Therapeutic Class Overview
Cardiovascular agents, miscellaneous

INTRODUCTION

- Approximately 6 million Americans aged ≥ 20 years have heart failure (HF). In 2018, 83,616 people died from HF in the United States (US) (*Virani et al 2021*). The total percentage of the population with HF is projected to rise from 2.4% in 2012 to 3.0% in 2030.
- Pediatric cardiomyopathies, which are the most common cause of pediatric HF, are rare diseases with an annual incidence of 1.13 cases per 100,000 among children < 18 years of age. Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are the most common forms observed in this patient population (*Lee et al 2017, Virani et al 2021*).
- Many conditions or comorbidities are associated with an increased risk for developing HF. Hypertension is the most important modifiable risk factor in the US. Other important risk factors for the development of HF include obesity, diabetes, metabolic syndrome, and atherosclerotic disease (*Yancy et al 2013*). In children, cardiomyopathy may be caused by coronary artery abnormalities, tachyarrhythmias, exposure to infection or toxins, or are secondary to other underlying disorders (*Lee et al 2017*).
- There are 2 forms of heart failure:
  - Heart failure with reduced ejection fraction (HFrEF): Ejection fraction (EF) ≤ 40%; also referred to as systolic heart failure
  - Heart failure with preserved ejection fraction (HFpEF): EF ≥ 50%; also referred to as diastolic heart failure (*Yancy et al 2013*).
- The following table outlines the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the New York Heart Association (NYHA) Functional classes for systolic heart failure (*Yancy et al 2013*):

Table 1. ACCF/AHA Heart Failure Stages and NYHA Classes for Systolic Heart Failure

ACCF/AHA Stages	NYHA Class
• **A:** At high risk for HF but without structural heart disease or symptoms of HF • **B:** Structural heart disease but without signs or symptoms of HF • **C:** Structural heart disease with prior or current symptoms of HF • **D:** Refractory HF requiring specialized treatment	• **I:** No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. • **II:** Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. • **III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF. • **IV:** Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

Abbrv: ACCF/AHA = American College of Cardiology Foundation/American Heart Association, NYHA = New York Heart Association, HF = heart failure.

- The cardinal symptoms of HF are dyspnea and fatigue. HF leads to exercise intolerance, fluid retention, pulmonary congestion, and peripheral edema often resulting in hospitalizations (*Yancy et al 2013*).
- The Atherosclerosis Risk in Communities (ARIC) study identified that African Americans have the highest risk for HF with a greater 5-year fatality rate than Caucasians ($p < 0.05$) (*Lloyd-Jones et al 2002, Virani et al 2021*).
- In order to predict one's risk of HF, a number of risk score models may be used including the Framingham Heart Failure Risk Score, Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) risk score, Seattle Heart Failure Model, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) risk score, and Heart Failure risk score (*National Heart, Lung, and Blood Institute [NHLBI] and Boston University 2015, Yancy et al 2013*).
- Corlanor (ivabradine) reduces spontaneous pacemaker activity at the cardiac sinus node by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel to selectively inhibit the funny-current (I_f), thus reducing the heart rate. Ventricular repolarization and myocardial contractility are not affected.

