CLINICAL REVIEW

Date: December 18, 2014

Reviewer: Thomas A. Marciniak, M.D.
               Cross-Discipline Team Leader (CDTL)

NDA: 206-143

Drug: ivabradine (Corlanor)

Subject: Summary of approval issues

Both the primary clinical reviewers and I have recommended approval of ivabradine for its heart failure (HF) indication, although with slightly different recommendations for the specifics of the indication. I judge that the combination of the primary clinical review and my CDTL review address well the details of the major efficacy and safety issues relevant to approval. However, the complexity of the issues and the standard templates required for reviews tradeoff succinctness of presentation for necessary details. For the late cycle meeting with the sponsor I produced a presentation that I believe summarizes the major issues for approval more succinctly than the reviews. I have included the presentation with comments on each slide as an Attachment.

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I believe that this presentation, prepared for the late cycle meeting with the sponsor, is the best succinct explanation of the major issues relevant to the approval of ivabradine. For this version I have corrected some typos and added one slide that I inadvertently omitted at the meeting. (I document the changes in the slide notes.)

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As I hope readers will appreciate after reviewing this presentation, my opinions are data driven: I do not hypothesize that the results should be a certain way based on any presumptions about mechanisms of action; I base all of my conclusions on observations of the data and justify them with comprehensive analyses.

Advisory Committee Meeting Postponed?

- The AC meeting scheduled for January 14, 2014, will (may?) be postponed until April 2014
- The reason for the postponement is that the issues are complex and the SIGNIFY study results may help to elucidate
- SIGNIFY was submitted too late for a complete review

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I recommended against postponing the AC meeting. I judge that the reviews are complete and incorporate the findings from SIGNIFY as applicable to the heart failure (HF) indication. I judge that the extensively reviewed evidence from the three ivabradine outcome trials (SHIFT, BEAUTIFUL, and SIGNIFY) document that ivabradine produces favorable outcomes for select HF patients for both HF hospitalizations and mortality. The remainder of this presentation justifies the selection of HF patients who benefit from ivabradine. Because the benefit is regarding serious morbidity and mortality, I believe that the FDA should not delay the approval of ivabradine. The Office Director overruled my recommendations against postponing the AC meeting and considering the SIGNIFY submission to be a major amendment extending the review clock.

Two Major Review Issues

- Inconsistences among the three trials
- Subgroup interpretations

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I characterize the major review issues as inconsistencies among the three trials and subgroup interpretations. The latter includes recommending that the indication be restricted to a subgroup of the pivotal SHIFT trial population, raising the usual concerns that we would be basing the indication on *post hoc* analyses. We have done so in several recent submissions, including the recent approval of vorapaxar, and to do so we require good justification. In the remainder of this presentation I describe the trial inconsistencies and resolve most of them and justify my proposed indication.

Ivabradine Outcome Trials

Trial	Population	N	Results
SHIFT	HF + LVEF≤35 + HR≥70	6,558	↓↓↓HF hospitalization; ± ↓CV death
BEAUTIFUL	Stable IHD + LVEF<40 + HR≥60	10,917	neutral for CV death & HF hospitalization; ↓MI ?
SIGNIFY	Stable IHD + LVEF>40 + HR≥70	19,102	↑CV death & MI in symptomatic angina

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Ivabradine has three major outcome trials:

- SHIFT, the pivotal trial for the HF indication. SHIFT enrolled patients with NYHA class 2-4 HF with a left ventricular ejection fraction (LVEF) ≤ 35 and heart rate (HR) ≥70. It succeeded on its primary endpoint with a highly significant reduction in HF hospitalizations and a favorable lean for cardiovascular (CV) mortality.

- BEAUTIFUL, a trial in patients with ischemic heart disease (IHD), a LVEF<40 and a HR ≥60. BEAUTIFUL failed on its primary endpoint, was neutral for CV death and HF hospitalizations, but suggested a possible benefit of decreased myocardial infarctions (MIs).

- SIGNIFY, a trial in IHD patients without systolic dysfunction. SIGNIFY reverted to the entry criterion HR ≥70 because the corresponding patients in BEAUTIFUL appeared to show a significant MI benefit. However, SIGNIFY failed on its primary MACE endpoint. In a pre-specified subgroup analysis in symptomatic angina patients (reduction of angina was the first approved indication for ivabradine in Europe) ivabradine produced higher MI and CV death rates than placebo.

About 68% of SHIFT patients had IHD as the etiology for their HF, so all three trials are relevant to the HF indication, at least regarding safety. This brief summary also starts to illustrate the inconsistencies among the trials.

