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Does Ivabradine Improve Quality of Life in Cardiovascular Disease Patients?

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ABSTRACT

Objective: The objective of this review is to determine whether ivabradine therapy can improve the quality of life in cardiovascular disease patients.

Study Design: The studies included in this review are one randomized control study and two double blind randomized control studies from 2008, 2010, and 2012.

Data Source: The three studies in this review were obtained by performing a PubMed search using the keywords "ivabradine" and random control trial." All articles were published in English and in peer-reviewed journals.

Outcomes Measured: The three studies ascertained whether there was a decrease in hospitalization events within coronary artery disease and heart failure patients, if there was a subjective increase in the quality of life in heart failure patients, and whether there was an improvement in NYHA heart failure classification after ivabradine treatment.

Results: Patients with a resting heart rate of 70 beats per minute or greater who were treated with ivabradine demonstrated a statistically significant reduction in hospital admissions for myocardial infarctions (HR=0.64; 95% CI 0.49–0.84; p=0.001). This is a 36% reduction in myocardial infarctions. Heart failure patients treated with ivabradine were found to have a significantly lower risk of suffering a hospitalization event for worsening heart failure than the placebo group (HR=0.75; 95% CI 0.65-0.87; $p<0.001$). Also, patients receiving ivabradine were statistically less likely to become hospitalized a second time as compared to the placebo group (HR=0.66; 95% CI 0.55-0.79; $p<0.001$). After three months of treatment with ivabradine, there was a significant decline in the NYHA functional class of heart failure within the ivabradine treatment group ($p<0.0001$), and a significant improvement in the quality of life scores within the ivabradine treated group ($p<0.0001$).

Conclusions: Based on the systematic reviews of the three randomized controlled trials, one can conclusively say that Corlanor (ivabradine) can improve the quality of life in cardiovascular disease patients. All three studies demonstrated statistically significant changes compared to control/placebo groups. These studies also demonstrate that ivabradine is efficacious and is well tolerated in terms of being safe for human use.

Key Words: Ivabradine, Heart Failure, Coronary Artery Disease, Quality of Life, NHYA.

INTRODUCTION

Heart failure (HF) is the end result from many etiological factors that should be considered a clinical syndrome and should not be considered a single entity.[1] One of the most common causes of HF is coronary artery disease (CAD).[1] Other risks and causes of HF are dyslipidemia, obesity, type 1 and 2 diabetes, hypertension, arrhythmias, cardiomyopathy, congenital heart defects, and heart valve diseases.[1] Also cigarette smoking, alcohol abuse, drug abuse, hyperthyroidism, hypothyroidism, vitamin E intoxication, radiation to the thorax, and chemotherapy can contribute to HF.[1] The end result of these complex interactions is the loss of functioning of the cardiac myocytes and/or an abnormality of cardiac muscle contraction, relaxation, or both.[2]

HF is relevant to both patients and practitioners for many reasons because it is a very common condition with approximately 5.1 million patients in the U.S. with a greater occurrence in men than in women, and an increasing prevalence with increasing age.[3-4] Also, within the U.S., the incidence of HF is estimated to be 2-5 per 1,000 person-years.[4] CAD, as the leading cause of HF, is the number one cause of death in both men and women where each year approximately 370,000-375,000 men and women die as a result.[5]

HF costs the U.S. an estimated $32 billion each year.[6] This large number includes cost of health services, medications, and missed days of work.[6] Secondly, the most common cause of HF, CAD, costs the U.S. an estimated $108.9 billion every year, which also includes the cost of health services, medications to treat, and lost time of productivity.[7] Most of the cost arising from HF is from hospitalization events where 80% of hospitalizations are found to be within the aging U.S. Medicare population.[4,8-9] Therefore, the rates of hospitalization and cost are expected to continually rise in the future with the increasing age of the U.S. population.[9] There were over 1

million hospitalizations for HF in 2000 and in 2010.[10] Interestingly, during this same time period, hospitalization rates for CAD declined by 43% for the total U.S. population.[11]