- Verquvo (vericiguat) stimulates soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide signaling pathway. By directly stimulating sGC, independently of and synergistically with nitric oxide, vericiguat augments levels of intracellular cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and vasodilation (*Verquvo prescribing information 2021*).
- HF guidelines state that ivabradine is an alternative (not first-choice) addition to the treatment regimen of selected patients who are not adequately controlled by their current therapy (*Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017*). HF guidelines do not currently contain recommendations for vericiguat. Of note, for most of the agents used in the management of pediatric patients with HF, the evidence supporting efficacy comes largely from adult studies (*Singh 2019*).
- Angina is a symptom of coronary artery or heart disease (CAD/CHD), also referred to as ischemic heart disease (IHD). (*Centers for Disease Control and Prevention [CDC] 2019*). According to the AHA, CHD is the leading cause of cardiovascular (CV) death in the US (*Virani et al 2021*). In 2018, CHD mortality across all ages in the US included 365,744 individuals.
- Stable angina (SA) occurs upon physical exertion or during mental or emotional stress and typically resolves upon rest (*CDC 2019*). Coronary artery stenosis results in reduced blood flow that manifests as chest pain/discomfort when myocardial oxygen demand is increased upon exertion (*Kones 2010[a]*).
- Factors that increase risk of CHD include smoking, dyslipidemia, hypertension, diabetes, and a family history of these risk factors (*Dobesh et al 2020*). Therefore, one aspect of management involves lifestyle and pharmacologic interventions of these factors to slow progression of CHD. The other aspect of treatment involves reducing the number of angina episodes and increasing the duration of exercise before angina occurs.
- Ranexa (ranolazine ER) is an antianginal agent that does not impact heart rate or blood pressure (*Kones 2010[b], Ranexa prescribing information 2019*). Although its exact mechanism on reducing anginal symptoms is unknown, it is postulated that inhibition of the late phase of the inward sodium channel in cardiac myocytes reduces intracellular calcium. This, in turn, may reduce myocardial oxygen consumption and ventricular tension resulting in myocardial relaxation and reduction in anginal symptoms.
- Ranolazine ER is an alternative for initial therapy in relieving anginal symptoms when other treatments cannot be used or are contraindicated. In fact, ranolazine ER is considered a third line agent (after either a calcium channel blocker or long-acting nitrate) for patients who cannot take a β-blocker due to a contraindication or intolerance (*Fihn et al 2012, Dobesh et al 2020*). Ranolazine ER can also be considered for combination therapy with β-blockers when symptoms are not controlled with initial β-blocker treatment.
- This review includes miscellaneous drugs, which modify the CV system. The current review includes the sinus node inhibitor, Corlanor (ivabradine), the sGC stimulator, Verquvo (vericiguat), and Ranexa (ranolazine ER), an antianginal inhibitor.
- Medispan class: Cardiovascular Agents – Misc; Sinus Node Inhibitors; Ivabradine; Antianginals-Other; Ranolazine

Table 2. Medications Included Within Class Review

Drug	Generic Availability
Corlanor (ivabradine)	-
Ranexa (ranolazine ER)	✔
Verquvo (vericiguat)	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 3. Food and Drug Administration Approved Indications

Indication	Corlanor (ivabradine)	Ranexa (ranolazine ER)	Verquvo (vericiguat)
To reduce the risk of hospitalization for worsening HF in adult patients with stable, symptomatic chronic HF with left ventricular ejection fraction (LVEF) ≤ 35%, who are in sinus rhythm with resting heart rate	✔		

Indication	Corlanor (ivabradine)	Ranexa (ranolazine ER)	Verquvo (vericiguat)
≥ 70 beats per minute (bpm) and either are on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use			
Treatment of stable symptomatic heart failure due to DCM in pediatric patients ≥ 6 months of age, who are in sinus rhythm with an elevated heart rate	✔		
Treatment of chronic angina		✔	
To reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF < 45%			✔

(*Prescribing information: Corlanor 2019, Ranexa 2019, Verquvo 2021*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Ivabradine

