Efficacy Profile of Ivabradine in Patients With Heart Failure Plus Angina Pectoris

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Running head: SHIFT angina

Target Journal: *Cardiology*

Word count: 2242 (not including abstract or table/figs; no limit specified)

Reference count: 18

Tables/Figures: 2/2

ABSTRACT

Objectives: Heart rate slowing with ivabradine reduced cardiovascular death or heart failure hospitalizations among patients with chronic systolic heart failure (CHF) in the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT). Subsequently, heart rate slowing in the Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease (SIGNIFY) in patients without CHF provided no benefit for cardiovascular death or nonfatal myocardial infarction (primary composite endpoint); secondary analyses suggested possible harm in the angina subgroup. Therefore, we examined the impact of ivabradine among patients with CHF plus angina in SHIFT.

Methods: SHIFT enrolled adults with stable, symptomatic CHF; left ventricular ejection fraction ≤35%; and sinus rhythm with resting heart rate ≥70 bpm. Outcomes were the SHIFT and SIGNIFY primary composite endpoints and their components.

Results: Of 6505 patients in SHIFT, 2220 (34%) reported angina at randomization. Ivabradine numerically, but not significantly, reduced the SIGNIFY primary composite endpoint by 8%, 11%, and 11% in the SHIFT angina subgroup, nonangina subgroup, and overall population, respectively. Ivabradine also reduced the SHIFT primary composite endpoint in all three subgroups.

Conclusions: Ivabradine did not increase cardiovascular death or nonfatal myocardial infarction in CHF patients with angina.

Word Count: **199**

Keywords: angina, heart failure, heart rate, ivabradine

INTRODUCTION

Resting heart rate, as it increases, is directly associated with increased mortality and morbidity in patients with chronic systolic heart failure (CHF) in sinus rhythm [1,2]. Pharmacologically reducing heart rate improves outcomes in patients with systolic CHF, as is demonstrated in trials of beta blockers [3,4] and, most recently, of ivabradine, in the Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT) [5].

Relatively high resting heart rate also is directly associated with mortality and myocardial infarction in patients with chronic stable coronary artery disease (CAD) [6,7]. However, in two large, randomized trials of ivabradine in patients with CAD, Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left Ventricular Dysfunction (BEAUTIFUL) and Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease (SIGNIFY), ivabradine did not alter cardiac outcomes in patients with CAD with or without left-ventricular dysfunction [8,9]. However, a prespecified subgroup analysis of SIGNIFY suggested that patients with CAD and angina had worse outcomes with ivabradine than with placebo [8].

These contrasting results raise concern that ivabradine may be associated with reduced efficacy or worsened cardiovascular outcomes in patients with CHF who have CAD, particularly those with angina [10]. To resolve this issue, we conducted a post hoc analysis to determine the outcomes of the patients in SHIFT who reported angina at enrollment and compared these results with those of the overall SHIFT population and with those who did not report angina. We also assessed the SIGNIFY outcomes in these SHIFT-based subgroups.

METHODS

Patients

In SHIFT, enrolled adults had stable, symptomatic CHF, left ventricular ejection fraction (LVEF) ≤35% and were in sinus rhythm with resting heart rate ≥70 bpm. Full eligibility criteria have been described previously [5]. Evaluable patients from SHIFT were divided into subgroups based on the presence or absence of angina as reported by the investigator at study enrollment. The angina subgroup included all patients with a history of angina (reported as angina pectoris, microvascular angina, postinfarction angina, Prinzmetal angina, etc.) who answered “yes” to the question, “is the disease still present?” at enrollment. The SHIFT nonangina subgroup included all other patients in the overall SHIFT population.

