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A Novel Agent for Heart Failure

By: Patrick O'Day, Pharm.D.

Heart Failure at a Glance: In 2011, heart failure (HF) was mentioned in 1 of every 9 death certificates in the United States.[1] Practice guidelines developed by the American College of Cardiology (ACC) and American Heart Association (AHA) can be a valuable resource in treating HF patients.[2] However, in some cases, guideline-driven treatments may not be adequate, prompting investigators to explore alternative therapies.

A New Agent Emerges: Resting heart rate has been shown to be a predictor of mortality and morbidity in a wide range of patients, including those with chronic HF.[3] In response to the association between slower heart rate and lower risk of cardiovascular complications, ivabradine (Corlanor®; Amgen Pharmaceuticals) was developed. This novel agent was specifically designed to reduce heart rate by selectively inhibiting the cardiac pacemaker I_f ionic current (also known as the funny channel) in a dose-dependent manner.[3]

Indications for Use: Ivabradine was approved by the Food and Drug Administration (FDA) in April 2015 for reducing the risk of hospitalizations for worsening HF in patients meeting the following clinical criteria:

1. Stable, symptomatic chronic HF
2. Normal sinus rhythm
3. Left ventricular ejection fraction (LVEF) ≤35%
4. Resting heart rate ≥70 beats per minute (bpm)
5. Beta-blockers contraindicated or on maximally tolerated doses[4]

Pharmacokinetics: Ivabradine reaches peak levels around 1 hour after oral administration and has an effective half-life of 6 hours.[4] When administered with food, absorption is delayed; however, plasma concentrations are

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Anoro™ Ellipta® for Chronic Obstructive Pulmonary Disease

By: Jason Yerke, Pharm.D.

Background: Chronic obstructive pulmonary disease (COPD) refers to a group of diseases that are characterized by blockage of airflow that can cause difficulty breathing and lead to considerable morbidity and mortality.[1] In the United States, the main cause of COPD is smoking although other risk factors like air pollutants and respiratory infections may also contribute to its development.[1] As of 2011, 15 million U.S. patients reported a diagnosis of COPD, including 7.6% of Ohio residents[1,2]. Additionally, COPD and other chronic lower respiratory diseases were the third leading cause of death in U.S. in 2011.[1,2] Clinical suspicion for COPD is raised in a patient with chronic cough, dyspnea, and sputum production with documented risk factors.[3] Spirometry is needed to confirm the presence of COPD, with a forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of <0.70 post-bronchodilator being indicative of the disease. Treatment options include smoking cessation, avoidance of air pol-

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increased by 20-40%. Ivabradine and its equipotent active metabolite are primarily metabolized via the cytochrome P450 (CYP) 3A4 enzyme system.

Key Clinical Trial: Swedberg and colleagues conducted a key investigation entitled the **S**ystolic **H**eart Failure treatment with the $\mathbf{I_f}$ inhibitor ivabradine **T**rial (SHIFT).[5,6] In this randomized, double-blind, placebo-controlled study, patients (N=6558) received either ivabradine (n=3268) or placebo (n=3290). The initial dose of ivabradine (5 mg twice daily) was titrated to a maximum dose of 7.5 mg twice daily; the dose could be adjusted based on resting heart rate and tolerability. Participants needed to be in normal sinus rhythm and were required to have a prior hospital admission for worsening heart failure within the previous 12 months. All enrollees were receiving guideline-driven heart failure therapy for a minimum of 4 weeks. The primary endpoint was the composite of time-to-first event leading to either cardiovascular death or hospital admission for worsening HF. The percentage of patients attaining the primary endpoint was significantly greater in the placebo group than the ivabradine group (29% versus 24%, respectively; hazard ratio 0.82, 95% CI: 0.75-0.90, p<0.0001). This outcome was mainly driven by the occurrence of hospitalization due to worsening of HF since the rate of cardiovascular death was not significantly different between study groups (p=0.128). A significant reduction in the primary endpoint was mainly apparent in patients with elevated baseline heart rates (>77 bpm).