- The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) enrolled 6588 patients in NYHA Functional Class II to IV, sinus rhythm with a rate of ≥ 70 bpm, and an EF ≤ 35%. Patients were also required to have had a HF hospitalization in the previous 12 months and no sustained atrial fibrillation or flutter. Patients were randomized to ivabradine (titrated to a maximal dosage of 7.5 mg twice daily) or placebo with standard therapy. Standard therapy included placebo added to a diuretic (in 84%), digoxin (22%), an angiotensin-converting enzyme inhibitor (ACE-I) (79%), an angiotensin receptor blocker (ARB) (14%), a β-blocker (90%), and a mineralocorticoid receptor antagonist (60%). Only 26% of patients were, however, on an optimized β-blocker dose. The median follow-up was approximately 23 months. The primary composite outcome of CV-related death or HF hospitalization was observed in 24% of ivabradine-treated patients and 29% of placebo-treated patients with an absolute risk reduction (ARR) of 4.24% ($p < 0.0001$). However, the reduction in CV death (or all-cause death) was not significant, but the ARR for HF hospitalization was 4.73%, equating to a number needed to treat (NNT) of 21 (*Swedberg et al 2010*).
  - Although inclusion criteria for the SHIFT trial included patients with a heart rate of ≥ 70 bpm, a pre-specified subgroup analysis of the primary endpoint demonstrated significantly more patients with a baseline heart rate of ≥ 77 bpm benefited from ivabradine-treatment compared to < 77 bpm ($p = 0.03$).
  - In terms of safety, ivabradine treatment was associated with more bradycardia (difference, 7.9%), phosphenes (difference, 2%), atrial fibrillation (difference, 1%), and blurred vision (difference, < 1%); of which, only bradycardia led to higher rates of discontinuation with ivabradine treatment (difference, 1.18%; $p < 0.002$).
- One post-hoc analysis of the SHIFT trial examined the correlation between different co-morbidity loads and key endpoints with each treatment group. Those co-morbidities analyzed (from the largest to smallest proportions) included hypertension, myocardial infarction (MI), diabetes, estimated glomerular filtration rate (eGFR) < 60 mL, chronic obstructive pulmonary disease (COPD), anemia, stroke, and peripheral artery disease (PAD). Based on the HF population from SHIFT, cardiac and non-cardiac co-morbidities significantly affected CV outcomes. The primary endpoint, the composite of CV death or HF hospitalization rate, increased with the co-morbidity load ($p < 0.0001$) with most events in patients with ≥ 4 comorbidities for both ivabradine and placebo (*Böhm et al 2015*).
- Another post-hoc analysis of the SHIFT trial assessed the impact of ivabradine on early readmissions in patients hospitalized for HF. A total of 1186 patients were identified with ≥ 1 HF hospitalization; of these, 334 patients were readmitted within 3 months for any reason. Ivabradine significantly reduced the risk of early recurrent hospitalizations following a first HF hospitalization. This reduction of risk was significant from the first month onwards (30% relative risk reduction; incidence rate ratio [IRR], 0.70; $p < 0.05$) and ranged from a relative risk reduction of 21 to 25% within 2 and 3 months following a HF hospitalization. However, mortality rates were similar to placebo within the first 3 months following a HF hospitalization. It is important to note, SHIFT was not designed or powered to determine the effect of treatment in patients hospitalized for HF; therefore, the role of ivabradine before and after hospitalization cannot be fully concluded and further studies are needed (*Komajda et al 2016*).