Ivabradine Outcome Trials
"Inconsistencies"

Trial	Population	CVD		HF hospital		MI	
		RR	p*	RR	p*	RR	p*
SHIFT	HF + LVEF≤35	0.9	0.1	0.7	<0.001	1.0	0.2
	IHD (68%)	0.9	0.2	0.8	0.003	1.0	0.8
BEAUTIFUL	IHD + LVEF<40	1.0	0.8	1.0	0.9	0.9	0.1
	HR≥70 (49%)	1.0	0.8	1.0	0.8	0.6	0.001
SIGNIFY	IHD + LVEF>40	1.1	0.3	1.2	0.08	1.1	0.4
	symptomatic (63%)	1.2	0.1	1.2	0.2	1.2	0.04

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The table above highlights the inconsistencies among the trials. SHIFT showed a highly statistical significant reduction in HF hospitalizations with ivabradine, including in the IHD subgroup. Yet BEAUTIFUL was neutral for HF hospitalizations and SIGNIFY results leaned the wrong way. CV death (CVD) leaned favorably in SHIFT, neutral in BEAUTIFUL, and detrimentally in SIGNIFY. MI results were neutral in SHIFT, highly favorable in the pre-specified BEAUTIFUL subgroup with HR ≥70, and detrimental for ivabradine in the pre-specified SIGNIFY subgroup with symptomatic angina. I argue that we need to understand the reasons for these "inconsistencies" in order to know how to use ivabradine safely and effectively.

Factors Explaining the
Inconsistencies
= Related to Ivabradine Efficacy

- Loop diuretic use
- Heart rate
- Ischemic etiology
- Beta blocker dosage

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From the trial data I have identified four factors that explain most of the "inconsistencies" among the trials. The four factors are loop diuretic use, heart rate, ischemic etiology, and beta blocker dosage. These four factors are all related to ivabradine efficacy, i.e., they are effect modifiers for efficacy. We need to consider and potentially adjust for these factors in most analyses; if one fails to account for one of these critical factors, analysis results can be very misleading. I document the effects of these factors in the remainder of this presentation.

In addition, the two components of the SHIFT primary composite endpoint (CV death and HF hospitalizations) behave differently with regard to these factors. I show the differences towards the end of this presentation after elucidating the effects of the four factors.

Concomitant Medications

	SHIFT	BEAUTIFUL	SIGNIFY
BB-any	90%	87%	83%
BB-at target	23%	12%	
MRA	60%	27%	5%
loop diuretic	73%	43%	8%
ACEI	79%	80%	59%
ARB	14%	11%	23%
digitalis	22%	9%	0.5%
statin	57%	74%	92%

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Because two of the factors are drugs (loop diuretics and beta blockers) I have listed in the table above the usage rates at baseline in the three trials of the most relevant concomitant CV medications. BB is a beta blocker, MRA is a mineralocorticoid receptor antagonist (predominantly spironolactone or eplerenone), ACEI is an ACE inhibitor, and ARB is an angiotensin receptor blocker. One can also appreciate the different levels of HF in the three trials by noting the declining use of MRAs, loop diuretics, and digitalis from SHIFT to BEAUTIFUL to SIGNIFY.

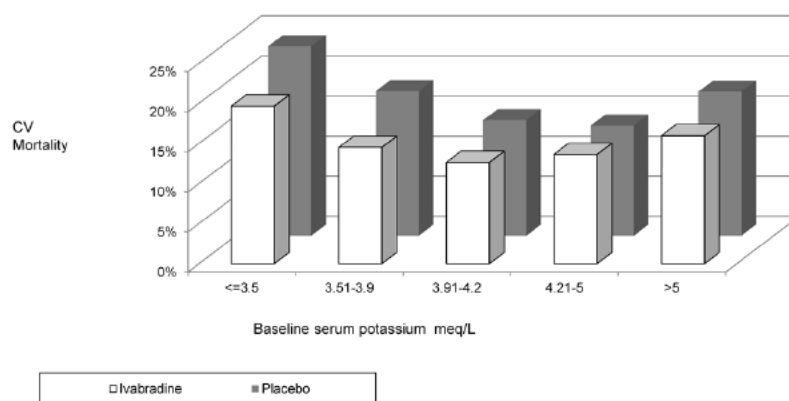Loop diuretics are 2-edged swords: CV Deaths vs. Baseline K in MRA* trials
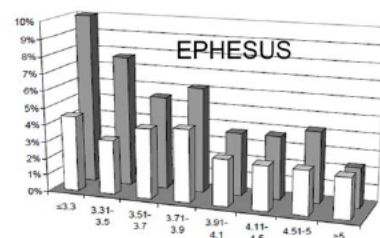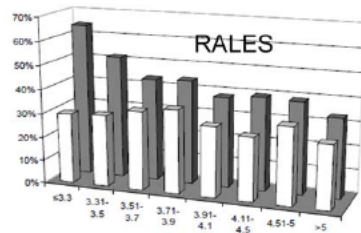
*MRA = mineralocorticoid receptor antagonist = aldosterone blocker

The strongest effect modifier for ivabradine is loop diuretic use. While loop diuretic dosages may also be a biomarker for HF severity, they also have detrimental effects that are independent of HF severity. One of their detrimental effects is potassium depletion that predisposes to a risk of arrhythmias. The MRA trials document this risk, and its reduction by MRA use, well. The bar graphs above show CV death rates on the y-axes vs. baseline serum potassium levels on the x-axes for the (b) (4) placebo-controlled outcome trials of MRAs in HF: RALES for spironolactone in class 3-4 HF with entry criterion for loop diuretic use; (b) (4) EPHESUS for eplerenone in systolic dysfunction post-MI; (b) (4) The white bars are the MRA rates and the black bars are the placebo rates by baseline serum potassium level. An abnormally low serum potassium level at baseline, i.e., 3.5 or lower, was a significant risk factor for CV death in the placebo arms of all (b) (4) studies, e.g., >60% mortality during RALES, the study requiring loop diuretic use for entry. MRA use almost levels the CV death risk across the potassium levels. (b) (4) That the effect is likely related to arrhythmias is demonstrated by the fact the relationship to potassium is evident for CV death but not for HF hospitalizations (not shown on this slide.)

