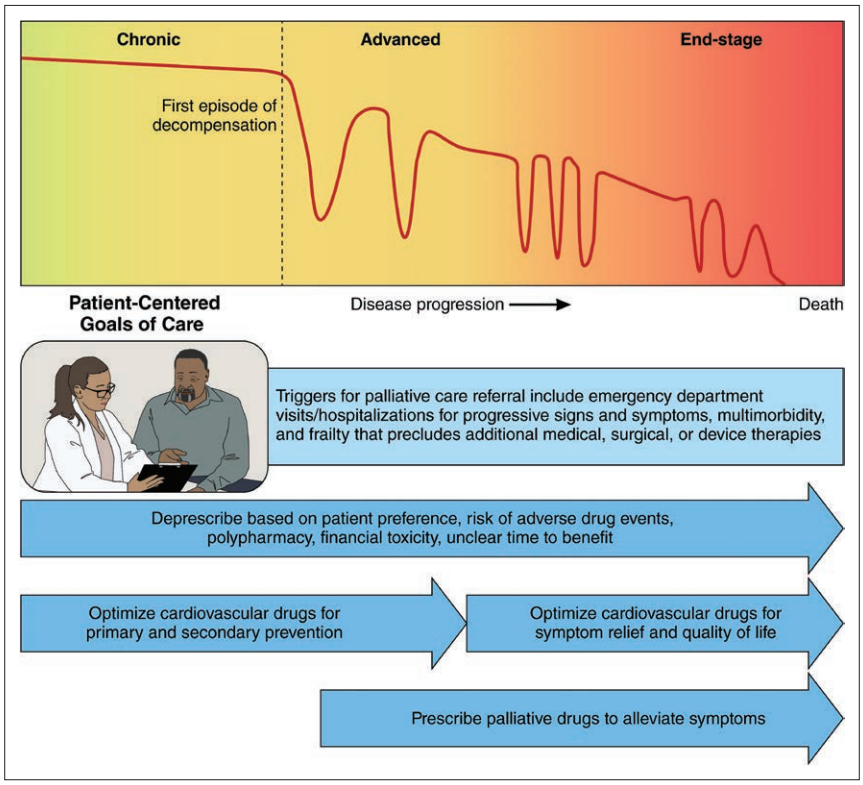

Figure. Palliative pharmacotherapy across the clinical course of cardiovascular disease.[15]

side effects, nonadherence, hospital readmissions, and mortality.[16] Excessive out-of-pocket drug costs or financial toxicity, defined as the harmful effects and unintended consequences of medical expenses on quality of life, may also trigger evaluation. Furthermore, complex pharmaceutical regimens, which are associated with high potential for drug-drug interactions, drug-disease interactions, and medication errors, may also reveal candidates for deprescribing.[17]

Nonetheless, many clinicians perceive cardiovascular drugs as implicitly too essential to deprescribe.[18] Yet, these drugs may no longer have value when continued for prevention in the setting of a limited life span or for an emergency issue that is now resolved. Several tools are available to identify potentially inappropriate cardiovascular medications. One of the most widely used tools is the American Geriatrics Society's Beers Criteria, intended to support shared decision-making about pharmacotherapy in older adults and reduce exposure to drugs that may cause harm.[19] Cardiovascular drugs that should be avoided per these criteria include peripheral α-1 blockers (terazosin, doxazosin) and central α-agonists (clonidine) for hypertension, antiarrhythmics (dronedarone and immediate-release nifedipine), and certain anticoagulants/antiplatelets (dabigatran, prasugrel, and ticagrelor). Drugs that may worsen HF such as cilostazol and nondihydropyridine calcium channel blockers (diltiazem, verapamil) should also be avoided or deprescribed.[20]

However, deprescribing may not be warranted in cases of appropriate polypharmacy, provided that the medication is evidence based, aligns with goals of care, and has benefits that offset any side effects.[21] For example, prescribing palliative inotropes, renin-angiotensin-aldosterone system inhibitors, and diuretics to manage symptoms is considered appropriate polypharmacy in patients with advanced HF. Patients may likewise want to continue a statin if they feel that it is preserving their cognition or cardiovascular stability. It is also important to acknowledge that for some patients deprescribing could be perceived as a signal of "giving up," which may aggravate emotional distress. In such cases, ensuring drug safety is prudent to enable appropriate polypharmacy. This can be achieved through rational prescribing and includes selecting the most appropriate treatment based on diagnosis, prognosis, and goals, with careful monitoring for effects. As a feature of optimal care, clinicians, particularly cardiology experts, should routinely evaluate the risks, benefits, indication, and expected time to benefit of each medication as part of a logical framework for complementary deprescribing and rational prescribing.

UTILITY OF CARDIOVASCULAR DRUGS AS PALLIATIVE PHARMACOTHERAPY

The following section outlines cardiovascular drugs for common CVDs and conditions. Table 1 summarizes therapies that treat and control symptoms, improve survival, and prevent clinical events according to landmark clinical trials. The information presented in this section can offer

Table 1. Drug Therapy for Cardiovascular Disease

	Reduces mortality	Reduces clinical events	Treats or controls symptoms
HF with reduced or mildly reduced ejection fraction			
ARNI/ACE inhibitors/ARBs	✓	✓ HF hospitalizations	✓
β-Blockers	✓	✓ HF hospitalizations	
MRAs	✓	✓ HF hospitalizations	✓
SGLT2 inhibitors	✓	✓ HF hospitalizations	
Loop diuretics		✓ HF hospitalizations	✓
Ivabradine		✓ HF hospitalizations	
Vericiguat		✓ HF hospitalizations	
Vasodilators	✓	✓ HF hospitalizations	✓
Digoxin		✓ HF hospitalizations	✓
Inotropes			✓
HF with preserved ejection fraction			
ARNI/ACE inhibitors/ARBs		✓ HF hospitalizations	✓
MRAs		✓ HF hospitalizations	✓
SGLT2 inhibitors		✓ HF hospitalizations	✓
Loop diuretics		✓ HF hospitalizations	✓
Transthyretin cardiac amyloidosis			
Tafamidis	✓	✓ Cardiovascular hospitalizations	
Loop diuretics			✓
MRAs			✓
SGLT2 inhibitors			✓
Hypertrophic cardiomyopathy			
β-Blockers			✓
Calcium channel blockers			✓
Disopyramide			✓
Mavacamten			✓
Coronary heart disease			
Aspirin	✓	✓ MI ✓ Stroke ✓ Stent thrombosis	
P2Y12 inhibitors	✓	✓ MI ✓ Stroke ✓ Stent thrombosis	
Statins	✓	✓ MI ✓ Stroke	
PCSK9 inhibitors		✓ MI ✓ Stroke	
Ezetimibe		✓ MI ✓ Stroke	
Nitrates			✓
β-Blockers	✓	✓ MI ✓ HF hospitalizations	✓
Dihydropyridine calcium channel blockers			✓
Ranolazine			✓
Atrial fibrillation			
Direct oral anticoagulants		✓ Stroke	
Vitamin K antagonists		✓ Stroke	
β-Blockers			✓
Nondihydropyridine calcium channel blockers			✓
Digoxin			✓
Amiodarone			✓