- Additional safety evidence for ivabradine comes from the MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) trial, a randomized controlled trial (RCT) in which 10,917 patients with CHD and an EF < 40% were assigned to treatment with ivabradine 7.5 mg twice daily or placebo (with standard therapy) and followed for a median of 19 months. Ivabradine did not reduce the primary outcome of CV-related death, MI, or HF hospitalization. In a pre-specified subgroup of patients with a heart rate of ≥ 70 bpm (total population, N = 5392; ivabradine, n = 2699), ivabradine did significantly reduce the incidence of hospitalization due to fatal and nonfatal MI, MI or unstable angina, and coronary revascularization, after a median of 19 months (*Fox et al 2008*).
  - There was no significant difference in the incidences of serious adverse events (23% for both; p = 0.7); however, more psychiatric disorders were observed with ivabradine treatment compared to placebo (0.3 vs 0.1%, respectively; p = 0.01).
- Ivabradine has also been studied in the Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure study (SIGNIFY). This study included patients who had stable coronary artery disease without clinical HF (N = 19,102) and with a heart rate of ≥ 70 bpm. The addition of ivabradine 10 mg twice daily to standard therapy did not reduce the risk of death from CV causes or nonfatal MI after a median of 27.8 months (*Fox et al 2014*).
  - The incidence of bradycardia was significantly greater with ivabradine (at the higher 10 mg twice daily dosing) compared to placebo (18 vs 2.3%, respectively; p < 0.001). Other adverse events that occurred significantly more often with ivabradine included atrial fibrillation (5.3 vs 3.8%, respectively) and phosphenes (5.4% vs 0.5%, respectively) (p < 0.001 for both).
  - Significantly more serious adverse events were observed with ivabradine (p = 0.001). Those serious adverse events included cardiac disorders (19 vs 16.7%; p < 0.001) and eye disorders (1.8 vs 1.4%; p = 0.02).
- The approval of ivabradine's pediatric DCM indication was based on a double-blind (DB) clinical trial of 116 patients aged 6 months to < 18 years with DCM in sinus rhythm, NYHA/Ross class II to IV HF, and LVEF ≤ 45%. Patients were randomized to receive ivabradine or placebo. The majority of patients were treated concomitantly with ACE-Is (94%). Doses of study medication were titrated over a 2- to 8-week period to achieve a 20% heart rate reduction without inducing bradycardia (*Bonnet et al 2017*).
  - The target heart rate reduction was obtained at the end of the titration period in a significantly higher proportion of patients treated with ivabradine vs placebo (70% vs 12% respectively; odds ratio = 17.24; 95% confidence interval (CI), 5.91 to 50.30; p < 0.0001).
  - A statistically significant reduction in heart rate was observed with ivabradine vs placebo at the end of the titration period (-21.2 ± 13.3 bpm vs -1.4 ± 11.5 bpm, respectively).
- A Cochrane review evaluated the effectiveness and safety of ivabradine in patients with chronic HF via an analysis of data from 19 RCTs involving a total of 19,628 individuals (*Benstoem et al 2020*). Two meta-analyses, focusing on patients with HFrEF and long-term ivabradine treatment, were performed. Results from these analyses revealed no difference between ivabradine and placebo/usual care/no treatment for mortality from cardiovascular causes (relative risk [RR] 0.99; 95% CI, 0.88 to 1.11 [n=3 studies; moderate certainty evidence]) and no difference in the rate of serious adverse events (RR 0.96; 95% CI, 0.92 to 1.00 [n=2 studies; moderate certainty evidence]). Overall, few studies contributed data to the meta-analyses due to inconsistency in trial design and outcome reporting and measurement. Additionally, the risk of bias among studies varied from low to high, with several studies containing insufficient detail to inform a judgment.

Ranolazine ER

- The Combination Assessment of Ranolazine in Stable Angina (CARISA) study was a randomized, DB trial that compared exercise duration in 823 patients with chronic SA who received either ranolazine ER (750 mg twice daily [n = 272] or 1000 mg twice daily [n = 261]) or placebo (n = 258). Time to angina during exercise, weekly angina frequency, and weekly nitroglycerin use were secondary outcomes. Patients continued on either atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg daily (*Chaitman et al 2004*).
  - The mean differences from placebo in modified Bruce treadmill exercise duration at trough ranolazine ER levels (12 hours after dosing) were 23.7 seconds with ranolazine ER 750 mg and 24 seconds with ranolazine ER 1000 mg (p = 0.03).
  - The time to angina was also found to be statistically significant between each ranolazine ER dose and placebo.
  - The mean number of angina attacks per week was 3.3, 2.5, and 2.1 for placebo, ranolazine ER 750 mg (p = 0.006 vs placebo), and ranolazine ER 1000 mg (p < 0.001 vs placebo), respectively.