Dosing: Initial dosing of ivabradine is 5 mg twice daily with meals with a maximum dose of 7.5 mg twice daily.[4] Ivabradine is titrated to a heart rate of 50-60 bpm. Dosage adjustments based on heart rate are summarized in Table 1. There are no recommended dosage adjustments for hepatic or renal impairment.

Table 1: Ivabradine Recommended Dosage Adjustments[4]

HR Measurement	Recommended Dosage Adjustment
>60 bpm	Increase the dose by 2.5 mg (given twice daily) up to a maximum of 7.5 mg twice daily
50 to 60 bpm	Maintain dose
<50 bpm or signs and symptoms of bradycardia	Decrease dose by 2.5 mg (given twice daily); If the current dose is 2.5 mg twice daily, ivabradine should be discontinued

bpm=beats per minute HR=heart rate

Adverse Events and Monitoring: Fetal toxicity has been reported.[4] Common adverse events include bradycardia (10%), hypertension (8.9%), and atrial fibrillation (8.3%). Luminous phenomena (disturbances involving enhanced brightness in the visual field) may occur usually within 2 months after initiation of therapy. Heart rate, blood pressure, and cardiac rhythm should be closely monitored. It is important to note that therapy should be discontinued if atrial fibrillation develops.

Where Does Ivabradine Fit into the HF Regimen? Ivabradine has been shown to be beneficial in reducing hospitalizations in HF patients who possess the specific clinical criteria outlined in its FDA-approved indications for use. It should be used as add-on therapy to an optimized, guideline-driven regimen in that select patient population.

Availability and Cost: Ivabradine is supplied as either a scored 5 mg tablet or a 7.5 mg tablet. The 5 mg tablet may be split in half to achieve a 2.5 mg dose. The suggested wholesale price (SWP) of 60 tablets (a month supply) of Corlanor® 5 mg or 7.5 mg is $450.[7]

Formulary Status: Ivabradine was added to the CCHS Formulary restricted to the Department of Cardiology for initiation of therapy. There are no restrictions for continuation of home therapy.

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lution and tobacco smoke, pharmacologic therapies, pulmonary rehabilitation, influenza and pneumococcal vaccinations, and supplemental oxygen.[1] Treatment is determined based upon the patient's airflow restriction, symptoms, and risk for exacerbations potentially leading to hospitalization.[3]

Once-Daily Combination Inhaler for COPD: Anoro™ Ellipta® [(umeclidinium 62.5 mcg + vilanterol 25 mcg); GlaxoSmithKline], a long-acting muscarinic antagonist in combination with a long-acting beta$_2$ agonist (LAMA + LABA), was approved by the Food and Drug Administration (FDA) in December 2013 for maintenance of COPD. It is not FDA-approved for the acute treatment of bronchospasm or asthma.[4] The recommended dosage of this medication is one inhalation once daily. No dosage adjustment is necessary for hepatic or renal dysfunction.

Pharmacology: Umeclidinium acts in airway tissue predominantly through M_3 antagonism. This antagonism leads to smooth muscle relaxation, bronchodilation, and improvement in pulmonary function.[4,5] Vilanterol produces a similar pharmacological effect as umeclidinium.

Clinical Trial Experience: In clinical trials, Anoro™ Ellipta® significantly improved lung function versus placebo following the first dose and throughout therapy.[6,7] It was also associated with improvements in many lung function outcomes in comparison to umeclidinium alone, vilanterol alone, tiotropium, and fluticasone propionate in combination with salmeterol.[6, 8-11] In addition, Anoro™ Ellipta® was associated with significant improvements in some quality of life measures in comparison with placebo, vilanterol, umeclidinium, tiotropium, and fluticasone propionate plus salmeterol.[6-11] In regards to safety, a 52 week trial found very little difference in drug-related adverse effects when comparing umeclidinium/vilanterol, umeclidinium, and placebo.[12] Post-marketing reports have shown Anoro™ Ellipta® to be well tolerated, with diarrhea (2%), limb pain (2%), and pharyngitis (2%) as the most common adverse events. [5]