Clinical Outcomes

The ivabradine and placebo groups from SHIFT were compared in the overall randomized set, the angina subgroup, and the nonangina subgroup. Outcomes were the primary composite endpoints of the SHIFT and SIGNIFY trials, as well as their individual components [5,8]. For SHIFT [5], these components included cardiovascular death or first hospitalization for worsening heart failure; for SIGNIFY [8], they included cardiovascular death or first nonfatal myocardial infarction. Adverse events were tabulated by randomized treatment group and angina and nonangina subgroups.

Statistical Analysis

The treatment effect was estimated using an adjusted Cox proportional hazards model with beta blocker intake at randomization as a covariate, as described in previous SHIFT publications; *P*-values for interaction between randomized treatment and

subgroup status were also provided by addition of treatment by subgroup interaction to the model [5]. The safety analysis set included all patients who received at least one dose of ivabradine.

RESULTS

Patients

Of the 6505 patients randomized in SHIFT, 2220 (34%) reported angina at enrollment and comprised the angina subgroup. The remaining 4285 patients (66%) formed the nonangina subgroup. Demographic and disease characteristics are summarized in **Table 1**. Briefly, patients with angina at baseline tended to be slightly older, numerically had higher blood pressure, more severe heart failure, and more beta blocker use than those without angina. Within each subgroup, there were no significant differences between those who received ivabradine and those who received placebo.

Clinical Outcomes

Placebo-corrected average change in heart rate at 28 days for patients treated with ivabradine was –10.9 bpm (95% CI, −11.4 to −10.4) for the overall SHIFT population [5] and –10.8 bpm (95% CI, −11.7 to −10.0) and –11.0 bpm (95% CI, −11.6 to −10.3) for the angina and nonangina subgroups, respectively.

Results for the SHIFT primary composite endpoint (cardiovascular death or hospital admission for worsening heart failure) were similar for those with and without angina and for the overall population (**Figure 1**). In the SHIFT angina subgroup there were 15% fewer events in the ivabradine arm compared with placebo but this did not reach statistical significance (hazard ratio [HR], 0.85; 95% CI, 0.73–1.00; *P*=0.055). There was a 20% reduction of events in the nonangina subgroup (HR, 0.80; 95% CI, 0.71–0.90; *P*<0.0001), and 18% reduction in the overall SHIFT population (HR, 0.82; 95% CI, 0.75–0.90; *P*<0.0001). The effects of ivabradine on the components of the SHIFT primary

composite endpoint were also similar among the overall SHIFT population, the SHIFT angina subgroup, and the SHIFT nonangina subgroup.

The rates of on-treatment adverse events and adverse events of interest (defined in **Table 2**) in the angina and nonangina subgroups were consistent with those for the overall SHIFT population, with bradycardia and phosphenes/blurred vision being reported more frequently with ivabradine than placebo (**Table 2**)

When the SIGNIFY endpoints were applied to the SHIFT population, results were similar among the three SHIFT-based groups for the primary composite endpoint of cardiovascular death and nonfatal myocardial infarction as well as for its components (**Figure 2**). A test of interaction between randomized treatment and presence/absence of angina showed no significant interaction (*P*=0.80). There were numerically fewer cases of cardiovascular death or nonfatal myocardial infarction in the ivabradine group compared with placebo in the SHIFT angina subgroup (HR, 0.92; 95% CI, 0.75–1.12; *P*=0.38); this tendency was similar in the SHIFT nonangina subgroup (HR, 0.89; 95% CI, 0.76–1.03; *P*=0.12), and in the overall SHIFT population (HR, 0.89; 95% CI, 0.79–1.01; *P*=0.07), but none of these differences reached statistical significance. There were numerically fewer nonfatal myocardial infarctions in the ivabradine arm versus placebo (HR, 0.86; 95% CI, 0.53–1.40; *P*=0.55) in the SHIFT angina subgroup and the SHIFT overall population (HR, 0.93; 95% CI, 0.67–1.30; *P*=0.68), whereas there were similar numbers of non-fatal infarctions in both treatment arms in the nonangina subgroup (HR, 1.02; 95% CI, 0.65–1.60; *P*=0.12) .