- Similarly, a significant reduction in mean nitroglycerin doses per week was observed with 3.1 for placebo, 2.1 for ranolazine ER 750 mg (p = 0.016), and 1.8 for ranolazine ER 1000 mg (p < 0.001).
- In the Efficacy of Ranolazine in Chronic Angina (ERICA) trial, the efficacy of ranolazine ER was evaluated in 565 patients with chronic SA with symptoms despite treatment with a maximum dose of amlodipine. Patients were randomized to receive either ranolazine ER 1000 mg twice daily (n = 281) or placebo (n = 284) for 6 weeks. All patients received amlodipine 10 mg daily and 45% of patients also took long-acting nitrates (*Stone et al 2006*).
  - The mean number of angina attacks per week was 4.3 with placebo and 3.3 with ranolazine ER (p = 0.028).
  - The mean number of nitroglycerin doses per week was significantly less with ranolazine ER compared to placebo (2.7 vs 3.6, p = 0.014).
- A systematic review of 7 RCTs evaluated ranolazine ER efficacy in 3,317 patients with chronic SA due to CAD compared to placebo or conventional treatment. Outcomes included exercise stress test duration, time to onset of angina or ST-segment depression, weekly nitroglycerin use, weekly anginal attacks, and quality of life. Generally, these outcomes were shown to be improved with use of ranolazine ER at higher doses (at least 750 mg twice daily) compared to placebo. One study that compared ranolazine ER 400 mg 3 times daily to atenolol demonstrated a small benefit in exercise outcomes when evaluated at peak time (1 hour after ranolazine ER dosing). Improvements in exercise duration were generally between 25 and 30 seconds and the difference in the decrease in weekly anginal attacks or nitroglycerin use between ranolazine ER and placebo was ≤ 1 (*Banon et al 2014*).

Vericiguat

- In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) Phase 3, multinational trial, 5,050 patients with NYHA class II to IV chronic HF and an EF < 45% were randomly assigned to a target dose of vericiguat 10 mg once daily (n = 2,526) or placebo (n = 2,524), in addition to guideline-based medical therapy. Enrolled patients also had to have evidence of worsening HF. The primary outcome was a composite of death from CV causes or first hospitalization for HF, which occurred in 897 patients (35.5%) in the vericiguat group vs 972 patients (38.5%) in the placebo group (hazard ratio [HR], 0.90; 95% CI, 0.82 to 0.98; p = 0.02) at a median of 10.8 months. However, death from CV causes (16.4% vericiguat vs 17.5% placebo; HR, 0.93; 95% CI, 0.81 to 1.06) and hospitalization for HF (27.4% vs 29.6%; HR, 0.90; 95% CI, 0.81 to 1.00) were not significantly different between groups. Total hospitalizations for HF (initial and recurrent) were significantly reduced with vericiguat (1,223 vs 1,336; p = 0.02) as was the composite of death from any cause or first HF hospitalization (37.9% vericiguat vs 40.9% placebo; HR, 0.90; 95% CI, 0.83 to 0.98; p = 0.02). Serious adverse events occurred in 32.8% of patients in the vericiguat group vs 34.8% of patients in the placebo group. Symptomatic hypotension (9.1% vs 7.9%) and syncope (4% vs 3.5%) were observed more frequently in the vericiguat group (*Armstrong et al 2020a*).

- Of note, ivabradine and vericiguat have been studied separately in patients with HFpEF via the EDIFY and VITALITY-HFpEF trials, respectively. Both trials were placebo-controlled, multicenter trials. EDIFY included 179 HF patients in sinus rhythm with a heart rate of ≥ 70 bpm, N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥ 220 pg/mL, and LVEF ≥ 45%. Patients were randomly assigned to ivabradine 7.5 mg twice daily or placebo and followed up for 8 months. At trial conclusion, reductions in heart rate with ivabradine did not improve outcomes (*Komajda et al 2017*). Additionally, VITALITY included 789 chronic HF patients with a LVEF ≥ 45% and NYHA class II to III symptoms. Patients were randomly assigned to vericiguat up-titrated to 15 mg once daily (n = 264), 10 mg once daily (n = 263), or placebo (n = 262). Results revealed that vericiguat 15 or 10 mg once daily did not improve the Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitation score (PLS) compared to placebo after 24 weeks (*Armstrong et al 2020b*).