There is a high risk of HF worsening or having an acute symptomatic attack, and there has been a reported high readmission rate to hospitals after newly diagnosed HF.[12] Within the U.S. Medicare population, where HF is the most common reason for readmission to a hospital, a study showed that 27% of patients become readmitted within a 30-day period.[12] There have also been high rates of re-admission after HF diagnosis reported in Canada.[13] It has also been reported that patients with preserved left ventricular ejection fraction (LVEF) have re-admission rates as high as 29% after 60-90 days of leaving the hospital with a first incidence of HF.[14]

In HF, it is medically recognized that the heart muscle cannot pump blood adequately to the bodily tissues because the muscle becomes too weak or too stiff to fill the heart chambers.[2] The most common cause of HF is from systolic dysfunction, which most commonly arises from myocardial infarcts related to CAD.[1,2,5] The causes of CAD arise from smoking, high levels of cholesterol in the bloodstream, high blood pressure, insulin resistance or diabetes, and blood vessel inflammation.[1,2,5]

Symptoms of CAD can include dysrhythmias, chest pain or discomfort, angina, discomfort in one or both arms, the back, neck, jaw, or in the epigastric region, shortness of breath, nausea, vomiting, light-headedness or syncope, cold sweats, sleep disturbances, and fatigue.[1,5] Signs of HF include edema of the ankles, feet, legs, abdomen, and distension in the veins of the neck.[5,15]

The most common way to classify HF is the New York Heart Association's (NYHA) four functional classes. Class IV are patients that have symptoms at rest.[15] Class III have symptoms with less-than-ordinary types of exertion.[15] Class II have symptoms with ordinary exertion, and

Class I patients have no symptoms attributable to heart disease or HF.[15] NYHA class is also utilized to determine the prognosis of HF with increasing morbidity and mortality rates being directly proportional to increasing class scores.[15]

The treatment of HF is multifaceted. In those with systolic HF, the main goal of treatment is to reduce symptoms, prolong survival, improve quality of life, and prevent disease progression.[16] For those who have a structural issues of the heart, the therapy depends on the NYHA classification.[16] For those that are Class I and asymptomatic, the goal is to deter any cardiac remodeling.[16] For those that have symptoms (Classes II to IV), the goal is to deter fluid retention, decrease disability, and deter the progression of disease.[16] Standard therapy for patients with HF who have a decreased LVEF should consist of angiotensin-converting enzyme inhibitor (ACEi) and a beta-blocker (BB).[16] Other and additional therapy must be considered if a patient has persistent symptoms.[16] These include angiotensin receptor blockers (NYHA Classes II to IV), spironolactone (NYHA Classes III and IV), a combination of hydralazine and isosorbide dinitrate (NYHA Classes III and IV), and eventually digitalis.[16] Lastly, implantation of internal cardiac defibrillator, cardiac resynchronization, and heart transplants are down-the-line choices of treatment.[16] If HF is from CAD, then revascularization of the coronary vessels may be performed.[16]

Importantly, it has been noted that resting heart rate (HR) is related to mortality both within the general population without heart disease and in patients with myocardial infarcts or HF.[17] It is also reported that heart related death is increased by 14% with an increase of 10 beats per minute (bpm) in HR, and that this increase is independent of age, exercise, blood pressure, and BMI.[18-19]

Thereby, it seems that resting HR can be considered a modifiable cardiovascular disease

risk factor in both the general population and in patients with HF and CAD. Ivabradine is a heart rate-lowering agent that is selective for and a specific inhibitor of the sinus node. It inhibits the I_f channel of the cardiac pacemaker.[20-21] It reduces diastolic depolarization rates set forth by the sinoarterial node, therefore purely decreasing HR.[20-21] Compared to BBs, which also lower HR, ivabradine does not lower blood pressure and may also reduce mortality and cardiac events independently or in conjunction with BBs.[22]

OBJECTIVE

The objective of this systematic review is to determine whether or not ivabradine therapy can improve quality of life in cardiovascular disease patients?