(*Continued*)

Table 1. Continued

	Reduces mortality	Reduces clinical events	Treats or controls symptoms
Ventricular arrhythmias			
β-Blockers	✓		✓
Amiodarone	✓		✓
Pulmonary arterial hypertension			
PDE5 inhibitors			✓
Endothelin receptor antagonists			✓
Prostanoids	✓		✓
sGC stimulators			✓
Calcium channel blockers			✓
Primary prevention of atherosclerotic cardiovascular disease			
Antihypertensive agents		✓ MI ✓ Stroke	
Statins		✓ MI ✓ Stroke	
PCSK9 inhibitors		✓ MI ✓ Stroke	
Ezetimibe		✓ MI ✓ Stroke	
Aspirin		✓ MI ✓ Stroke	

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; HF, heart failure; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; PCSK9, proprotein convertase subtilisin/kexin type 9; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase; and SGLT2, sodium-glucose cotransporter 2.

a reference for clinicians engaging in shared decision-making concerning cardiovascular medications, specifically in determining whether evidence-based therapies should be maintained or de-escalated, in patients with ESCVD.

Heart Failure

Pharmacotherapy for HF with reduced ejection fraction, commonly referred to as GDMT, now includes 10 agents that can improve life expectancy and prevent clinical events.[8] Of note, although HF with mildly reduced ejection fraction is its own unique phenotype, many of the drugs used to treat HF with reduced ejection fraction are also recommended to treat HF with mildly reduced ejection fraction because the underlying pathophysiological mechanisms are believed to be shared. Even when prolonging life is no longer the priority, most GDMT can maintain euvolemia and abate symptoms and should not be de-escalated or discontinued without compelling reason.[15]

For example, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor–neprilysin inhibitors, and vasodilators can decrease intracardiac filling pressures to improve shortness of breath. However, dose and timing are important to minimize hemodynamic perturbations such as hypotension that exacerbate risk for falls. Loop diuretics are frequently continued or escalated to achieve adequate decongestion. For select patients, home administration of intravenous or subcutaneous furosemide can be considered.[22,23] At commonly used HF doses, mineralocorticoid receptor antagonists are relatively weak diuretics but can aid in symptom relief through neurohormonal blockade with minimal effect on blood pressure. Sodium-glucose cotransporter 2 inhibitors have a multitude of benefits, including hemodynamic and diuretic effects, and are not associated with typical adverse effects attributed to renin-angiotensin-aldosterone system inhibitors and β-blockers, including hyperkalemia, hypotension, and bradycardia. Given their tolerability, which is especially advantageous in older, frail adults, it may be reasonable to continue sodium-glucose cotransporter 2 inhibitors for the potential benefit on quality of life, but this should be balanced with the need or desire to reduce pill burden.[24]

In the absence of other indications, β-blockers may not exert a direct benefit on symptoms. Furthermore, they may contribute to fatigue and functional decline, especially in the setting of low cardiac index and chronotropic incompetence. β-Blockers may also require de-escalation in patients with severe congestion and symptomatic hypotension. Deprescribing should follow a slow tapering schedule to reduce the risk of rebound hypertension or other adverse withdrawal events that can occur when large doses are abruptly stopped. Ivabradine may also be reasonable to deprescribe because it specifically targets heart

rate as a mechanism to improve long-term outcomes. Although vericiguat is well tolerated without meaningful effects on blood pressure, it did not improve quality of life in its landmark clinical trial, which may prompt deprescribing.[25]

To date, no drug studied specifically for HF with preserved ejection fraction has demonstrated mortality benefit, although angiotensin receptor blockers, mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, and angiotensin receptor–neprilysin inhibitors are supported in clinical practice guidelines because of their capacity to prevent HF hospitalization.[8] Like HF with reduced ejection fraction, drugs that optimize filling pressures (renin-angiotensin system inhibitors and diuretics) may be reasonable to continue for symptom relief. Toward the end of life, these drugs may become less tolerable and require downtitration for severe or symptomatic hypotension.

Patients with advanced (stage D) HF may benefit from inotrope therapy as a means of palliation. There are conflicting data on survival among patients on palliative inotropes; however, they can be used to improve symptoms, functional status, and quality of life.[26] The potential risks of ambulatory inotrope therapy, which include arrhythmias, infection from an indwelling venous catheter, cost, and the burden of living with a continuous intravenous infusion, should be discussed as part of shared decision-making.

Transthyretin Cardiac Amyloidosis and Hypertrophic Cardiomyopathy

As of 2023, the only US Food and Drug Administration–approved therapy for transthyretin cardiac amyloidosis is tafamidis. Mechanistically, tafamidis can delay progression and forestall decline in quality of life but cannot reverse disease. Prior data suggest that the benefit of tafamidis is attenuated with advanced amyloidosis.[27] With high associated drug costs, it may be judicious to deprescribe because its incremental value is limited. Volume management with loop diuretics and mineralocorticoid receptor antagonists remains essential for symptom control with theoretical benefit from sodium-glucose cotransporter 2 inhibitors regardless of ejection fraction. Due to physiological changes resulting in low stroke volume and relative dependence on chronotropy to preserve cardiac output, β-blockers and other atrioventricular nodal agents should be used with caution or deprescribed.[28] Because patients with transthyretin cardiac amyloidosis are prone to autonomic orthostatic hypotension, it may be reasonable to deprescribe renin-angiotensin system inhibitors and vasodilators in the setting of lightheadedness and dizziness.

The key objective of hypertrophic cardiomyopathy pharmacotherapy is to improve quality of life by treating elevated intracavitary gradients and optimizing cardiac filling. In patients with end-stage hypertrophic cardiomyopathy, defined as systolic dysfunction with an ejection fraction <50%, HF with reduced ejection fraction GDMT can be continued to control symptoms, whereas calcium channel blockers, disopyramide, and mavacamten should be discontinued because of profound negative inotropic effects.[29,30]

Coronary Heart Disease

Medical management of coronary heart disease includes therapies for primary and secondary prevention of future cardiac events and symptom relief. Antiplatelets, anticoagulants, and lipid-lowering agents are the cornerstone for reducing ischemic events. The utility of aspirin in the immediate phase after myocardial infarction is well established; however, the prolonged use of aspirin as secondary prevention in patients without stents is not well supported, and deprescribing may be considered.[31] Similarly, P2Y12 inhibitor (clopidogrel, ticagrelor) use in patients with ESCVD but without stents should be reassessed, especially for those prescribed concomitant antithrombotics. With data suggesting shorter duration of dual antiplatelet therapy after stents, even those who have had prior revascularization may be candidates for deprescribing P2Y12 inhibitors. Antianginal agents such as β-blockers, dihydropyridine calcium channel blockers (amlodipine), nitrates, and ranolazine can reduce myocardial demand through vasodilatation, negative chronotropic effects, or inotropic effects. Continuing these therapies can control symptoms, and monitoring for hypotension, orthostasis, headache, and syncope can facilitate safe use.