CLINICAL GUIDELINES

Heart Failure

- The 2016 and 2017 focused updates of the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) HF guidelines recommend the following medications in patients with HFrEF (Stage C and D; NYHA Class I to IV): (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017*).
  - First line treatments include an ACE-I or ARB in conjunction with an evidence-based β-blocker and diuretics, as needed.
    - Entresto (sacubitril/valsartan) has been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE-Is or ARBs. Angiotensin receptor neprilysin inhibitors (ARNIs) may be considered first line; however, recommendations are made with a lower level of evidence than those associated with ACE-Is or ARBs

and recommendations are made only if a patient can tolerate an ACE-I or ARB. For those patients for whom an ARNI is not appropriate, continued use of an ACE-I, followed by an ARB, for all classes of HFrEF remains strongly advised.
  - Add-on treatments vary according to the patient specific factors, but may include an aldosterone antagonist, hydralazine-nitrates, an ARNI, ivabradine, digoxin, and device therapy (ie, implantable cardioverter-defibrillator [ICD] or cardiac resynchronization therapy [CRT]).
  - Ivabradine can be beneficial in patients who have stable, symptomatic (NYHA Class II or III) chronic HFrEF, are in normal sinus rhythm, have a heart rate of ≥ 70 bpm at rest, and are on the maximally tolerated dose of β-blockers
- Based on the 2016 European Society of Cardiology/Heart Failure Association (ESC/HFA) HF guidelines, ivabradine is recommended to be prescribed after treatment failure with maximally tolerated doses of ACE-I/ARB/ARNIs, β-blockers, mineralocorticoid receptor antagonists, and in patients still symptomatic with a LVEF ≤ 35%, in sinus rhythm, and with a heart rate ≥ 70 bpm. If patients still have resistant symptoms, then clinicians may consider adding digoxin, hydralazine plus isosorbide dinitrate, or propose a left ventricular assist device (LVAD) or heart transplant (*Ponikowski et al 2016).*
  - Diuretics and ACE-Is/ARBs are considered first-line therapies, whereas β-blockers and devices for electric therapy are used less often in children than in adults. In end-stage disease, heart transplantation is the best choice of treatment, while a left ventricular assist device can be used as a bridge to transplantation (due to the difficulties in finding organ donors), recovery (in the case of myocarditis), or destination therapy (for patients with systemic disease).
- In 2014, the European Medicine's Agency (EMA) published updated guidance for ivabradine in the treatment of angina. Updated guidance states that ivabradine should only be used to alleviate angina symptoms, but should be stopped if no to limited benefit is observed after 3 months of treatment. Additionally, increased incidences of atrial fibrillation and bradycardia were observed in trials; although study doses were higher than EMA-approved doses (*EMA 2014, Fox et al 2014*).
- Due to vericiguat's recent approval, official recommendations regarding its use are not incorporated in current HF practice guidelines.

Ischemic heart disease/chronic stable angina

- Guidelines for treatment of chronic stable angina, including AHA and ACCF, on the diagnosis and management of stable IHD include the following recommendations (*Fihn et al 2012*):

  Class I recommendations (all have level of evidence B)
  - β-blockers for initial therapy for relief of anginal symptoms.
  - Calcium channel blockers or long-acting nitrates for initial therapy for relief of anginal symptoms for patients in whom β-blockers are contraindicated or not tolerated.
  - Calcium channel blockers or long-acting nitrates in combination with a β-blocker for patients in whom β-blockers do not provide adequate control of symptoms.
  - Short-acting nitroglycerin (sublingual or spray) is recommended for immediate relief of angina.

  Class IIa recommendations (all level of evidence B unless indicated otherwise)
  - Long-acting, non-dihyrodpyridine calcium channel blockers can be used instead of β-blockers for initial therapy.
  - Ranolazine ER can be useful as a substitute for β-blockers for relief of symptoms for patients who cannot tolerate, who have a contraindication to, or in whom β-blockers are not successful.
  - Ranolazine ER can be used in combination with a β-blocker for relief of symptoms for patients in whom initial treatment with a β-blocker alone is not adequate (Level of evidence: A)

SAFETY SUMMARY

- Ivabradine is contraindicated in patients with acute decompensated heart failure, clinically significant hypotension or bradycardia, severe hepatic impairment, pacemaker dependence (heart rate maintained exclusively by the pacemaker), concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors, and sick sinus syndrome, sinoatrial block or third degree atrioventricular (AV) block, unless a functioning demand pacemaker is present.
- Key warnings and precautions include the following:
  - Fetal toxicity: Embryo-fetal toxicity and cardiac teratogenic effects were observed in animal models. Females should use effective contraception when taking ivabradine.