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CV Deaths vs. Baseline K in SHIFT

CV Mortality

25%
20%
15%
10%
5%
0%

<=3.5   3.51-3.9   3.91-4.2   4.21-5   >5

Baseline serum potassium meq/L

☐ Ivabradine   ■ Placebo

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However, while I show later that ivabradine also appears to have a beneficial impact upon CV mortality in IHD patients, ivabradine does not appear to work through a mechanism related to potassium depletion. The graph above shows CV mortality in the two arms of SHIFT by baseline serum potassium level. While it again shows the increased risk of CV death with lower potassium levels, the risk reduction with ivabradine use is relatively independent of serum potassium levels. Ivabradine did not affect potassium levels in SHIFT, e.g., the mean change from baseline to month 4 (the first visit with repeat lab values) was -0.036 in the ivabradine arm and -0.033 in the placebo arm. The sponsor has not elucidated for ivabradine any mechanisms that affect potassium metabolism nor would we expect any based on its receptor interactions. Finally, the investigators have published—and I have confirmed—that ivabradine and MRAs do not interact in SHIFT. Consistent with a lack of an interaction there is a preclinical model suggesting other, non-interacting mechanisms of action, e.g., in a rat MI model with HCN channel upregulation spironolactone reduced HCN upregulation and ventricular premature beats (VPBs) and ivabradine reduced VPBs in both spironolactone and untreated rats. (Song, T., J. Yang, et al. (2011). "Spironolactone diminishes spontaneous ventricular premature beats by reducing HCN4 protein expression in rats with myocardial infarction." Mol Med Rep 4(3): 569-73.)
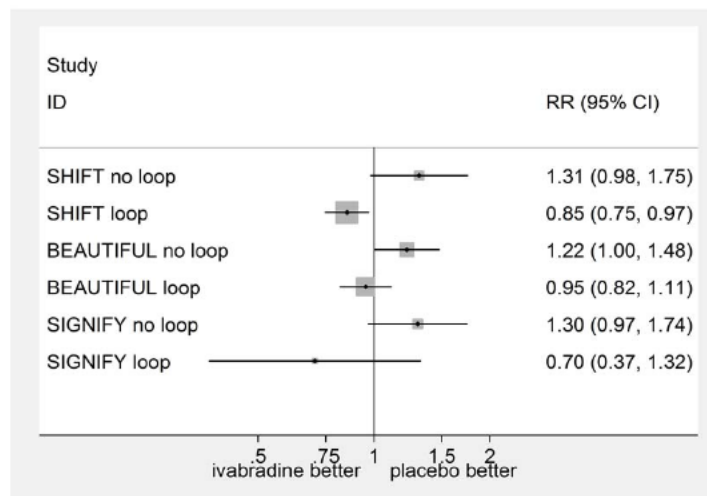
Loop Diuretic Use

		SHIFT	BEAUTIFUL	SIGNIFY
At randomization	%	73%	43%	8%
	Mean dosage*	43	47	31
Post randomization	%	79%	50%	16%
	Mean max dosage*	87	65	47

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Loop diuretic use at baseline was high in SHIFT, intermediate in BEAUTIFUL, and low in SIGNIFY. Mean dosage (equivalent to furosemide dosage, the most frequently used loop diuretic worldwide) at baseline was similar in SHIFT and BEAUTIFUL but lower in SIGNIFY. Because SIGNIFY excluded patients with systolic dysfunction, the typical indication for loop diuretic use at baseline in it was hypertension, an indication more common in Europe than in the U.S. and one for which lower dosages are used. The case report forms confirm hypertension as a common indication for loop diuretic use at baseline in SIGNIFY. Note that both the usage and the dosage of loop diuretics increased during the course of SIGNIFY, likely indicating increased usage for the treatment of HF.

CV Death by Loop Diuretic Use

Study ID		RR (95% CI)
SHIFT no loop		1.31 (0.98, 1.75)
SHIFT loop		0.85 (0.75, 0.97)
BEAUTIFUL no loop		1.22 (1.00, 1.48)
BEAUTIFUL loop		0.95 (0.82, 1.11)
SIGNIFY no loop		1.30 (0.97, 1.74)
SIGNIFY loop		0.70 (0.37, 1.32)