The optimal duration of statin therapy among individuals with ESCVD is unclear. Older adults with frailty experience similar, if not greater, benefits in respect to new statin use for primary prevention. In a retrospective study, statin use was associated with a lower risk of all-cause mortality and major adverse cardiovascular events with no significant interaction according to frailty group.[32] Statin-associated muscle symptoms, particularly myalgias, are a common complaint that can compound limitations associated with frailty. Although statin-associated muscle symptoms are more frequent among those receiving high-intensity statin regimens, no significant increase in prevalence has been reported with older age.[33]

A preponderance of literature indicates neutral or even positive statin-related cognitive effects. Most notably, a prospective observational study of older community-dwelling adults comparing statin users with nonusers over 6 years found no difference in the rate of memory decline or global cognition.[34] Statin initiation during the observation period was associated with blunting of the rate of memory decline. In a meta-analysis of 24 studies with >1 million participants ≥60 years of age, all 3

randomized clinical trials showed no significant association between statin use and adverse cognitive effects, 7 observational studies showed no association with incident dementia, and 2 observational studies showed similar declines in cognition.[35] The ongoing PREVENTABLE trial (Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults) and STAREE trial (Statins in Reducing Events in the Elderly) will study the relationship between statins for primary prevention, cognitive function, and quality of life more definitively.[36,37]

Although data suggest that the use of high-intensity statins for secondary prevention may reduce 1-year mortality, drug-drug interactions, tolerability, pill burden, and declining health status may prompt deprescribing.[38] In a study of adults with an estimated life expectancy of <1 year receiving statin therapy for primary or secondary prevention, statin discontinuation was associated with better quality of life and cost savings with no significant difference in 60-day mortality.[39] Shared decision-making that incorporates benefits and risks, in addition to preferences and goals of care, should drive continuation or withdrawal of statins among individuals with ESCVD.

Arrhythmias

Arrhythmia management involves prevention of hospitalizations and sudden cardiac death in addition to symptom relief. For patients with atrial arrhythmias, rate and rhythm control strategies may alleviate palpitations and dyspnea. Patient-specific factors can aid clinicians in drug selection. For example, digoxin can provide rate control for atrial fibrillation and prevent HF hospitalizations, which may be appreciated among patients with these comorbidities. Because of its narrow therapeutic window, routine monitoring and dose adjustment based on renal function are warranted to prevent digoxin toxicity.[20] Other antiarrhythmics, particularly amiodarone, are associated with a higher risk of fall-related injuries and syncope compared with rate-lowering therapies.[40]

β-Blockers are first-line therapy to reduce the risk of sudden cardiac death among patients with ventricular arrhythmias. Amiodarone can also be used to prevent recurrence, although side effects and monitoring necessitate cautious prescribing. Depending on the patient's goals of care, it may be appropriate to continue these therapies. Medications that can exacerbate underlying myocardial dysfunction such as flecainide, dronedarone, sotalol, and disopyramide should be avoided for arrhythmia management among patients with ESCVD or dosed appropriately according to renal function if continued.[20]

Shared decision-making for anticoagulation is especially prudent. In patients with ESCVD, the time to benefit may be longer than a patient's anticipated life expectancy; therefore, it may be practical to stop anticoagulation. The risk of bleeding, which is increased in patients >75 years of age or with renal impairment, along with falls and frailty, may also prompt consideration for deprescribing.[40] However, the potential consequences of discontinuing direct oral anticoagulants or warfarin should also be considered, because some patients may prefer to continue these therapies to avoid severe debilitation from stroke and thromboembolic events.

Pulmonary Arterial Hypertension

Most therapies for PAH can reduce symptom burden and maintain quality of life and can be continued, provided that these benefits outweigh any patient-specific risks. Registry data have shown that phosphodiesterase type 5 inhibitors are the most prescribed drug class for PAH in older adults with lower discontinuation rates compared with other therapies.[41] However, clinicians should be cognizant that sildenafil or tadalafil may cause more hypotension, headache, syncope, and visual disturbances in this cohort. Switching from a phosphodiesterase type 5 inhibitor to a soluble guanylate cyclase stimulator (riociguat) has been investigated as an alternative, although studies have excluded adults >75 years of age.[42] Although endothelin receptor antagonists improve exercise capacity and dyspnea, observational data have demonstrated significantly higher discontinuation rates in older adults.[41] Peripheral edema, drug-drug interactions, and potential for hepatotoxicity, which requires participation in drug safety programs, may limit access and use.

Prostanoids and the prostacyclin receptor agonist selexipag are commonly used in ESCVD because they are recommended for worsening PAH or in patients refractory to phosphodiesterase type 5 inhibitors and endothelin receptor antagonists.[43] However, parenteral and inhaled administration may be challenging for both patients and caregivers to manage on top of other end-of-life therapies. Adverse effects, including muscle aches, arthralgias, jaw pain, and increased risk of bloodstream infections through intravenous administration, may detract from their use.[44] Oral treprostinil, specifically 3-times-daily dosing, is preferred for more consistent serum drug concentrations and tolerability. If de-escalation of PAH-specific therapies is desired according to goals of care, abrupt discontinuation should be avoided.

COMMON DRUGS FOR PALLIATIVE CARE

The International Association for Hospice and Palliative Care has designated several drug classes as essential for the treatment of pain, fatigue, depression, and insomnia among patients with ESCVD and other serious illnesses.[45] These common palliative drugs can be used with cardiovascular therapies to manage symptoms and

optimize quality of life. Selection and use should be personalized; account for the patient's symptoms, clinical status, physiological vulnerabilities, and goals of care; and involve interprofessional collaboration. Although SAPC may be responsible for the management of complex pain requiring opioids or refractory dyspnea, the treatment of other symptoms such as constipation and depression can be safely managed by cardiovascular or primary care clinicians.

Clear communication from health care professionals to patients and families with regard to expected benefits and potential risks is requisite to prescribe common palliative drugs. For example, using atropine for excessive secretions may add anticholinergic burden and increase fatigue. Anxiolytics and sedating antidepressants can significantly increase the risk of falls, which may be amplified when these drugs are used in combination with certain cardiovascular medications such as antihypertensive agents and diuretics. Respiratory depression is infrequent among patients prescribed low-dose opioids for intermittent or as-needed use; however, high-dose and parenteral forms and rapid uptitration pose greater risk, particularly in the presence of obstructive sleep apnea. Other undesirable effects include oversedation, daytime sleepiness, orthostatic hypotension, and confusion. Table 2 highlights preferred common palliative drugs for individuals with ESCVD, and considerations for rational prescribing are reviewed here.

Pain

The reported prevalence of pain among people with ESCVD is 77%.[46] When able, clinicians should choose agents that target multiple symptoms and incorporate nonpharmacological modalities such as heat or massage therapy to promptly control pain. Nonopioid pharmacological therapies are typically preferred in the management of musculoskeletal or inflammatory pain, with acetaminophen widely used as initial therapy. Although generally well tolerated, doses of 4 g daily may increase systolic blood pressure among individuals with hypertension.[47] Other options include over-the-counter topicals (lidocaine, diclofenac, capsaicin) and less-sedating muscle relaxants (methocarbamol, metaxalone).