- Atrial fibrillation: Ivabradine increases the risk of atrial fibrillation (ivabradine 5% vs placebo 3.9% per patient per year). Cardiac rhythm should be regularly monitored and ivabradine should be discontinued if atrial fibrillation develops.
- Bradycardia and conduction disturbances: Bradycardia may increase the risk of QT prolongation leading to severe arrhythmias, especially in patients with risk factors such as use of QT prolonging medications. Bradycardia, sinus arrest, and heart block were observed in trials with ivabradine. Concomitant use of verapamil or diltiazem should be avoided, as they can lower heart rate. Ivabradine should be avoided in patients with second degree AV block, unless a functioning demand pacemaker is present.

- The most common adverse effects for ivabradine (incidence ≥ 1%) are bradycardia, hypertension, atrial fibrillation, and luminous phenomena (phosphenes).
- Ranolazine ER is contraindicated in patients with liver cirrhosis, concomitant use of strong CYP3A4 inhibitors (ie, ketoconazole, clarithromycin, nelfinavir) and concomitant use of CYP3A inducers (ie, rifampin, phenobarbital, St. John's wort).
- Key warnings and precautions include the following:
  - QT interval prolongation: Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death. There is little experience with use of ranolazine ER at doses higher than 1000 mg twice daily, with other QT-prolonging drugs, in patients with a family history of long QT syndrome, or with known acquired QT interval prolongation.
  - Renal failure: Ranolazine ER has caused acute renal failure in patients with a creatinine clearance (CrCL) < 30 mL/min. Renal function should be assessed at baseline and periodically in patients with moderate to severe renal impairment (CrCL < 60 mL/min). Ranolazine ER should be discontinued if marked increases in serum creatinine and blood urea nitrogen are observed.
- The most common adverse effects for ranolazine (incidence > 4% and more common than placebo) are dizziness, headache, constipation, and nausea. Adverse effects that led to discontinuation in controlled studies included dizziness, nausea, asthenia, constipation, and headache.
- In a long-term, open-label study evaluating the safety of ranolazine ER use for 2 years, 23.3% of approximately 750 patients discontinued treatment (*Koren et al 2007*). Slightly over 40% of the discontinuations were due to adverse events of which the most common were dizziness and constipation.
- Vericiguat is contraindicated in patients with concomitant use of other sGC stimulators and in pregnancy.
- Key warning and precaution with vericiguat include the risk for embryo-fetal toxicities. Women of childbearing potential should obtain a pregnancy test before treatment initiation and should use effective contraception during treatment and for at least 1 month after the final dose.
- The most common adverse effects for vericiguat (incidence ≥ 5%) are hypotension and anemia.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Corlanor (ivabradine)	Tablets, oral solution	Oral	Twice daily	For adults, the dose should be assessed and adjusted to a resting heart rate of 50 to 60 bpm after 2 weeks. For pediatric patients, the dose should be assessed and adjusted to target a heart rate reduction of ≥ 20% (based on tolerability) after 2 weeks. Should be taken with meals. Oral solution can also be used for adults who are unable to swallow tablets.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ranexa (ranolazine ER)	Extended-release tablets	Oral	Twice daily	Can be titrated to a maximum dose of 1000 mg twice daily based on symptoms. Dose greater than 500 mg twice daily should not be used in patients taking moderate CYP3A4 inhibitors such as diltiazem, verapamil, fluconazole, erythromycin, and grapefruit juice. Monitor clinical response and adverse effects closely in patients taking P-glycoprotein inhibitors such as cyclosporine as ranolazine ER concentrations may be increased.* Can be taken with or without meals. Tablets should not be crushed, chewed, or broken.
Verquvo (vericiguat)	Tablets	Oral	Once daily	Double the dose approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. Should be taken with meals. May be crushed and mixed with water immediately before administration for patients who are unable to swallow whole tablets.