DISCUSSION

Resting heart rate is a known and modifiable risk factor in heart failure when patients are in sinus rhythm. Thus, as heart rate increases, adverse outcomes increase, and when heart rate is pharmacologically slowed, adverse outcomes diminish [11]. However, in patients with cardiovascular disease without left ventricular dysfunction or CHF, increasing heart rate is a risk marker, indicating that other processes (eg, diabetes, smoking) are influencing the development of myocardial infarction or cardiovascular death [12]; modification of the marker does not appear to modify the disease [8,9]. Given the lack of efficacy of ivabradine in patients with angina and without CHF in the SIGNIFY trial, evaluation of the efficacy and safety of ivabradine in other patient groups with angina was needed. Because patients with systolic CHF often have underlying CAD and may also experience angina, it is possible that this subgroup of patients with CHF may have a different response to ivabradine compared to those with CHF without underlying angina. Therefore, this post hoc analysis evaluated the effects of heart rate slowing with ivabradine among the subgroup of SHIFT patients with CHF and angina.

The worsening outcomes seen in the SIGNIFY population with angina (which had no CHF and no overlap in LVEF with the SHIFT population) were not observed in the SHIFT population. For the SHIFT and SIGNIFY primary composite endpoints and their components, results for the SHIFT angina subgroup were directionally consistent with both the SHIFT overall population and the SHIFT nonangina subgroup. Specifically, ivabradine numerically (but not significantly) reduced the SIGNIFY primary composite endpoint of cardiovascular death or nonfatal myocardial infarction versus placebo for

both SHIFT subgroups and significantly in the overall SHIFT population. Similar results were observed for nonfatal myocardial infarction, with the exception of the nonangina group, in which a nonsignificant increase of 2% was observed for ivabradine versus placebo. However, patients without angina are known to have a lower risk of myocardial infarction compared with those with angina; therefore, any increase in myocardial infarction in these patients due to ivabradine is likely to be limited.

The results of this analysis suggest that in patients with systolic CHF (and specifically in a population defined as in SHIFT), the risk of cardiovascular death or hospitalization for worsening heart failure is consistently reduced by heart rate slowing with ivabradine among patients with or without angina. Patients in the nonangina subgroup who received ivabradine achieved a statistically significant reduction in the risk of the SHIFT primary composite endpoint (cardiovascular death or hospitalization for worsening heart failure) compared with placebo. Patients in the angina subgroup tended to benefit from ivabradine, although the treatment difference was not statistically significant versus placebo (P=0.055). The lack of significance may relate to the limited power to detect differences in the relatively small angina subgroup, which was half the size of the nonangina cohort. These results are consistent with those observed from previous post hoc analyses of ivabradine use in patients with stable CAD and left ventricular systolic dysfunction. BEAUTIFUL evaluated ivabradine up to 7.5 mg twice daily in 10,917 patients with CAD and LVEF <40% [9]. In that study, there was a significantly higher rate of cardiovascular death and hospital admissions for heart failure in patients with heart rate ≥70 bpm at baseline compared with those with heart rate <70 bpm at baseline [13]. Furthermore, ivabradine did not significantly affect the rate of the primary

composite endpoint (cardiovascular death or hospitalization for myocardial infarction or new-onset/worsening heart failure) or of cardiovascular death alone. However, it did lead to a reduction in the secondary endpoints (hospitalization for myocardial infarction and coronary revascularization) among patients in BEAUTIFUL whose heart rate was ≥70 bpm at randomization (a prespecified subanalysis) [9]. Conversely, in the 1507 patients from BEAUTIFUL whose limiting symptom at baseline was angina, ivabradine was associated with a 24% reduction in the primary composite endpoint (HR, 0.76; 95% CI, 0.58–1.00; *P*=0.05) [14]. In addition, a 12% reduction in cardiovascular death (HR, 0.88; 95% CI, 0.62–1.27; *P*=0.51) and a 16% reduction in hospitalization for worsening heart failure (HR, 0.84; 95% CI, 0.53–1.33; *P*=0.99) were seen, although these reductions did not reach statistical significance [14]. Our results and those observed in BEAUTIFUL suggest that the reduction in hospitalization for worsening heart failure observed in SHIFT is generalizable to the subset of patients with CHF and angina.