.5   .75   1   1.5   2
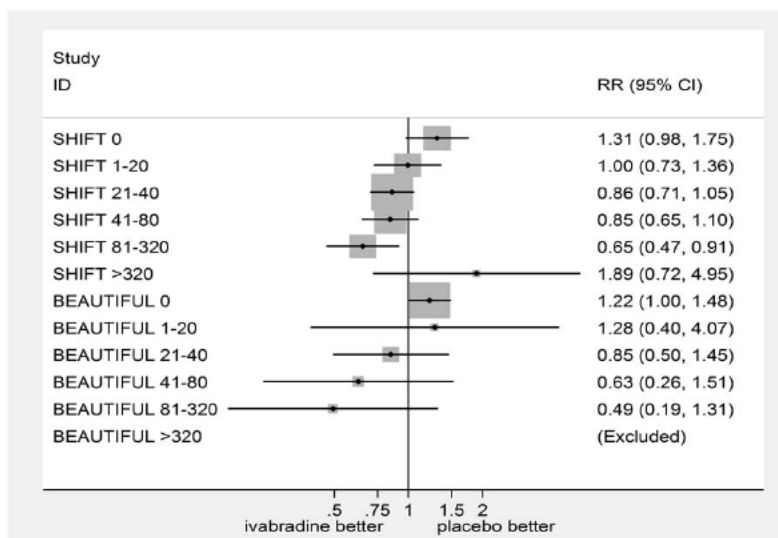ivabradine better | placebo better

P-values for ivabradine-loop interaction: 0.007 for SHIFT, 0.054 for BEAUTIFUL, 0.084 for SIGNIFY

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For ivabradine the strongest effect modifier, most consistent among the three trials, is its interaction with loop diuretics for CV mortality. The interaction is a qualitative one: With concomitant loop diuretic use at baseline in SHIFT ivabradine has a significantly favorable effect upon CV mortality; without loop diuretic use the effect is detrimental. (Please note: I document later that this interaction is predominantly in patients with IHD.) In SHIFT the interaction is highly statistically significant (p = 0.007). In BEAUTIFUL, with the lower loop diuretic use, the interaction is marginally significant but in the same direction. In SIGNIFY, with low baseline use and dosage of loop diuretics, the interaction is not significant. (Please note that I added the statistics for SIGNIFY to the graph above after the original presentation although I did mention them.) However, I commented regarding the last slide that loop diuretic use and dosage increased substantially post-randomization in SIGNIFY, likely reflecting use for HF. Using post-randomization loop diuretic use in SIGNIFY the interaction becomes nominally statistically significant (p = 0.021). I recognize that I am not correcting for multiplicity. However, the p value for SHIFT is reasonably extreme and the pattern of consistency among the three trials is striking.

The interaction is qualitative, i.e., reversing benefit. I hypothesize that there are two mechanisms responsible: an unfavorable one for ivabradine in IHD patients (bradycardia-related arrhythmias including re-entrant tachyarrhythmias?) and a favorable one in IHD patients on a loop diuretic (suppression of increased automaticity ventricular arrhythmias?)

CV Death by Loop Diuretic Dose

Study ID		RR (95% CI)
SHIFT 0		1.31 (0.98, 1.75)
SHIFT 1-20		1.00 (0.73, 1.36)
SHIFT 21-40		0.86 (0.71, 1.05)
SHIFT 41-80		0.85 (0.65, 1.10)
SHIFT 81-320		0.65 (0.47, 0.91)
SHIFT >320		1.89 (0.72, 4.95)
BEAUTIFUL 0		1.22 (1.00, 1.48)
BEAUTIFUL 1-20		1.28 (0.40, 4.07)
BEAUTIFUL 21-40		0.85 (0.50, 1.45)
BEAUTIFUL 41-80		0.63 (0.26, 1.51)
BEAUTIFUL 81-320		0.49 (0.19, 1.31)
BEAUTIFUL >320		(Excluded)

.5 .75 1 1.5 2
ivabradine better   placebo better

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An excellent way of confirming a drug effect is to demonstrate a dose-response. The graph above shows the dose-response for the interaction between ivabradine and loop diuretic dose at baseline in SHIFT and in BEAUTIFUL. (The SIGNIFY data are too sparse to be able to demonstrate a dose-response.) The doses are again furosemide-equivalent doses. There is a definite dose response in both studies with the exception of the SHIFT subgroup with dosages > 320 mg at baseline. Besides being a small subgroup these patients likely represent patients with severe congestive problems or unstable disease.

The beneficial impact of ivabradine on CV mortality doesn't appear to be evident until the loop diuretic dosage exceeds 20 mg. However, because the effects for CV mortality appear neutral at this dosage and there is a benefit regarding HF hospitalizations, I have specified my recommendation for labeling as loop diuretic use or not—in IHD patients only as I document later in this presentation.

The sponsor asserted during the meeting that an interaction between ivabradine and loop diuretic use lacks biologic plausibility. However, in preclinical models ivabradine has been shown to interact with ventricular HCN channels to reduce arrhythmias. I mentioned one model on slide 10. Another is a mouse HF model showed HCN channel overexpression and HCN channel blockade by ivabradine reduced lethal arrhythmias. (Kuwabara, Kuwahara et al. 2013) Overexpression of I_f has also been reported in ventricular myocytes from failing human hearts. (Stillitano, Lonardo et al. 2008) (See the CDTL review for full references.)