METHODS

The studies included in this review are one randomized control study and two double blind randomized control studies.[22-24] These studies were included since they did not discriminate between biological sex or ethnicity, patients had to be diagnosed with HF or CAD, utilized the same dosing of the intervening medication (ivabradine 2.5, 5.0, and 7.5mg), and compared the ivabradine treatment group to the control group.[22-24] These studies also included a wide range of age to test whether this intervention can be applied to a variety of age groups, but all patients had to be at least the age of 18.[22-24] Also, for a study to be considered for inclusion, it must have included over 50 persons within the study to achieve the power to detect a possible statistical significance, and must have utilized similar statistical methods for fair comparisons between studies. All articles were published in English within peer-reviewed journals and were investigated by the author for inclusion in this review. Keywords for the PubMed search were "ivabradine," and "randomized control trial," without any time restriction for how long ago the studies were published. The summary statistics utilized across the three studies were hazard ratio

(HR), p-values, control group event rate (CER), and experimental group event rate (EER), numbers needed to treat (NNT), relative benefit increase (RBI), absolute benefit increase (ABI), numbers needed to harm (NNH), relative risk increase (RRI), absolute risk increase (ARI). Table 1 summarizes the demographics and characteristics of the inclusion and exclusion criteria from each study.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# of Patients	Age (yrs)	Inclusion Criteria	Exclusion Criteria	Withdrawal	Interventions
Fox et al, 2008[22]	Double blind RCT	10,917	≥ 18 years old if diabetic or > 55.	MI, revascularisation, LV ejection fraction of less than 40%. Sinus rhythm, resting heart rate of 60 bpm or greater. Angina stable for 3 months. Medication at stable doses for 1 month	MI or revascularisation within previous 6 months; stroke or TIA within previous 3 months; pacemaker, defibrillator; valvular disease; arrhythmias,uncontrolled hypertension; NYHA Class IV. Excluded patients receiving strong CYP3A4 inhibitors	220	Ivabradine 5mg PO BID, can be increased to 7.5mg BID or 2.5 BID depending on tolerance
Borer et al, 2012[23]	Double blind RCT	6,505	≥ 18 years old	Symptomatic chronic HF of ≥4-week duration + left ventricular EF of ≤35%, hospitalized for worsening HF within 12 months, in sinus rhythm and heart rate of ≥70 b.p.m.	Those who are opposite of inclusion criteria, or non-compliant	131	Ivabradine 5mg PO BID, can be increased to 7.5mg BID or 2.5 BID depending on tolerance
Sarullo et al, 2010[24]	Single blind RCT	60	Mean 52.7 +/- 5.3	Left ventricular ejection fraction	UA, recent MI, decompensated CHF, valvular heart disease, AFib,	0	Ivabradine 5mg PO BID, can be increased to

			yrs.	(LVEF) <40%, NYHA classes II to III, sinus rhythm with heart rate at rest >70 bpm	uncontrolled arrhythmias, chronic pulmonary illness, renal insufficiency, abnormal exercise stress test, and neurological or orthopedic limitations.		7.5mg BID if HR is >70bpm after treatment began

OUTCOMES MEASURED

The outcomes measured encompassing the three studies were a decrease in hospitalization events (a proxy for increased quality of life), a subjectively measured increase in quality of life via a questionnaire, and whether there was an improvement in NYHA HF classification.[22-24] Fox et al[22] endpoint goal was to determine whether the rates of admission to the hospital for fatal and non-fatal acute myocardial infarction decreased with ivabradine treatment in a subgroup of patients that had resting heart rates >70 bpm.[22] This was ascertained by collecting data from interviews performed at 2 weeks, 1 month, 3 months, 6 months, and every 6 months till the study ended.[22] These author's also tested if there was a difference between all causes of serious adverse events between the groups. [22]

Borer et al[23] was interested in whether the treatment with ivabradine had any effect upon the rate of hospitalizations between the treatment group and the placebo group of HF patients. To ascertain this, hospitalization events were tracked via hospital records.[23] Based on the data available from Borer et al,[23] the determination of the number of patients needed to treat to decrease another hospitalization event was calculated.

Sarullo et al[24] tested whether there was a difference between NYHA functional class of HF after a three month period of treatment.[24] The functional class of HF was measured both in the treatment group and within the control group.[24] The author's also measured whether

treatment with ivabradine influenced the quality of life (QOL) in their patients.[24] QOL was ascertained by the application of the Minnesota Living with Heart Failure Questionnaire.[25] It is a validated, widely used, self-administered questionnaire composed of 21 items focused on the effects of HF upon a patient's physical, psychological, and socioeconomic level.[26-27] These studies have shown it to be sensitive to the changes in QOL within HF patients.[26-27]