It is not clear why the SHIFT results differ from those of SIGNIFY. Several possible explanations might be considered. First, of course, the phenotypes of the study populations differed markedly in SHIFT versus SIGNIFY. As noted previously, there was no overlap in the baseline LVEF between the two studies; CHF was present in all SHIFT patients but in no patients in SIGNIFY patients. Drug doses were allowed to be higher in SIGNIFY than in SHIFT, and the background therapies for CHF, required in SHIFT, were not required and often were absent in SIGNIFY, used only if indicated for some non-CHF comorbidity. Indeed, in an overarching review of the experience in SHIFT, BEAUTIFUL, and SIGNIFY, it was concluded that the efficacy of heart rate slowing with ivabradine in preventing angina does not translate into mitigation of pathologic

alterations in the coronary arteries or to the sudden or gradual progression of these lesions that underlie clinical sequelae in CAD. However, heart rate slowing has a profound effect on myocardial biology, leading to the functional improvement and relief of CHF and its sequelae [12].

Although the latter conclusion is empirically correct, the fundamental basis for the different effects of heart rate on arteries and myocardium is not clear and is the subject of speculation. The processes underlying these differences may include a differential depletion in myocardial norepinephrine levels in early-stage CHF that occurs before the onset of symptomatic heart failure [15], which may preferentially affect the myocardium compared with the coronary arteries. Another possible explanation is that heart rate slowing with ivabradine has a differential effect on arterial wave form reflections/arterial stiffness in patients with CHF [16] compared to those without, such as those with chronic CAD in SIGNIFY. Prior studies have suggested that beta blockers can increase pulse wave reflections/arterial stiffness, thereby negating the blood pressure–lowering effects on cardiovascular mortality and specifically precluding reduction of central aortic blood pressure, which may be attributable in part to heart rate reduction [17]. However, a crossover study specifically examining ivabradine versus beta blocker showed no effect of ivabradine on central aortic pressure [18]. Therefore, central pulse wave reflections and blood pressure effects are unlikely to explain the results of SIGNIFY or to negate the results of SHIFT in patients with CAD with or without angina.

Several limitations must be considered in interpreting the results of this study. This was a post hoc analysis; therefore, it was designed to generate rather than to test a hypothesis. Also, angina was reported by SHIFT investigators with no protocol-specified

definition. Consequently, the potential exists for bias in reporting or determination of the symptom. Finally, the power to discriminate among differences in group results was relatively limited, and several of the nominal differences did not reach statistical significance, limiting the strength of conclusions.

Nonetheless, this post hoc analysis demonstrates that ivabradine treatment is acceptably safe in patients with moderate to severe CHF and, specifically, among those who also have angina pectoris. The analysis also suggests that outcome benefits of ivabradine among such patients are similar to those seen in individuals without angina and to all patients with CHF.

ACKNOWLEDGMENTS

The authors acknowledge the assistance of Bret Fulton, RPh, from Complete Healthcare Communications, LLC (whose work was funded by Amgen, Inc.) and Tim Peoples, MA, of Amgen Inc., for assistance in initial drafting of this manuscript.