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Lack of Interactions with Heart Failure Severity in SHIFT

```
MFPIGEN - interaction analysis for dependent variable cvd (6558 observations)
-------------------------------------------------------------------------------
variable 1    function 1    variable 2    function 2   dev. diff.  d.f.    P    Sel
-------------------------------------------------------------------------------
ivabradine    Linear        loopdiur0     Linear         7.3027      1   0.0069  2
              Linear        lvef0         Linear         1.1606      1   0.2813  2
              Linear        nyha3to4      Linear         0.2043      1   0.6513  2

loopdiur0     Linear        lvef0         Linear         0.0076      1   0.9304  2
              Linear        nyha3to4      Linear         0.0055      1   0.9409  2

lvef0         Linear        nyha3to4      Linear         0.3095      1   0.5780  2
-------------------------------------------------------------------------------
Sel = number of variables selected in MFP adjustment model
Smallest P-value ( .0068853 ) is for ivabradine # loopdiur0
```

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While loop diuretic dose is correlated with HF severity, it (rather than HF severity) interacts with CV mortality. The interaction analysis above (performed using the STATA MFPIGEN procedure) documents that, while the interaction between ivabradine and loop diuretics is highly statistically significant, interactions with the two measures of HF severity available in SHIFT (NYHA class and LVEF) are remote from statistical significance. The lvef0 variable is the LVEF percentage at baseline, i.e., a continuous variable. The nyha3to4 variable is an indicator variable with value 0 for NYHA class 2 and value 1 for NYHA class 3 to 4 (almost all 3s because there were only 111 patients categorized as class 4 at baseline in SHIFT). In BEAUTIFUL the endpoint results were more favorable for ivabradine patients with lesser severity of HF by LVEF or NYHA class criteria. Hence I am not advocating that the ivabradine indication include a LVEF criterion other than class 2 to 4 with systolic dysfunction.

The sponsor has alleged that the loop diuretic interaction is due to the correlation with HF severity. The above analysis does not support that hypothesis. Even if it were, it would still be the most useful factor for differentiating patients who benefit from those who do not. The sponsor at the late cycle meeting objected that loop diuretic dosage was not an intrinsic patient factor and so physicians would have trouble classifying patients by it and would be confused if they had to start and stop ivabradine when loop diuretics were started or stopped. I replied that physicians can more reliably determine loop diuretic use than NYHA class and I would recommend starting and stopping ivabradine if the physician starts or stops all loop diuretics in IHD patients.
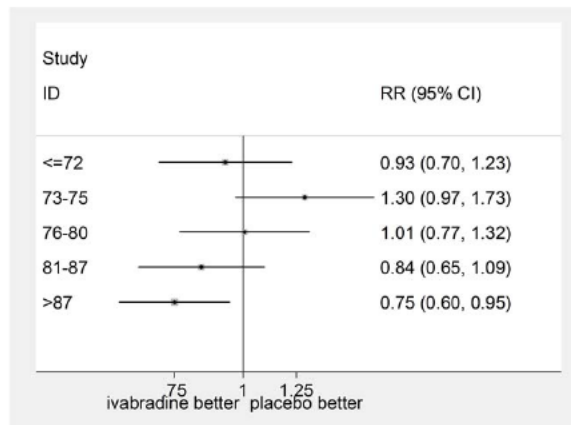
CV Deaths vs. Baseline HR Quintiles SHIFT
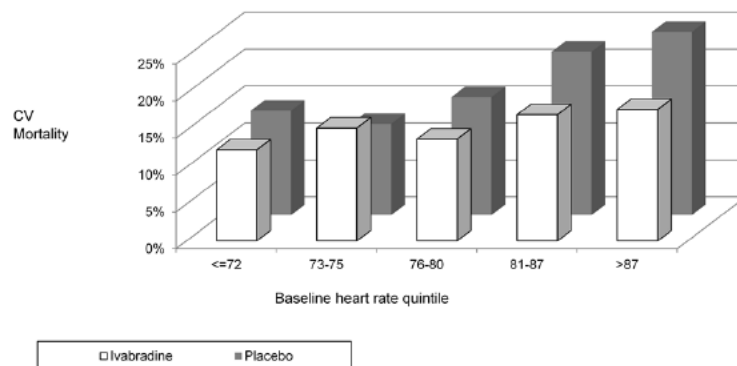
A second effect modifier for ivabradine is pre-treatment heart rate. The graph above shows that a lower baseline heart rate is a favorable prognostic factor while ivabradine only appears to be effective at heart rates greater than about 75. (This relationship could be confounded by beta blocker dosage—and ischemic etiology. I address both later in this presentation.)
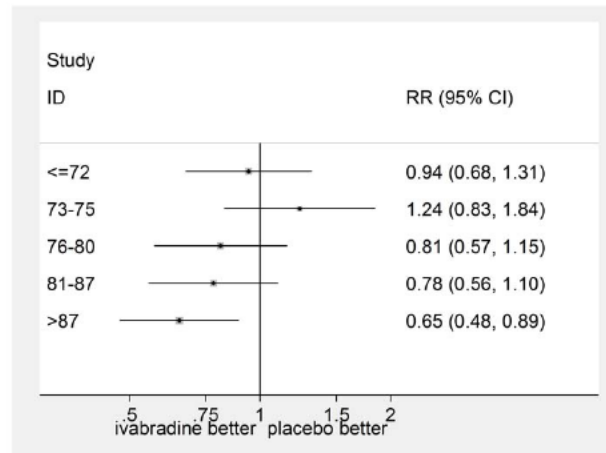
CV Death Risk vs. Baseline HR Quintile in SHIFT

Study ID		RR (95% CI)
<=72		0.93 (0.70, 1.23)
73-75		1.30 (0.97, 1.73)
76-80		1.01 (0.77, 1.32)
81-87		0.84 (0.65, 1.09)
>87		0.75 (0.60, 0.95)