Neuropathic pain can be managed effectively with selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors, although SSRIs may be preferable among patients with ESCVD because serotonin norepinephrine reuptake inhibitors cause hypertension at high doses.[48] Anticonvulsants such as gabapentin and pregabalin require renal dose adjustment and are typically not recommended because of risk of fluid retention, weight gain, and HF exacerbation.[20] Nonsteroidal anti-inflammatory drugs should also be avoided in individuals with ESCVD because of cardiovascular toxicity, renal toxicity, and increased risk of bleeding. Nonsteroidal anti-inflammatory drugs may also impair renal function in patients with decreased effective circulating volume and promote sodium and water retention, resulting in increased risk of HF hospitalization.[20]

Opioids can be used for persistent pain in patients with ESCVD. Low-dose oral opioids are generally well tolerated and safe. Typically, immediate-release formulations are initially prescribed for intermittent or as-needed use, with extended-release and long-acting formulations reserved for severe or continuous pain. Adverse effects, which are increased with high-dose and parenteral administration, include respiratory depression, falls, and confusion.[49,50] Patients receiving diuretic therapy may experience renal failure as a complication and require dose adjustments to pain medications to avoid accumulation of metabolites. Opioids without active metabolites, including methadone, buprenorphine, or fentanyl, may be more appropriate among patients with renal dysfunction and ESCVD.

Depression, Anxiety, and Insomnia

Psychological disorders, including depression, anxiety, and insomnia, are prevalent among all stages of CVD.[46,48] SSRIs are well studied in people with coronary heart disease and HF and appear to be safe; however, their efficacy in treating comorbid depression and anxiety is mixed.[48] Of the SSRIs, sertraline has been studied extensively and appears to have a lower risk of QTc prolongation than citalopram or escitalopram. Monoamine oxidase inhibitors and tricyclic antidepressants have significant cardiovascular side effects, including hypertension, hypotension, and arrhythmias, and should be avoided. Mirtazapine, an atypical antidepressant, has been shown to be safe; however, its efficacy in treating depression in patients with CVD has not been assessed.[48] However, mirtazapine offers additional benefits, including appetite stimulation, and may be used for sleep. The effect of SSRIs may take up to 6 weeks; thus, SSRIs may not be suitable to manage depressive symptoms at the immediate end of life. Instead, psychostimulants such as methylphenidate, which has an onset of 1 to 2 days, may be prescribed by SAPC clinicians in select populations with monitoring for cardiovascular risks, including tachycardia and hypertension.[51]

Sleep disturbances among patients with ESCVD may be related to symptoms or adverse drug effects. Cognitive behavioral therapy for insomnia is recommended as first-line treatment before the initiation of sedating antidepressants (trazadone, mirtazapine) or melatonin receptor agonists (ramelteon).[52] Hypnotics such as zolpidem and eszopiclone should be prescribed with caution because they may cause cognitive impairment and increase fall risk.

Table 2. Common Palliative Drugs for Cardiovascular Disease

Drug class	Common drugs	Utility as palliative therapy		Other indications	Cardiovascular adverse drug events
		As needed to treat symptoms in chronic and advanced disease	As needed to treat symptoms in end stage and end of life		
Musculoskeletal and inflammatory pain					
Topical analgesics	Diclofenac, lidocaine	✓	✓		
Nonopioid analgesics	Acetaminophen	✓	✓		Hypertension at doses >4 g
Opioids	Morphine, hydromorphone, oxycodone, tramadol		✓	Neuropathic pain	Bradyarrhythmias, hypotension with rapid titration, high-dose, or parenteral formulation
Neuropathic pain					
Tricyclic antidepressants	Nortriptyline	✓	✓	Insomnia	Tachycardia, arrhythmias
Depression and anxiety					
Selective serotonin reuptake inhibitors	Sertraline, citalopram	✓	✓	Neuropathic pain	QT prolongation at doses of citalopram >20 mg
Serotonin norepinephrine reuptake inhibitors	Duloxetine	✓	✓	Neuropathic pain	Hypertension
Atypical antidepressants	Mirtazapine	✓	✓	Appetite stimulation, insomnia	Orthostatic hypotension, QT prolongation, edema
Stimulants	Methylphenidate		✓	Appetite stimulation, fatigue	Tachycardia, hypertension
Insomnia					
Atypical antidepressants	Trazodone	✓	✓		Hypotension, orthostatic hypotension, arrhythmias
Melatonin receptor antagonists	Ramelteon	✓	✓		
Hypnotics	Zolpidem		✓		
Dyspnea and cough					
Antitussives	Dextromethorphan	✓	✓		
Benzodiazepines	Lorazepam		✓	Anxiety, nausea	
Opioids	Morphine, codeine		✓	Pain	Bradyarrhythmias, hypotension with rapid titration, high-dose, or parenteral formulation
Fatigue					
Steroids	Dexamethasone		✓	Inflammatory pain, mood, fatigue, appetite stimulation	Edema, hypertension
Stimulants	Methylphenidate, modafinil		✓		Tachycardia, hypertension
Nausea, vomiting, and constipation					
Laxatives	Bisacodyl, sennosides, polyethylene glycol	✓	✓		
Antiemetics	Prochlorperazine, ondansetron		✓		QT prolongation
Appetite stimulation					
Steroids	Dexamethasone		✓	Inflammatory pain, mood, fatigue, nausea	Edema, hypertension
Synthetic cannabinoids	Dronabinol		✓	Insomnia	Hypotension, hypertension, tachycardia
Progestins	Megestrol acetate		✓		Edema

Dyspnea and Cough

Dyspnea and cough are hallmark symptoms of HF and regularly described among individuals with other ESCVDs.[46] Management of acute dyspnea includes removal of reversible causes and decongestion. Opioids are the mainstay therapy for refractory dyspnea and are thought to modify perceptions of breathlessness and the urge to breathe.[53] Among people with HF, opioids may be indicated for patients with New York Heart Association class IV symptoms who are optimized on GDMT and nonresponsive to nonpharmacological therapy, which includes the use of fans to blow air. Studies of opioids for the treatment of dyspnea have used oral low-dose morphine 2.5 mg scheduled or as needed with mixed results.[54,55] Cough can be managed through diuresis and substituting cardiovascular drugs such as angiotensin-converting enzyme inhibitors as indicated. Over-the-counter dextromethorphan can be used if symptoms persist, with codeine reserved for severe cases.