DISCLOSURES

SHIFT was sponsored by SERVIER laboratories. No funding was provided to the co-authors specifically for this analysis or manuscript. The analysis presented here was made by independent investigators. The sponsor had no role in the design, analysis, drafting, or revision of the manuscript. **Conflicts of interest**: J.B. is or recently has been a consultant/advisor to Servier, Amgen, Novartis, Pfizer, Cardiorentis, ARMGO, Takeda USA, Celladon, Abbott Laboratories and AstraZeneca and is a stock shareholder in BioMARIN. K.S. received research support from Servier and honoraria from Amgen, AstraZeneca, and Novartis. M.K. reports fees for board membership for Astra-Zeneca, BMS, Menarini, and Novartis, consultancy fees from Amgen and Servier and speakers bureau for BMS, AstraZeneca, Menarini, MSD, Novartis, Sanofi, Servier, and Menarini. I.F. reports grants and personal fees from Servier and Amgen while conducting the study. L.T. reports personal fees from Servier, Boston Scientific, St Jude Medical, Medtronic, CVIE Therapeutics, and Cardiorentis while conducting the study, outside the submitted work. M.B. received grants from Medtronic and personal fees from Servier and Bayer, outside the submitted work. C.D., Y.W. and J.M. are employed by Amgen, Inc. F.D. is an employee of Servier.

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TABLES

Table 1. Demographic and Disease Characteristics*

	Angina Subgroup		Nonangina Subgroup	
Characteristic	Ivabradine (n=1085)	Placebo (n=1135)	Ivabradine (n=2156)	Placebo (n=2129)
Age, y	62.8±10.0	62.3±9.7	59.7±11.7	58.9±12.2
Men, n (%)	807 (74.4)	887 (78.1)	1655 (76.8)	1621 (76.1)
Current smoker, n (%)	208 (19.2)	211 (18.6)	333 (15.4)	366 (17.2)
BMI, kg/m^2	28.5±4.7	28.5±4.6	27.8±5.2	27.7±5.2
Resting heart rate, bpm	79.0±8.9	79.7±9.8	80.0±9.8	80.3±9.7
SBP, mmHg	124.7±14.9	124.1±15.1	120.6±16.5	119.9±16.0
DBP, mmHg	77.1±8.9	76.8±8.9	75.1±9.9	75.0±9.6
LVEF, %	30.1±4.6	30.0±4.5	28.5±5.3	28.4±5.4
eGFR, mL/min/1.73 m^2	73.5±21.1	73.0±20.5	75.1±23.8	75.8±24.2
NYHA class II, n (%)	405 (37.3)	431 (38.0)	1180 (54.7)	1153 (54.2)
NYHA class III/IV, n (%)	680 (62.7)	704 (62.0)	975 (45.2)	975 (45.8)
Beta blocker at baseline, n (%)	1005 (92.6)	1042 (91.8)	1892 (87.8)	1881 (88.4)
Beta blocker at target daily dose, n (%)	334 (30.8)	297 (26.2)	409 (19.0)	448 (21.0)

*Values are mean ± SD unless otherwise noted.

BMI=body mass index; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association; SBP=systolic blood pressure.

Table 2. Adverse Events

	Angina Subgroup		Nonangina Subgroup		SHIFT Safety Set	
Event, n (%)	**Ivabradine (n=1082)**	**Placebo (n=1132)**	**Ivabradine (n=2150)**	**Placebo (n=2128)**	**Ivabradine (n=3232)**	**Placebo (n=3260)**
Overall adverse events						
Any adverse event	838 (77.4)	860 (76.0)	1576 (73.3)	1532 (72.0)	2439 (75.5)	2423 (74.3)
Serious adverse events	485 (44.8)	529 (46.7)	884 (41.1)	952 (44.7)	1450 (44.9)	1553 (47.6)
Adverse event leading to treatment discontinuation	155 (14.3)	129 (11.4)	312 (14.5)	287 (13.5)	467 (14.5)	416 (12.8)
Adverse events of interest						
AV block II–III	10 (0.9)	3 (0.3)	23 (1.1)	15 (0.7)	33 (1.0)	18 (0.6)
Atrial fibrillation	88 (8.1)	81 (7.2)	179 (8.3)	136 (6.4)	267 (8.3)	217 (6.7)
Bradycardia*	142 (13.1)	39 (3.5)	180 (8.4)	33 (1.6)	322 (10.0)	72 (2.2)
Phosphenes-blurred vision	30 (2.8)	9 (0.8)	76 (3.5)	13 (0.6)	106 (3.3)	22 (0.7)