.75   1   1.25
ivabradine better   placebo better

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The forest plot above depicts explicitly the risk ratios (ivabradine/placebo) for CV death by baseline heart rate quintile. Clearly there is only an apparent benefit at higher baseline heart rates. While differences between the lowest two quintiles could be real, I did examine the distribution of baseline heart rates: The distribution shows digit preferences for 72, 75, and 80 bpm. Hence the lower heart rate recordings may not be completely accurate and the better representation may be combining the first two quintiles.
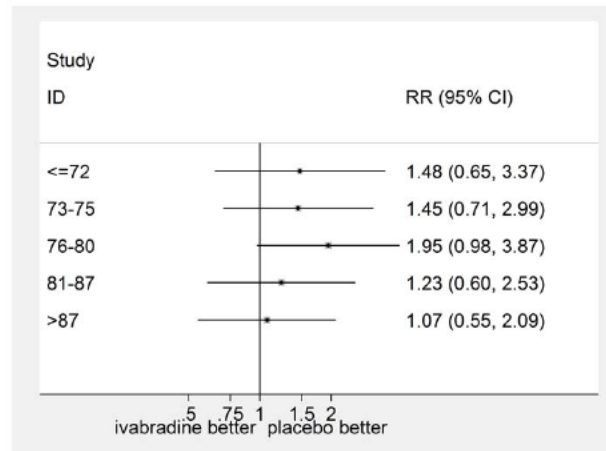
The pattern of CV death risk by baseline heart rate looks similar for the IHD subgroup on a loop diuretic to that for the study as a whole. The pattern is not the same for IHD patients not on a loop diuretic or for non-IHD patients as shown in the next two slides.
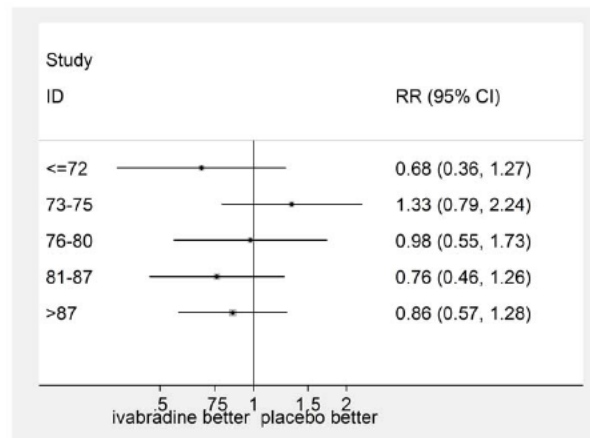
CVD Risk vs. Baseline HR SHIFT Ischemic without Loop

For IHD patients not on a loop diuretic at baseline there appears to be no benefit. The effects in the highest heart rate quintile appear neutral.

CVD Risk vs. Baseline HR SHIFT Nonischemic

Study ID	RR (95% CI)
<=72	0.68 (0.36, 1.27)
73-75	1.33 (0.79, 2.24)
76-80	0.98 (0.55, 1.73)
81-87	0.76 (0.46, 1.26)
>87	0.86 (0.57, 1.28)

ivabradine better   placebo better

The benefit in non-IHD patients appears less related to baseline heart rate. If one combines the first two quintiles, there appears to be a modest benefit regardless of baseline heart rate. Regardless, there is no trend for greater benefit at higher heart rates.

Despite the data presented in the last three slides the sponsor asserted at the meeting that ivabradine efficacy did not vary in patients with angina, allegedly the patients with more severe IHD, compared to patients without angina. I replied that that may appear to be true if the loop diuretic interaction is ignored but it is not true considering it. Ignoring loop diuretic use there is no interaction between ivabradine and history of angina for CV death by either Cox or logistic regression (HR or OR ≈ 1, p>0.7). However, for patients with a history of angina the qualitative interaction between ivabradine and loop diuretic use is strong and highly significant (HR or OR ≈ 0.5, p = 0.008-0.012) by either Cox or logistic regression. For patients without a history of angina or reported IHD there is no interaction (HR or OR ≈ 1, p>0.8) by either Cox or logistic regression.

The sponsor alleged at the meeting that they could not duplicate the results I presented using logistic regressions but that Cox regressions were preferable. I replied that the results are practically identical by Cox or logistic regressions. The statistics above support my claim.

Proposed Indicated Population

- All of the following:
  - Beta blocker maxed or intolerant
  - HR ≥ 70 bpm
  - Ischemic etiology only:
    - HR ≥ 75 bpm
    - On a loop diuretic
- SHIFT: 4,020 patients (61%)
- BEAUTIFUL: 1,716 patients (16%)

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Based on these analyses I propose the indicated population as follows:

- Beta blocker maxed or intolerant
- Pre-treatment heart rate ≥ 70 bpm
- Additionally for IHD patients:
  - Pre-treatment heart rate ≥ 75 bpm
  - On a loop diuretic