Fatigue

Tiredness, lack of energy, and exhaustion are frequently reported among patients with ESCVD.[46] Before essential palliative drugs are prescribed, cardiovascular medications that may cause fatigue, including diuretics and β-blockers, should be adjusted or administered at bedtime to avoid daytime drowsiness. Occupational therapy may also be considered as rehabilitative palliative care to maintain function and quality of life.[56] Treating iron deficiency, a common comorbidity, can also improve fatigue. In clinical trials, high-dose intravenous iron products (ferric carboxymaltose, ferric derisomaltose) were associated with improved functional status, quality of life, and reduced hospitalizations among patients with HF.[57] Dexamethasone may also be helpful; however, efficacy studies are limited primarily to patients with cancer.[47] Similarly, stimulants (methylphenidate, modafinil) and amantadine are commonly prescribed to treat fatigue in multiple sclerosis. Their effects in individuals with ESCVD are not known, and cardiovascular risks may limit their usefulness.

Nausea, Vomiting, and Constipation

Up to 48% of patients with ESCVD experience nausea.[46] Antiemetics (prochlorperazine, ondansetron) may be considered, along with de-escalation of cardiovascular medications. As an alternative, benzodiazepines (lorazepam) and dexamethasone may be initiated by SAPC clinicians; however, the efficacy of these medications in people with ESCVD is not known. Caution is required with these agents, given that antiemetics can prolong QT intervals and benzodiazepines have significant side effects, including sedation and increased risk of falls. Lifestyle changes for nausea include eating more frequent, smaller meals; avoiding spicy and high-fat foods; and sitting upright while eating. For constipation, stimulant laxatives (sennosides) and osmotic laxatives (polyethylene glycol) are suggested in addition to lifestyle changes, including increased consumption of high-fiber foods.[15]

Anorexia and Thirst

Anorexia, loss of appetite, and weight loss are features of cardiac cachexia and indicative of ESCVD.[58] Mirtazapine can be useful to stimulate appetite, particularly for patients with concomitant sleep difficulties or mood disorders, and anorexigenic medications (digoxin, amiodarone, and mexiletine) should be deprescribed when possible.[59] Other appetite-promoting agents such as dexamethasone and megestrol acetate have uncertain benefit in this population but may be suggested by SAPC clinicians on the basis of studies among patients with cancer.[59] Approximately 46% of patients with HF report thirst. However, there are no pharmacotherapy interventional studies to date. The management of thirst typically includes supportive therapies such as artificial saliva, ice chips, chewing gum, and candies.

Medicinal cannabis and dronabinol, a synthetic cannabinoid, are adjunct therapies to relieve multiple symptoms in the palliative care setting. In a meta-analysis of 52 studies, primarily in patients with cancer, positive treatment effects were reported for appetite, nausea, vomiting, pain, sleep, and fatigue for some products.[60] However, the quality of evidence, heterogeneity in cannabis products, including recreational cannabis products that may be available depending on state law, and inconclusive effects on cardiovascular health currently limit its clinical application among patients with ESCVD.

IMPORTANCE OF TEAM-BASED CARE IN ESCVD

Decisions about initiating, titrating, or deprescribing palliative pharmacotherapy require input from multiple specialties, including cardiology and SAPC, in close collaboration with primary care clinicians. Because goals of care and treatment options may change rapidly amid fluctuating health status, organization and communication are essential to deliver effective care. Although a multidisciplinary team approach is recommended across the span of CVD, clinicians must align to effectively navigate patients and caregivers through transitions of care toward end of life. A systematic review and meta-analysis evaluating the effectiveness of palliative care interventions among patients with HF demonstrated that home-based and team-based care improved documentation of preferences and lowered risk of rehospitalization.[61]

USE OF SAPC

Although no ideal template for shared prescribing currently exists and local context and resources affect implementation, SAPC represents an evolution in care delivery. Successful models necessitate trust building, expectation setting, and clear delineation of roles and responsibilities, including copharmacotherapy management. In addition to clinical expertise, SAPC teams often include clinicians who manage nonpharmacological aspects of ESCVD such as spiritual distress and coordinate additional support through home care or home hospice. In a controlled trial of patients with advanced HF and high 6-month mortality risk, an interdisciplinary intervention that added a certified SAPC nurse practitioner to evidence-based care improved quality of life, functional status, depression, anxiety, and spiritual well-being compared with usual care alone.[62]

However, insufficient use of SAPC remains a prevalent issue despite current guideline recommendations.[4,8] Fewer than 20% of people with end-stage HF receive palliative care within 1 year of their index hospitalization.[63] Administration of palliative care occurs primarily during hospitalization, which subsequently restricts access to the acutely ill, delays referrals, and limits opportunities for ongoing palliative management after discharge. Underuse and delayed use of SAPC among patients with ESCVD can be attributed to several factors, including unpredictability of disease course, lack of understanding of its role in CVD management by health care professionals, and lack of awareness of the availability of options by patients and their families. Although several criteria to facilitate SAPC referrals have been suggested, such as patient prognosis using clinician judgment, prognostic risk scores, symptoms, and other palliative needs,[64] research is needed to determine the best ways to provide timely and targeted access. Additional research is also necessary to evaluate the effectiveness of SAPC on patient-reported outcomes specifically related to symptom relief at the end of life to provide direction on initiating or de-escalating palliative pharmacotherapy. Because much of the evidence base for palliative pharmacotherapy is derived from serious, noncardiac illnesses or advanced HF, it is imperative that future interventional studies include individuals with various ESCVDs.

DISPARITIES IN PRACTICE

Despite significant progress in cardiovascular care, disparities in quality and outcomes based on race, ethnicity, sex, and social determinants of health persist.[4] This includes SAPC, which remains underused at the end of life among excluded or historically excluded people. For example, people with HF who are referred to palliative care are predominantly White individuals with higher socioeconomic status and are cared for within academic medical centers.[65,66] Ensuring equitable access to optimal medical and SAPC services for all individuals with ESCVD is imperative and requires a deeper understanding of the interaction of factors attributing to disparate care. Future research opportunities may include educational interventions to aid clinicians in identifying primary palliative needs, including deprescribing, for people with ESCVD from underrepresented racial and ethnic groups. Recruitment and SAPC training of clinicians from underrepresented backgrounds are also paramount.

CONCLUSIONS

Palliative pharmacotherapy encompassing cardiovascular drugs and essential palliative medicines can be implemented across the clinical course of CVD to improve quality of life and decrease burden. Early warning signs of decompensation such as refractory symptoms and increased health care use should prompt clinicians to intensify palliative pharmacotherapy among individuals with ESCVD and refer to SAPC teams. The cardinal principles of goals of care and shared decision-making are foundational for a patient-centered approach to palliative prescribing and deprescribing.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on April 11, 2024, and the American Heart Association Executive Committee on May 7, 2024. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

The American Heart Association requests that this document be cited as follows: Di Palo KE, Feder S, Baggenstos YT, Cornelio CK, Forman DE, Goyal P, Kwak MJ, McIlvennan CK; on behalf of the American Heart Association Clinical Pharmacology Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing. Palliative pharmacotherapy for cardiovascular disease: a scientific statement from the American Heart Association. *Circ Cardiovasc Qual Outcomes.* 2024;17:e•••••••••. doi: 10.1161/HCQ.0000000000000131