AV=atrioventricular.
*Includes symptomatic and asymptomatic bradycardia

FIGURE LEGENDS

Figure 1. Effect of ivabradine versus placebo on clinical outcomes (SHIFT endpoints) among patients with moderate to severe chronic systolic heart failure with left ventricular dysfunction (SHIFT trial population) with and without angina. CV=cardiovascular; CHF=chronic heart failure; SHIFT=Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial.

Figure 2. Effect of ivabradine versus placebo on clinical outcomes (SIGNIFY endpoints) among patients with moderate to severe chronic systolic heart failure with left ventricular dysfunction (SHIFT trial population) with and without angina. CV=cardiovascular; MI=myocardial infarction; SHIFT=Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial; SIGNIFY=Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients With Coronary Artery Disease.

FIGURES

Figure 1.

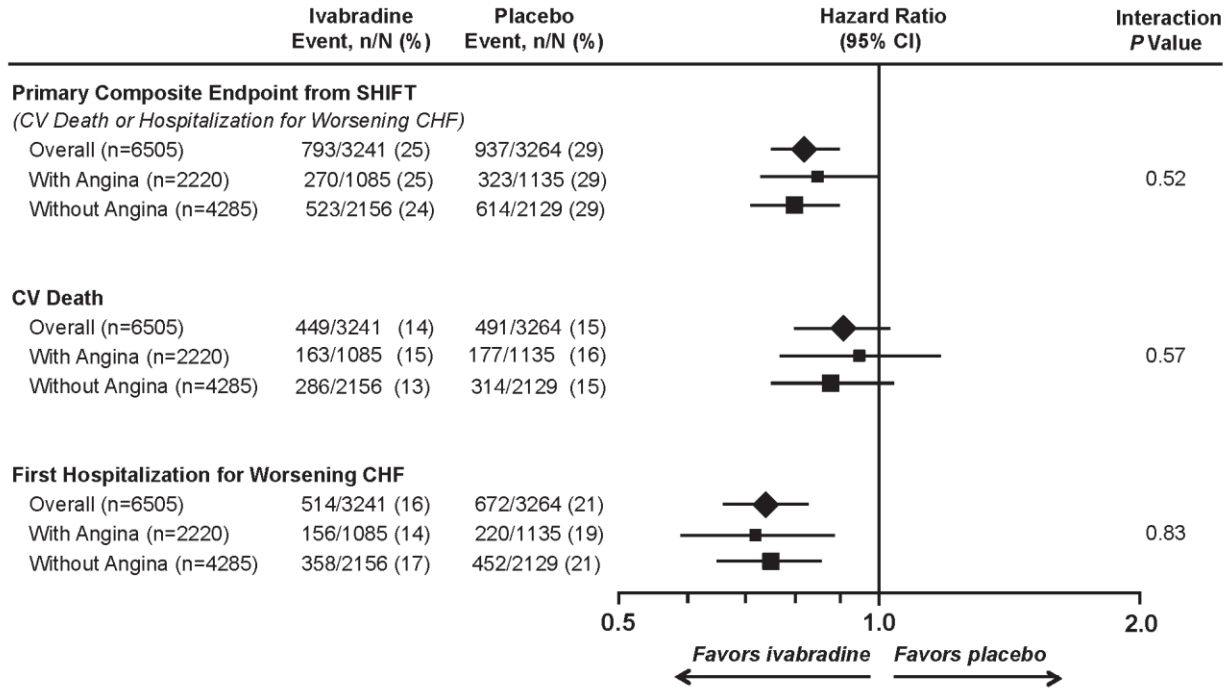
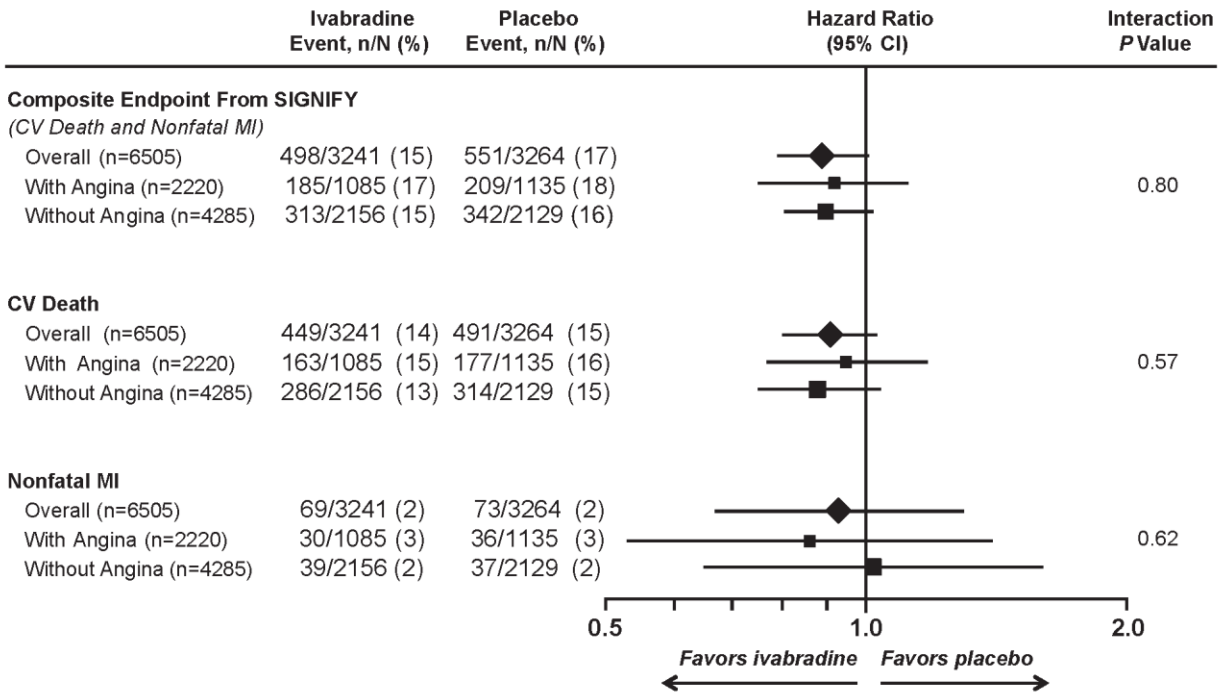


Figure 2.


Ivabradine Event, n/N (%)
Placebo Event, n/N (%)
Hazard Ratio (95% CI)
Interaction P Value
Composite Endpoint From SIGNIFY
(CV Death and Nonfatal MI)
Overall (n=6505) 498/3241 (15) 551/3264 (17)
With Angina (n=2220) 185/1085 (17) 209/1135 (18)
Without Angina (n=4285) 313/2156 (15) 342/2129 (16)
0.80
CV Death
Overall (n=6505) 449/3241 (14) 491/3264 (15)
With Angina (n=2220) 163/1085 (15) 177/1135 (16)
Without Angina (n=4285) 286/2156 (13) 314/2129 (15)
0.57
Nonfatal MI
Overall (n=6505) 69/3241 (2) 73/3264 (2)
With Angina (n=2220) 30/1085 (3) 36/1135 (3)
Without Angina (n=4285) 39/2156 (2) 37/2129 (2)
0.62
0.5
1.0
2.0
Favors ivabradine
Favors placebo