Medical management of CHF: A New Class of Medication

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Disclosures

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Background

- Chronic systolic congestive heart failure remains a major health problem despite well established guidelines for medical therapy.
- The diagnosis is fraught with symptoms, increased mortality and readmissions to the hospital.
- Beta blockers, Ace inhibitors, ARB’s, and Aldosterone agonists are felt to improve left ventricular remodeling, symptoms and survivability.
- Diuretics especially loop diuretics are often used for symptomatic relief and improvement in volume status.
Positive effects of beta blockers also include heart rate and blood pressure reduction and thereby reduction in myocardial workload.

However beta blockers may also cause hypotension and decreased myocardial contractility (negative inotrope) which limit titration of the drug.

There is a 34% increased risk of cardiovascular death and a 53% increased risk of hospitalization for congestive heart failure in patients with resting heart rate greater than 70 compared to those patients with resting heart rates less than 70 who have systolic congestive heart failure and coronary artery disease. Heart rate correlates with likelihood of death, cardiovascular death or hospitalization in the setting of congestive heart failure.

A therapeutic decrease in heart rate also correlates with improvement in outcomes.

Unfortunately many patients remain with elevated heart rates despite optimized medical therapy.
Ivabradine

- Selective inhibitor of the If current at the Na+/K+ channel in the sinus node. Prolongation of the diastolic phase.
- At therapeutic doses, there is no effect of decreased myocardial contractility and blood pressure.
- Potential benefit from heart rate reduction above what is already achieved from maximum tolerated standard medical therapy.
- Hepatic clearance.
SHIFT Trial

- Ivabradine and outcomes in chronic heart failure (SHIFT): A randomized placebo-controlled study. Karl Swedberg et al...
- Trade name – Corlanor
- 677 cm in 37 countries
- Study enrollment from October 2006 to June 2009
- Randomized, double blinded, placebo-controlled study
- Primary endpoint was cardiovascular death or hospital admission for worsening heart failure.
Methods
Inclusion criteria

- Age greater than 18
- Excluding congenital heart disease or primary severe valvular disease, patients with any other cause of left ventricular systolic congestive heart failure with ejection fraction less than or equal to 35% were eligible.
- Sinus rhythm with heart rate greater than 70.
- Stable symptomatic chronic heart failure of at least 4 weeks duration.
- A previous admission for congestive heart failure within the previous 12 months.
- Stable standard medical therapy for at least 4 weeks prior to inclusion.
Methods
Exclusion criteria

- Recent myocardial infarction within the previous 2 months.
- 40% or more ventricular or atrial pacing.
- Atrial fibrillation or flutter
- Symptomatic hypotension
- Non-dihydropyridine calcium channel blockers, class I antiarrhythmics, and strong inhibitors of cytochrome P450 3A4.
Dose titration
goal heart rate 50-60 bpm

- 5 mg twice a day was initiated
- Dose was maintained if heart rate was between 50 and 60. Dose was increased to 7.5 mg twice a day if heart rate was greater than 60. Dose was decreased to 2.5 mg twice a day if heart rate was less than 50 or if patient had symptoms related to bradycardia. If patient had heart rate less than 50 or symptoms of bradycardia while on a dose of 2.5 mg twice a day, study treatment was stopped.
- Patient’s were seen on a routine 4 month basis at which time placebo or study drug could be adjusted as above.
Demographics

- 3241 in study group
- 3264 in placebo group
- The 2 groups were very similar in terms of age, sex, ethnicity, smoking status, BMI, duration of heart failure, primary cause of heart failure such as ischemic or nonischemic, hypertension, diabetes, renal function, history of atrial fibrillation or flutter.
- Baseline medical therapy was also similar.
- Very few patients with defibrillators or cardiac resynchronization therapy.
NYHA CHF Class

- Baseline heart failure class was identical between the 2 groups with
  - Class II – 49%
  - Class III – 50%
  - Class IV – 2%
Heart rate and blood pressure

- Resting heart rate was 79.7 in the study group and 80.1 in the placebo group.
- Blood pressure was 122/75.7 in the study group and 121.4/75.6 in the placebo group.
LV Systolic Function

- LVEF 29% in both groups.
Results

- 15.4 absolute reduction in heart rate at 28 days and 9.1 absolute reduction at one year with ivabradine compared to placebo.
- When corrected for a decrease in heart rate in the placebo group, there 9.1 and 8.1 absolute reduction in heart rate in the study group at 28 days and one year, respectively.
Primary Endpoint
Cardiovascular death or hospital admission for worsening heart failure

- Ivabradine – 24% (18% relative risk reduction)
- Placebo – 29%
Secondary endpoints

Mortality

- All cause mortality or cardiovascular mortality - no significant difference.
- Death due to heart failure was 3% in the ivabradine group and 5% in the placebo group with a P value of 0.014.
Secondary endpoints
Hospital admission

- All cause re-admission was reduced in the ivabradine group.
- There was a 26% percent relative risk reduction in first hospitalization secondary to worsening heart failure in the ivabradine group.
Adverse events

- There was only a 21% withdrawal rate in the ivabradine group compared to 19% in the placebo group.
- Bradycardia was noted in 10% in study group vs 2.2% in placebo group. Bradycardia led to drug withdrawal in 1% of patients in both study and placebo group.
- There was a 8.3% rate of atrial fibrillation in the study group compared to an 6.6% rate in the placebo group.
- A 2.8% rate of phosphenes (transient enhanced brightness in a restricted area of the visual field) noted in the study group compared to 0.5% rate in the placebo group.
- Increased blood pressure (8.9% vs 7.8%).
Contraindications

- Acutely decompensated heart failure.
- Hypotension with blood pressure less than 90/50
- High-grade conduction system disease such as third-degree heart block, second-degree heart block, sick sinus syndrome, sinoatrial block, unless a pacemaker is present.
- Pacer dependence.
- Resting heart rate less than 60.
- Severe hepatic impairment.
- Atrial fibrillation or flutter.
- Concomitant use with strong or moderate cytochrome P450 3A4 inhibitors such as azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone, diltiazem, verapamil, and grapefruit juice.
- Concomitant use of cytochrome P450 3A4 inducers such as St. John’s wort, rifampicin, barbiturates and phenytoin.
Ivabradine

- New medication which inhibits the $I_f$ current in the sinoatrial node and thereby prolongs the diastolic phase and slows heart rate.
- No significant hypotension or negative inotropic effects.
- Shown to reduce hospital admissions for decompensated systolic congestive heart failure in patients who were on optimized standard medical therapy.
AM Heart Rate By Day

(ivabradine started)