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit https://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Katherine E. Di Palo	Montefiore Medical Center	None	None	None	None	None	None	None
Shelli Feder	Yale University School of Nursing	None	None	None	None	None	None	None
Yleana T. Baggenstos	M Health Fairview Pharmacy	None	None	None	None	None	None	None
Cyrille K. Cornelio	University of South Florida	None	None	None	None	None	None	None
Daniel E. Forman	University of Pittsburgh Medical Center	None	None	None	None	None	None	None
Parag Goyal	Weill Cornell Medicine	NIH (PI grant K76AG064428)†; NIH (PI of grant R21AG077092)†; NIH (PI of pilot grant funded by R24AG064025)†	None	None	None	None	None	None
Min Ji Kwak	McGovern Medical School, University of Texas Health Science Center at Houston	None	None	None	None	None	Novo Nordisk (unpaid)*	None
Colleen K. McIlvennan	University of Colorado	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Sarah Chuzi	Northwestern University Feinberg School of Medicine	None	None	None	None	None	None	None
Nathan Goldstein	Icahn School of Medicine at Mount Sinai	NIA/NIH† (1R01AG067045–Palliative Care at Home for Patients with Dementia)	None	None	None	None	agilon health†	None
James N. Kirkpatrick	University of Washington	National Institutes of Health–NIDDK (I am a coinvestigator with salary support on an ethics supplement to the KIND-HF trial. The supplement examines, in part, advance care planning in patients with kidney disease and ADHF.)†	None	Division of cardiology grand rounds on topics related to palliative care and cardiology*	None	None	None	None
Robert L. Page II	University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

REFERENCES

1. Radbruch L, De Lima L, Knaul F, Wenk R, Ali Z, Bhatnaghar S, Blanchard C, Bruera E, Buitrago R, Burla C, et al. Redefining palliative care: a new consensus-based definition. *J Pain Symptom Manage*. 2020;60:754–764. doi: 10.1016/j.jpainsymman.2020.04.027
2. Connor SR, Gwyther E. The worldwide hospice palliative care alliance. *J Pain Symptom Manage*. 2018;55:S112–S116. doi: 10.1016/j.jpainsymman.2017.03.020
3. Warraich HJ, Hernandez AF, Allen LA. How medicine has changed the end of life for patients with cardiovascular disease. *J Am Coll Cardiol*. 2017;70:1276–1289. doi: 10.1016/j.jacc.2017.07.735
4. McClellan M, Brown N, Califf RM, Warner JJ. Call to action: urgent challenges in cardiovascular disease: a presidential advisory from the American Heart Association. *Circulation*. 2019;139:e44–e54. doi: 10.1161/CIR.0000000000000652
5. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, et al; ESC/ERS Scientific Document Group. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618–3731. doi: 10.1093/eurheartj/ehac237
6. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published corrections appear in *Circulation*. 2021;143:e229, *Circulation*. 2023;148:e8, and *Circulation*. 2023;148:e185]. *Circulation*. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000932
7. Birtcher KK, Allen LA, Anderson JL, Bonaca MP, Gluckman TJ, Hussain A, Kosiborod M, Mehta LS, Virani SS; Writing Committee. 2022 ACC expert consensus decision pathway for integrating atherosclerotic cardiovascular disease and multimorbidity treatment: a framework for pragmatic, patient-centered care: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2023;81:292–317. doi: 10.1016/j.jacc.2022.08.754
8. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895–e1032. doi: 10.1161/CIR.0000000000001063
9. Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, Baker-Smith CM, Beaton AZ, Boehme AK, Buxton AE, et al; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics–2023 update: a report from the American Heart Association [published corrections appear in *Circulation*. 2023;147:e622 and *Circulation*. 2023;148:e4]. *Circulation*. 2023;147:e93–e621. doi: 10.1161/CIR.0000000000001123
10. Kavalieratos D, Gelfman LP, Tycon LE, Riegel B, Bekelman DB, Ikejiani DZ, Goldstein N, Kimmel SE, Bakitas MA, Arnold RM. Palliative care in heart failure: rationale, evidence, and future priorities. *J Am Coll Cardiol*. 2017;70:1919–1930. doi: 10.1016/j.jacc.2017.08.036
11. Leiter RE, Bischoff KE, Carey EC, Gelfand SL, Iyer AS, Jain N, Kramer NM, Lally K, Landzberg MJ, Lever N, et al. Top ten tips palliative care clinicians should know about delivering specialty-aligned palliative care. *J Palliat Med*. 2023;26:1401–1407. doi: 10.1089/jpm.2023.0116
12. Bozkurt B. Nonresponse to heart failure therapy: an important trajectory. *JACC Heart Fail*. 2023;11:729–732. doi: 10.1016/j.jchf.2023.05.002
13. Kearns T, Cornally N, Molloy W. Patient reported outcome measures of quality of end-of-life care: a systematic review. *Maturitas*. 2017;96:16–25. doi: 10.1016/j.maturitas.2016.11.004
14. Jankowska EA, Liu PP, Cowie MR, Groenhart M, Cobey KD, Howlett J, Komajda M, Lund LH, Magaña Serrano JA, Mourilhe-Rocha R, et al. Personalized care of patients with heart failure: are we ready for a REWOLUTION? Insights from two international surveys on healthcare professionals' needs and patients' perceptions. *Eur J Heart Fail*. 2023;25:364–372. doi: 10.1002/ejhf.2798
15. Hill L, Prager Geller T, Baruah R, Beattie JM, Boyne J, de Stoutz N, Di Stolfo G, Lambrinou E, Skibelund AK, Uchmanowicz I, et al. Integration of a palliative approach into heart failure care: a European Society of Cardiology Heart Failure Association position paper. *Eur J Heart Fail*. 2020;22:2327–2339. doi: 10.1002/ejhf.1994
16. Elbeddini A, Sawhney M, Tayefehchamani Y, Yilmaz Z, Elshahawi A, Josh Villegas J, Dela Cruz J. Deprescribing for all: a narrative review identifying inappropriate polypharmacy for all ages in hospital settings. *BMJ Open Qual*. 2021;10:e001509. doi: 10.1136/bmjoq-2021-001509
17. Krishnaswami A, Steinman MA, Goyal P, Zullo AR, Anderson TS, Birtcher KK, Goodlin SJ, Maurer MS, Alexander KP, Rich MW, et al; Geriatric Cardiology Section Leadership Council, American College of Cardiology. Deprescribing in older adults with cardiovascular disease. *J Am Coll Cardiol*. 2019;73:2584–2595. doi: 10.1016/j.jacc.2019.03.467
18. Goyal P, Anderson TS, Bernacki GM, Marcum ZA, Orkaby AR, Kim D, Zullo A, Krishnaswami A, Weissman A, Steinman MA, et al. Physician perspectives on deprescribing cardiovascular medications for older adults. *J Am Geriatr Soc*. 2020;68:78–86. doi: 10.1111/jgs.16157
19. 2023 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71:2052–2081. doi: 10.1111/jgs.18372
20. Page RL 2nd, O'Bryant CL, Cheng D, Dow TJ, Ky B, Stein CM, Spencer AP, Trupp RJ, Lindenfeld J; on behalf of the American Heart Association Clinical Pharmacology and Heart Failure and Transplantation Committees of the Council on Clinical Cardiology; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Drugs that may cause or exacerbate heart failure: a scientific statement from the American Heart Association [published correction appears in *Circulation*. 2016;134:e261]. *Circulation*. 2016;134:e32–e69. doi: 10.1161/CIR.0000000000000426
21. Cadogan CA, Ryan C, Hughes CM. Appropriate polypharmacy and medicine safety: when many is not too many. *Drug Saf*. 2016;39:109–116. doi: 10.1007/s40264-015-0378-5
22. Afari ME, Aoun J, Khare S, Tsao L. Subcutaneous furosemide for the treatment of heart failure: a state-of-the art review. *Heart Fail Rev*. 2019;24:309–313. doi: 10.1007/s10741-018-9760-6
23. Tomasoni D, Vishram-Nielsen JKK, Pagnesi M, Adamo M, Lombardi CM, Gustafsson F, Metra M. Advanced heart failure: guideline-directed medical therapy, diuretics, inotropes, and palliative care. *ESC Heart Fail*. 2022;9:1507–1523. doi: 10.1002/ehf2.13859
24. Vaduganathan M, Docherty KF, Claggett BL, Jhund PS, de Boer RA, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. *Lancet*. 2022;400:757–767. doi: 10.1016/S0140-6736(22)01429-5
25. Butler J, Stebbins A, Melenovský V, Sweitzer NK, Cowie MR, Stehlik J, Khan MS, Blaustein RO, Ezekowitz JA, Hernandez AF, et al; VICTORIA Study Group. Vericiguat and health-related quality of life in patients with heart failure with reduced ejection fraction: insights from the VICTORIA Trial. *Circ Heart Fail*. 2022;15:e009337. doi: 10.1161/CIRCHEARTFAILURE.121.009337
26. Nizamic T, Murad MH, Allen LA, McIlvennan CK, Wordingham SE, Matlock DD, Dunlay SM. Ambulatory inotrope infusions in advanced heart failure: a systematic review and meta-analysis. *JACC Heart Fail*. 2018;6:757–767. doi: 10.1016/j.jchf.2018.03.019
27. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, et al; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007–1016. doi: 10.1056/NEJMoa1805689
28. Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, Dember LM, Frantz JG, Hershberger RE, Maurer MS, et al; Writing Committee. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis. *J Am Coll Cardiol*. 2023;81:1076–1126. doi: 10.1016/j.jacc.2022.11.022
29. Ommen SR, Mital S, Burke MA, Day SM, Deswal A, Elliott P, Evanovich LL, Hung J, Joglar JA, Kantor P, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in *Circulation*. 2020;142:e633]. *Circulation*. 2020;142:e558–e631. doi: 10.1161/CIR.0000000000000937
30. Dong T, Alencherry B, Ospina S, Desai MY. Review of mavacamten for obstructive hypertrophic cardiomyopathy and future directions. *Drug Des Devel Ther*. 2023;17:1097–1106. doi: 10.2147/DDDT.S368590
31. Jacobsen AP, Raber I, McCarthy CP, Blumenthal RS, Bhatt DL, Cusack RW, Serruys P, Wijns W, McEvoy JW. Lifelong aspirin for all in the secondary prevention of chronic coronary syndrome: still sacrosanct