See the current prescribing information for full details; *Dose adjustment of other agents used concomitantly with ranolazine ER may be required; refer to prescribing information for ranolazine ER and concomitant medications for details.

CONCLUSION

- Ivabradine has a novel mechanism action for the treatment of adult and pediatric patients with HF and specific cardiac abnormalities.
- Ivabradine 10 mg twice daily has demonstrated no clinical benefit in patients with stable coronary heart disease without clinical HF based on results from the SIGNIFY trial (*Fox et al 2014*).
- In 2014, the EMA published updated guidance for ivabradine in the treatment of angina. Updated guidance states that ivabradine should only be used to alleviate angina symptoms, but should be stopped if no to limited benefit is observed after 3 months of treatment. Additionally, increased incidences of atrial fibrillation and bradycardia were observed in trials; although study doses were higher than EMA-approved doses (*EMA 2014, Fox et al 2014*).
- In the BEAUTIFUL and SHIFT trials, HF patients with ≥ 70 bpm had clinical benefit, specifically for reducing the rate of hospitalizations (*Fox et al 2014, Swedberg et al 2010*).
- The SHIFT trial measured effects of ivabradine in a very niche HF population, most whom were not dose optimized on β-blockers. Compared to placebo plus standard care, ivabradine plus standard care significantly reduced the composite endpoint of CV-related deaths and HF hospitalizations; however, this was primarily driven by rates of HF hospitalization as the rates of CV-related deaths were no different from placebo.

- In all trials, ivabradine has demonstrated increased incidences of bradycardia, eye disturbances (e.g., blurred vision or phosphenes), and atrial fibrillation (*Fox et al 2008, Fox et al 2014, Swedberg et al 2010*).
- Based on HF guidelines, ivabradine can be beneficial in patients who have stable, symptomatic (NYHA Class II or III) chronic HFrEF, are in normal sinus rhythm, have a heart rate of ≥ 70 bpm at rest, and are on maximally tolerated doses of β-blockers (*Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017*).
- Ranolazine ER is an antianginal agent that does not impact hemodynamic parameters such as heart rate or blood pressure. Although its exact mechanism of action is unknown, it is postulated that its action reduces intracellular calcium in cardiac myocytes leading to myocardial relaxation.
- Clinical trials have demonstrated statistical improvement in exercise duration, weekly anginal attacks, and weekly nitroglycerin use compared to placebo in patients with SA receiving background standard of care treatment (*Chaitman et al 2004, Stone et al 2006, Banon et al 2014*). Well-designed trials comparing ranolazine ER to standard of care treatments such as β-blockers or calcium channel blockers are lacking.
- According to guidelines, including the ACCF and AHA, ranolazine ER is an alternative treatment option for the relief of anginal symptoms in patients with stable IHD (*Fihn et al 2012*). Ranolazine ER can be considered as a third line agent (after either a calcium channel blocker or long-acting nitrate) for patients who cannot take a β-blocker due to a contraindication or intolerance. For patients who have persistent symptoms despite β-blocker therapy, ranolazine ER can be used in combination with a β-blocker However, the use of either a calcium channel blocker or long-acting nitrate in combination with a β-blocker should be considered first.
- The mechanism of action of vericiguat (sGC stimulation) is also unique for the treatment of adults with symptomatic chronic HF and an EF <45%.
- In the VICTORIA trial, vericiguat was associated with significantly less occurrences of the composite of death from CV causes or first hospitalization for HF as compared to placebo at a median of 10.8 months. However, death from CV causes and hospitalization for HF were not significantly different between groups. Serious adverse events in VICTORIA occurred in 32.8% of patients in the vericiguat group vs. 34.8% of patients in the placebo group.
- Due to vericiguat's recent approval, official recommendations regarding its use are not incorporated in current HF practice guidelines.

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