Clinical Application: As a once-daily inhaled medication, Anoro™ Ellipta® may be able to improve adherence in the outpatient setting. Another advantage is that Anoro™ Ellipta® may be less expensive than combining individual LABA and LAMA products. Anoro™ Ellipta® is available in an institutional size (7 days of therapy) for $100.19 per dry powder inhaler ($14.31/day of therapy).[13] If Spiriva™ Handihaler® (tiotropium, a LAMA) and Serevent™ Diskus® (salmeterol, a LABA) were used in combination, the cost for a day of therapy would be $33.10.

Formulary Status: Anoro™ Ellipta® is not currently on the CCHS Formulary.

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Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Ivabradine (Corlanor®)	Cardiovascular Agent	Heart Failure	Restriction: Restricted to the Department of Cardiology for initiation of therapy There are no restrictions for the continuation of home therapy.
Nintedanib (Ofev®)	Tyrosine Kinase Inhibitor	Idiopathic Pulmonary Fibrosis	Restriction: Restricted to the continuation of home therapy
Sacubitril/valsartan (Entresto®)	Neprilysin Inhibitor/ARB	Heart Failure	Restriction: Restricted to the Department of Cardiology for initiation of therapy in patients with NYHA Class II-IV heart failure AND are on guideline-directed targeted doses of ACE inhibitor or the equivalent ARB therapy for at least 2 weeks. There are no restrictions for the continuation of home therapy.
Treprostinil extended-release tablets (Orenitram®)	Vasodilator	Pulmonary Arterial Hypertension	Restriction: Restricted to continuation of home therapy

ACE=Angiotensin-converting enzyme ARB=Angiotensin II receptor blocker NYHA=New York Heart Association

Changes in Restrictions and Therapeutic Interchange in the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Aprepitant (Emend®)	Neurokinin 1 Receptor Antagonist	Antiemetic	New restriction: Use in the EP Lab for PONV in patients at risk for QT interval prolongation
Calcitonin (Miacalcin®)	Antidote/Hormone	Treatment of Hypercalcemia	Restriction: Restricted to patients that have moderate-to-severe cardiac or neuro-logic symptoms and a corrected serum calcium ≥ 12 mg/dL Patients who do not meet these parameters may receive calcitonin if there is a contraindication to standard therapy (hydration and bisphosphonates). Calcitonin will be ordered via Hyper-calcemia Medication Order Set. Calcitonin dose will be 4 units/kg SQ every 12 hours for 4 doses (48 hours).
Desvenlafaxine (Khedezla®, Pristiq®)	SNRI	Antidepressant	Therapeutic Interchange: All orders for desvenlafaxine fumarate (Khedezla®) will be converted to desvenlafaxine succinate (Pristiq®). The dose conversion from Khedezla® to Pristiq® is a one-to-one conversion.
Valproic acid injection (Depacon®)	Anticonvulsant	Seizures	All formulary restrictions have been removed.

EP=Electrophysiology PONV=Post-operative nausea and vomiting SNRI=Serotonin norepinephrine reuptake inhibitor

Addition to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Dinutuximab (Unituxin®)	Antineoplastic Agent	High–Risk Neuroblastoma	Restriction: Restricted to Department of Pediatric Hematology/Oncology and Bone Marrow Transplant for high-risk neuroblastoma patients

Changes in Formulary Restrictions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Meningococcal Group B Vaccine (Bexsero®)	Vaccine	Meningococcal disease prevention	Restriction: Modify current restriction to include college-entry students aged 16-18 years
Menigococcal Groups A/C/Y and W-135 Diphtheria Conjugate Vaccine (Menveo®)	Vaccine	Meningococcal disease prevention	Restriction: Modify current restriction to include use in adult patients undergoing emergent splenectomy or scheduled elective splenectomy in less than 8 weeks
Intravenous Immune Globulin (Gammagard® 10% Liquid)	Immune Globulin	Multiple Indications	Restriction: Modify current restriction to include pediatric patients with myocarditis