or is reappraisal warranted? *Circulation*. 2020;142:1579–1590. doi: 10.1161/circulationaha.120.045695
32. Orkaby AR, Lu B, Ho YL, Treu T, Galloway A, Wilson PWF, Cho K, Gaziano JM, Alexander KP, Gagnon DR, et al. New statin use, mortality and first cardiovascular events in older US veterans by frailty status. *J Am Geriatr Soc*. 2023;72:410–422. doi: 10.1111/jgs.18700
33. Nanna MG, Navar AM, Wang TY, Mi X, Virani SS, Louie MJ, Lee LV, Goldberg AC, Roger VL, Robinson J, et al. Statin use and adverse effects among adults >75 years of age: insights from the Patient and Provider Assessment of Lipid Management (PALM) Registry. *J Am Heart Assoc*. 2018;7:e008546. doi: 10.1161/JAHA.118.008546
34. Samaras K, Makkar SR, Crawford JD, Kochan NA, Slavin MJ, Wen W, Trollor JN, Brodaty H, Sachdev PS. Effects of statins on memory, cognition, and brain volume in the elderly. *J Am Coll Cardiol*. 2019;74:2554–2568. doi: 10.1016/j.jacc.2019.09.041
35. Adhikari A, Tripathy S, Chuzi S, Peterson J, Stone NJ. Association between statin use and cognitive function: a systematic review of randomized clinical trials and observational studies. *J Clin Lipidol*. 2021;15:22–32.e12. doi: 10.1016/j.jacl.2020.10.007
36. Joseph J, Pajewski NM, Dolor RJ, Sellers MA, Perdue LH, Peeples SR, Henrie AM, Woolard N, Jones WS, Benziger CP, et al; PREVENTABLE Trial Research Group. Pragmatic evaluation of events and benefits of lipid lowering in older adults (PREVENTABLE): trial design and rationale. *J Am Geriatr Soc*. 2023;71:1701–1713. doi: 10.1111/jgs.18312
37. Zoungas S, Curtis A, Spark S, Wolfe R, McNeil JJ, Beilin L, Chong TT, Cloud G, Hopper I, Kost A, et al; STAREE Investigator Group. Statins for extension of disability-free survival and primary prevention of cardiovascular events among older people: protocol for a randomised controlled trial in primary care (STAREE trial). *BMJ Open*. 2023;13:e069915. doi: 10.1136/bmjopen-2022-069915
38. van der Ploeg MA, Floriani C, Achterberg WP, Bogaerts JMK, Gussekloo J, Mooijaart SP, Streit S, Poortvliet RKE, Drewes YM. Recommendations for (discontinuation of) statin treatment in older adults: review of guidelines. *J Am Geriatr Soc*. 2020;68:417–425. doi: 10.1111/jgs.16219
39. Kutner JS, Blatchford PJ, Taylor DH Jr, Ritchie CS, Bull JH, Fairclough DL, Hanson LC, LeBlanc TW, Samsa GP, Wolf S, et al. Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA Intern Med*. 2015;175:691–700. doi: 10.1001/jamainternmed.2015.0289
40. Volgman AS, Nair G, Lyubarova R, Merchant FM, Mason P, Curtis AB, Wenger NK, Aggarwal NT, Kirkpatrick JN, Benjamin EJ. Management of atrial fibrillation in patients 75 years and older: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79:166–179. doi: 10.1016/j.jacc.2021.10.037
41. Hoeper MM, Huscher D, Ghofrani HA, Delcroix M, Distler O, Schweiger C, Grunig E, Staehler G, Rosenkranz S, Halank M, et al. Elderly patients diagnosed with idiopathic pulmonary arterial hypertension: results from the COMPERA registry. *Int J Cardiol*. 2013;168:871–880. doi: 10.1016/j.ijcard.2012.10.026
42. Hoeper MM, Al-Hiti H, Benza RL, Chang SA, Corris PA, Gibbs JSR, Grünig E, Jansa P, Klinger JR, Langleben D, et al; REPLACE Investigators. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med*. 2021;9:573–584. doi: 10.1016/S2213-2600(20)30532-4
43. Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, Frantsve-Hawley J, Kawut SM, Ryan JJ, Rosenzweig EB, et al. Therapy for pulmonary arterial hypertension in adults: update of the CHEST Guideline and Expert Panel report. *Chest*. 2019;155:565–586. doi: 10.1016/j.chest.2018.11.030
44. Mayeux JD, Pan IZ, Dechand J, Jacobs JA, Jones TL, McKellar SH, Beck E, Hatton ND, Ryan JJ. Management of pulmonary arterial hypertension. *Curr Cardiovasc Risk Rep*. 2021;15:2. doi: 10.1007/s12170-020-00663-3
45. De Lima L, Krakauer EL, Lorenz K, Praill D, Macdonald N, Doyle D. Ensuring palliative medicine availability: the development of the IAHPC list of essential medicines for palliative care. *J Pain Symptom Manage*. 2007;33:521–526. doi: 10.1016/j.jpainsymman.2007.02.006
46. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage*. 2006;31:58–69. doi: 10.1016/j.jpainsymman.2005.06.007
47. MacIntyre IM, Turtle EJ, Farrah TE, Graham C, Dear JW, Webb DJ; PATH-BP (Paracetamol in Hypertension–Blood Pressure) Investigators. Regular acetaminophen use and blood pressure in people with hypertension: the PATH-BP trial. *Circulation*. 2022;145:416–423. doi: 10.1161/CIRCULATIONAHA.121.056015