The subgroup of SHIFT corresponding to these additional restrictions is 4,020 patients, about 61% of SHIFT. Compare that to the EMA's (and the primary efficacy reviewer's recommended) restriction to ≥ 75 bpm regardless of etiology or loop diuretic use. The latter corresponds to a SHIFT subgroup of about 64% of SHIFT. For BEAUTIFUL the corresponding subgroup to my proposed indication is 1,716 patients, about 16% of BEAUTIFUL. I show in the following slides how my proposed indication and the EMA/primary efficacy reviewer's indication discriminate between patients who benefit from ivabradine and those who do not.
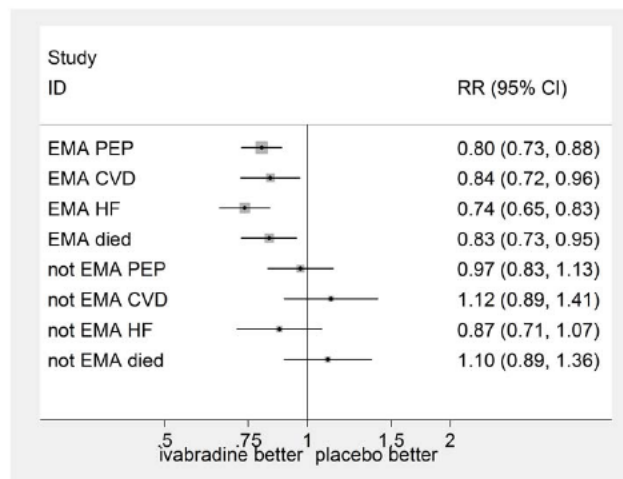
EPs in SHIFT
Proposed Indicated Subgroup
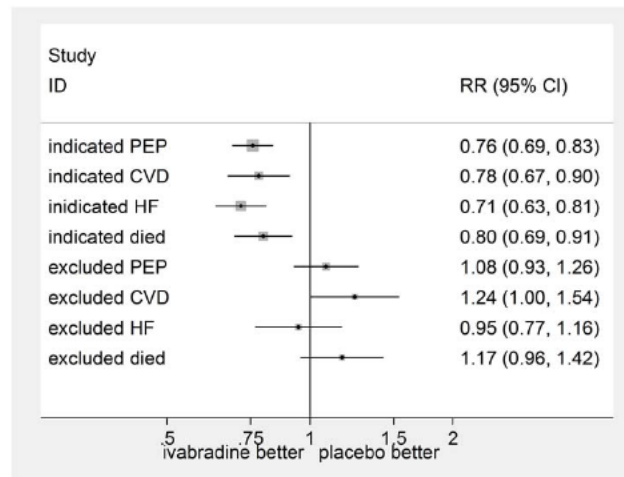
In the forest plot above PEP is the primary SHIFT endpoint (CV death and HF hospitalization—plotted for BEAUTIFUL above); CVD is CV death; HF is heart failure hospitalization; and died is all cause mortality. The "indicated" designates the statistics for the subgroup corresponding to my proposed indicated population while the "excluded" is the subgroup excluded by my proposed indication. The results for all endpoints in the indicated subgroup are highly significantly favorable for all endpoints, including all cause mortality. The results for all endpoints in the excluded subgroup appear unfavorable with possibly neutral or slightly favorable results for HF hospitalizations.

I note that the results in indicated subgroup, i.e., a 29% reduction in HF hospitalizations and a 20% reduction in all cause mortality,   (b) (4)

Note: The first title of this slide (and the next) in the original presentation was "EPs in SHIFT and BEAUTIFUL". I have corrected the title because the forest plots are for SHIFT data only.

EPs in SHIFT
HR ≥ 75 Subgroup (EMA)

The forest plot of endpoints in SHIFT for the subgroup with heart rate ≥ 75 bpm at baseline (the EMA indication) looks similar to that for my proposed indication. However, note that every risk ratio for my indicated subgroup is more favorable than the corresponding one for the EMA indication and every risk ratio for my excluded subgroup is less favorable than the corresponding one for the EMA indication. My proposed indication discriminates better between patients who benefit from ivabradine and those who don't than the EMA's (or the primary efficacy reviewer's). I believe that the better discrimination by my proposed indicated population is based on my selecting factors and criteria that I had demonstrated to be significant effect modifiers for ivabradine.