RESULTS

In the study conducted by Fox et al,[22] there were no statistically significant differences between baseline characteristics. The utilization of cardiac medications was high between all patients, where 94% patients were receiving an aspirin or anticoagulant, 74% were on statins, 90% were prescribed an ACEi or an angiotensin II receptor blocker, and 87% of all patients were receiving BBs.[22] When the author's included all study participants in their analysis, there was no statistical difference in the safety of treatment demonstrated between the two groups.[22] There were 1,233 (22.5%) patients that experienced serious adverse events in the ivabradine group and 1,239 (22.8%) in the placebo group (p=0.70). With this event rate, the calculated NNH, which is the number of patients who need to be treated to have a person incur a serious adverse event, was calculated to be -333 (Table 2). Meaning, for every 333 patients treated with ivabradine rather than placebo there will be one less patient with a serious adverse event.

Table 2: Number Needed to Harm to avoid all serious adverse events

Study	CER	EER	RRI	ARI	NNH
Fox et al	0.228	0.225	-0.013	-0.003	-333

The authors' performed a subgroup analysis of patients with a resting heart rate of 70 bpm or greater.[22] This group was composed of 463 (17%) patients in the ivabradine group and 498 (19%) patients in the placebo group who reached the primary endpoint of the study.[22] Within this subset of patients, there was a statistically significant reduction in the rates of hospital

admission for both fatal and non-fatal acute myocardial infarctions (HR=0.64; 95% CI 0.49–0.84; p=0.001).[22] This is a 36% reduction in myocardial infarction for patients on ivabradine whose heart rate is >70 bpm compared to placebo (Table 3).[22]

In the study performed by Borer et al,[23] the results in baseline characteristics for patients with HF had statistically significant differences between the treatment and placebo groups. Patients were significantly older in the treatment group (p=0.007), and the placebo group were more likely to be smokers (p=0.023).[23] Heart rate was significantly greater within the placebo group compared to the treatment group (p=0.024).[23] The placebo group were more likely to have suffered a stroke (p=0.033), to have been diagnosed with CAD (p=0.021), and were more likely to be on diuretics (p=0.034).[23] There was no statistical differences between the two groups in gender, BMI, blood pressure, NYHA function classes, estimated glomerular filtration rate, duration of heart failure, causes of HF (ischemia, hypertension, diabetes, atrial fibrillation), and in the many types of treatment regimens.[23]

Comparing the groups after two years of follow-up, the study demonstrated that patients treated with ivabradine were significantly at a lower risk of suffering a hospitalization event for worsening HF than were patients receiving the placebo (HR=0.75; 95% CI 0.65-0.87; p<0.001)(Table 3).[23] In terms of suffering a secondary hospitalization event, patients receiving ivabradine were statistically less likely to become hospitalized a second time as compared to the placebo group (HR=0.66; 95% CI 0.55-0.79; p<0.001) (Table 3).[23]

Table 3: Statistical Significance of Treatment Endpoints

Study	Prevention Endpoint	Hazard Ratio	95% Confidence Interval	P-value
Fox et al[22]	Admission to hospital for myocardial infarction	0.64	0.49-0.84	0.001
Borer et al[23]	First hospitalization event from HF	0.75	0.65-0.87	<0.001
Borer et al[23]	Second hospitalization event from HF	0.66	0.55-0.79	<0.001

Sixteen percent of patients treated with ivabradine suffered a hospitalization event compared to 21% of from the placebo group (Table 4).[23] After calculating the NNT, for every 20 patients treated with ivabradine there was one fewer hospitalization event due to worsening HF. In terms of having a second hospitalization event, six percent of patients treated with ivabradine had two events compared to the placebo group that had nine percent of patients experiencing two hospitalizations (Table 4). These calculations show that the number of patients needed to treat with ivabradine to prevent one less first or second hospitalization event is 20 and 33, respectively.