48. Piña IL, Di Palo KE, Ventura HO. Psychopharmacology and cardiovascular disease. *J Am Coll Cardiol*. 2018;71:2346–2359. doi: 10.1016/j.jacc.2018.03.458
49. Gupta K, Prasad A, Nagappa M, Wong J, Abrahamyan L, Chung FF. Risk factors for opioid-induced respiratory depression and failure to rescue: a review. *Curr Opin Anaesthesiol*. 2018;31:110–119. doi: 10.1097/ACO.0000000000000541
50. Childers JW, King LA, Arnold RM. Chronic pain and risk factors for opioid misuse in a palliative care clinic. *Am J Hosp Palliat Care*. 2015;32:654–659. doi: 10.1177/1049909114531445
51. Klasson C, Helde Frankling M, Lundh Hagelin C, Björkhem-Bergman L. Fatigue in cancer patients in palliative care: a review on pharmacological interventions. *Cancers (Basel)*. 2021;13:985. doi: 10.3390/cancers13050985
52. Di Palo KE. Psychological disorders in heart failure. *Heart Fail Clin*. 2020;16:131–138. doi: 10.1016/j.hfc.2019.08.011
53. Johnson MJ, Currow DC. Opioids for breathlessness: a narrative review. *BMJ Support Palliat Care*. 2020;10:287–295. doi: 10.1136/bmjspcare-2020-002314
54. Gaertner J, Fusi-Schmidhauser T, Stock S, Siemens W, Vennedey V. Effect of opioids for breathlessness in heart failure: a systematic review and meta-analysis. *Heart*. 2023;109:1064–1071. doi: 10.1136/heartjnl-2022-322074
55. Kawaguchi J, Hamatani Y, Hirayama A, Nishimura K, Nakai E, Nakamura E, Miyata M, Kawano Y, Takada Y, Anchi Y, et al. Experience of morphine therapy for refractory dyspnea as palliative care in advanced heart failure patients. *J Cardiol*. 2020;75:682–688. doi: 10.1016/j.jjcc.2019.12.015
56. Sobanski PZ, Alt-Epping B, Currow DC, Goodlin SJ, Grodzicki T, Hogg K, Janssen DJA, Johnson MJ, Krajnik M, Leget C, et al. Palliative care for people living with heart failure: European Association for Palliative Care Task Force expert position statement. *Cardiovasc Res*. 2020;116:12–27. doi: 10.1093/cvr/cvz200
57. Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. *Eur J Heart Fail*. 2023;25:528–537. doi: 10.1002/ejhf.2810
58. von Haehling S, Lainscak M, Springer J, Anker SD. Cardiac cachexia: a systematic overview. *Pharmacol Ther*. 2009;121:227–252. doi: 10.1016/j.pharmthera.2008.09.009
59. Vest AR, Chan M, Deswal A, Givertz MM, Lekavich C, Lennie T, Litwin SE, Parsly L, Rodgers JE, Rich MW, et al. Nutrition, obesity, and cachexia in patients with heart failure: a consensus statement from the Heart Failure Society of America Scientific Statements Committee. *J Card Fail*. 2019;25:380–400. doi: 10.1016/j.cardfail.2019.03.007
60. Doppen M, Kung S, Maijers I, John M, Dunphy H, Townsley H, Eathorne A, Semprini A, Braithwaite I. Cannabis in palliative care: a systematic review of current evidence. *J Pain Symptom Manage*. 2022;64:e260–e284. doi: 10.1016/j.jpainsymman.2022.06.002
61. Diop MS, Rudolph JL, Zimmerman KM, Richter MA, Skarf LM. Palliative care interventions for patients with heart failure: a systematic review and meta-analysis. *J Palliat Med*. 2017;20:84–92. doi: 10.1089/jpm.2016.0330
62. Rogers JG, Patel CB, Mentz RJ, Granger BB, Steinhauser KE, Fiuzat M, Adams PA, Speck A, Johnson KS, Krishnamoorthy A, et al. Palliative care in heart failure: the PAL-HF randomized, controlled clinical trial. *J Am Coll Cardiol*. 2017;70:331–341. doi: 10.1016/j.jacc.2017.05.030
63. Mandawat A, Heidenreich PA, Mandawat A, Bhatt DL. Trends in palliative care use in veterans with severe heart failure using a large national cohort. *JAMA Cardiol*. 2016;1:617–619. doi: 10.1001/jamacardio.2016.1687
64. Chang YK, Kaplan H, Geng Y, Mo L, Philip J, Collins A, Allen LA, McClung JA, Denvir MA, Hui D. Referral criteria to palliative care for patients with heart failure: a systematic review. *Circ Heart Fail*. 2020;13:e006881. doi: 10.1161/CIRCHEARTFAILURE.120.006881
65. Warraich HJ, Wolf SP, Mentz RJ, Rogers JG, Samsa G, Kamal AH. Characteristics and trends among patients with cardiovascular disease referred to palliative care. *JAMA Netw Open*. 2019;2:e192375. doi: 10.1001/jamanetworkopen.2019.2375
66. Feder SL, Murphy TE, Abel EA, Akgün KM, Warraich HJ, Ersek M, Fried T, Redeker NS. Incidence and trends in the use of palliative care among patients with reduced, middle-range, and preserved ejection fraction heart failure. *J Palliat Med*. 2022;25:1774–1781. doi: 10.1089/jpm.2022.0093