Table 4: NNT to reduce hospitalization events in HF patients (Borer et al 2012)

Event	CER	EER	RRR	ARR	NNT
1st hospitalization event	0.21	0.16	-0.24	-0.05	-20
2nd hospitalization event	0.09	0.06	-0.333	-0.03	-33

As seen from the studies above, HF due to its progressive disease course can cause multiple exacerbations and hospitalizations leading to both high monetary costs and morbidity.[6-7,22-24] An important aspect in treating HF is to reduce disease progression and increase the quality of life within these patients. Sarrulo et al[24] attempted to ascertain whether NYHA functional class of HF changed after ivabradine treatment, and whether QOL improved with ivabradine treatment. At baseline, there was no difference between the ivabradine treatment group and the control group in terms of NYHA functional class (ivabradine group 2.5±0.1 [mean and standard deviation] versus the control group 2.6±0.1).[24] However, after three months of treatment, there was a statistically significant decline in the NYHA class within the ivabradine treatment group (1.6±0.1; $p<0.0001$).[24] There was no such decline in NYHA class found within the control group (Table 5).[24] At baseline, there was no statistical difference between the QOL life scores between the treatment and control group (ivabradine 30.9±2.3 versus controls 30.6±2.1).[24] After three months of treatment, there was a significant improvement in QOL scores within the ivabradine

group (37.5±1.9; p<0.0001), and there was no such significant improvement found within the control group.[24]

Table 5: Mean and Standard Deviations between Groups (Sarullo et al 2010)

Variable	Ivabradine Group		Control Group	
	Baseline	Post 3 Months Treatment	Baseline	Post 3 Months Treatment
NYHA Class	2.5±0.1	1.6±0.1 (p<0.0001)	2.6±0.1	2.4±0.2
Quality of Life	30.9±2.3	37.5±1.9 (p<0.0001)	30.6±2.1	31.2±2.6

DISCUSSION

With these statistical findings it should be noted that there were also findings where ivabradine treated groups did not differ from control groups. Fox et al reported[22] no statistical difference between all-causes of death, cardiovascular death, and admission to the hospital for new-onset or worsening heart failure in all patients regardless of HR. Therefore, it is hypothesized that ivabradine may have specific criteria within the treatment of CAD and HF.

Ivabradine was approved by the European Medicines Agency in 2005 and the data described in this review comes from European research.[22-24] Very recently, as of April 2015, the FDA approved the use of ivabradine under the brand name of Corlanor.[28-29] It is indicated to reduce the risk of hospitalization in worsening HF patients that have stable, symptomatic chronic HF with LVEF ≤35%, who are in sinus rhythm with resting heart rate ≥70 bpm, and are either on maximally tolerated doses of BBs or have a contraindication to BB use.[30] According to the manufacturer, Corlanor is contraindicated in patients with decompensated heart failure, a blood pressure less than 90/50 mmHg, in those with sick sinus syndrome, have a sinoatrial block or 3rd degree AV block, a resting heart rate of <60 bpm, severe hepatic impairment from any cause, have a pacemaker, and consume strong medications or foods that inhibit cytochrome P450 3A4.[30] Currently, wholesale costs for Corlanor is around $4,500 per year, or $375 per month, and patient costs vary according to insurance coverage.[29]

CONCLUSION

Based on the systematic reviews of the three randomized controlled trials, one can conclusively say that Corlanor (ivabradine) can improve the quality of life in cardiovascular disease patients. These three studies demonstrate that ivabradine treatment, by means of heart rate reduction, can significantly reduce the incidence of myocardial infarction in CAD, decrease hospitalization events in HF patients, decrease HF severity in terms of NYHA functional class, and increases HF patient's perception of their QOL.[22-24] These three studies demonstrate the utility, safety, and efficacy of ivabradine. These studies have some limitations as well, such as a fair amount bradycardia in the treatment group which may have resulted from the low average heart rate to begin with (all patients average = 71.9 bpm)[22], one study was a post hoc analysis of a RCT where hospitalization rates may have been influenced by differing admission criteria between the health systems involved and between the different countries participating in the study[23], and one study was a single-blind randomization study because it was the first study that had patients exercising while on ivabradine. Therefore, as a safety precaution, doctors were not blinded to who was receiving treatment.[24]

These studies also leave open many doors for an expanded off-label use of ivabradine. In the United Kingdom ivabradine is utilized for the treatment of inappropriate sinus tachycardia (IST).[31-32] Future studies within the U.S. are warranted to determine if ivabradine is a viable and safe option for those with an IST diagnosis or other dysrhythmias by performing high quality random control trials. Also, there are currently 17 open clinical trials involving ivabradine, so it is expected that a plethora of data and evidence for off-label use will arise in the future.[33]

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