EPs in BEAUTIFUL
Proposed Indicated Subgroup
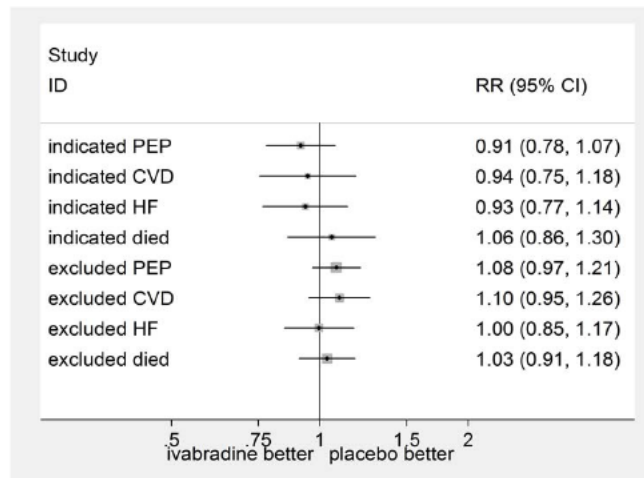
This slide is the one I inadvertently left out of the original presentation. PEP above uses the SHIFT definition of the primary endpoint (CV death and HF hospitalization) not the BEAUTIFUL definition. The endpoint results in the proposed indicated subgroup of BEAUTIFUL lean favorably for ivabradine except the point estimate for all cause mortality risk is neutral to slightly unfavorable. They lean unfavorably in the excluded subgroup except HF hospitalization risk has a neutral point estimate. None of the differences are statistically significant; note that the indicated subgroup comprises 1,716 patients, about 16% of BEAUTIFUL. I do not trust the sponsor's "calibrated" subgroup analyses (which are more favorable for ivabradine) because the "calibrated" subgroup includes patients who would not be eligible for SHIFT. I consider BEAUTIFUL to be weakly supportive of ivabradine efficacy.
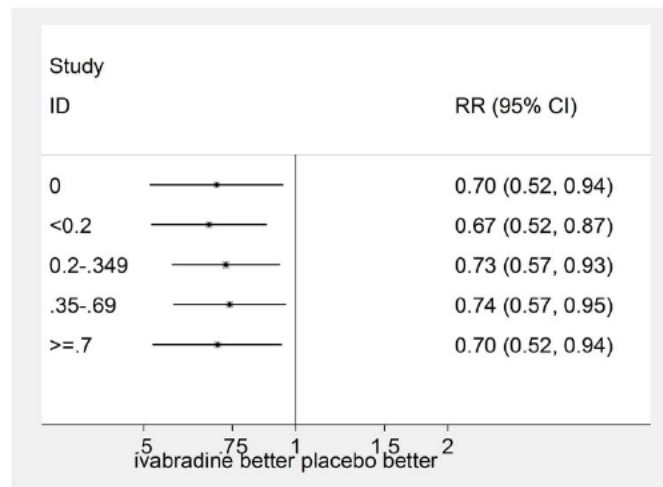
CVD Risk by Beta Blocker Dose
SHIFT Indicated Subgroup
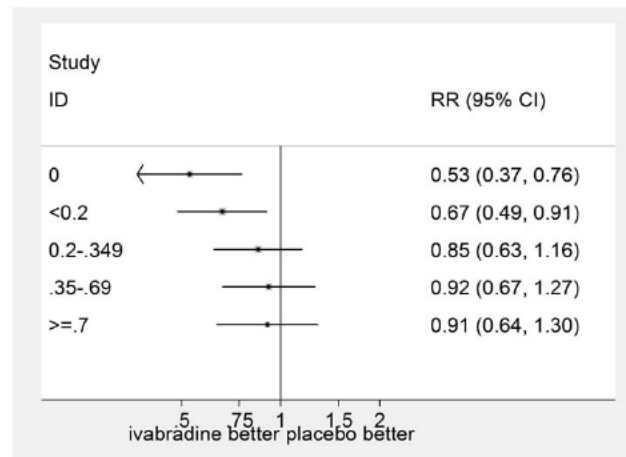
The fourth effect modifier for ivabradine efficacy is beta blocker dose. The fractions on the left side of the graph above are the fractions of the guideline-recommended dosages. Beta blocker use is the only one of the four factors that the SHIFT eligibility criteria addressed, i.e., SHIFT patients were supposed to be on a maximum tolerated dose of a beta blocker or intolerant of any dose. It remains an important effect modifier for the ivabradine benefit for CV mortality as shown by the forest plot above. The ivabradine CV mortality benefit becomes progressively less as beta blocker dose increases and may disappear for dosages near or above the guideline recommended dose. However, the ivabradine HF hospitalization benefit is not dependent upon beta blocker dose as shown in the next slide.

HF Hosp Risk by Beta Blocker Dose
SHIFT Indicated Subgroup

Study ID		RR (95% CI)
0		0.70 (0.52, 0.94)
<0.2		0.67 (0.52, 0.87)
0.2-.349		0.73 (0.57, 0.93)
.35-.69		0.74 (0.57, 0.95)
>=.7		0.70 (0.52, 0.94)

.5   .75   1   1.5   2
ivabradine better   placebo better

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The ivabradine benefit for reducing HF hospitalizations appears to be independent of beta blocker dose. It appears to be so robust in SHIFT that I have a concern that it is not robust at all in BEAUTIFUL. The most consistent effect between SHIFT and BEAUTIFUL and among all three studies is the ivabradine-loop diuretic interaction for CV mortality. Because HF hospitalization in SHIFT involved hospitalization practices in Eastern Europe and elsewhere that differ from U.S. practices, I consider the ivabradine CV mortality benefit to be the benefit that will be most applicable to U.S. patients.

The primary clinical review raises the question of whether ivabradine should be used with negative chronotropic drugs such as digitalis and amiodarone. The review bases its objection on the lack of a significant benefit for the subgroup of patients taking digitalis in the entire study. However, the interaction between digitalis and ivabradine is nonsignificant both in the entire study and in the proposed indicated subgroup. Furthermore, the digitalis subgroup of the indicated subgroup has a favorable odds ratio that is borderline statistically significant in that subgroup as shown in the table above. While I believe there are some additive effects of ivabradine and other negative chronotropes such as digitalis, the patients who are harmed by that interaction are excluded by my proposed indicated population criteria. I don't believe an additional specific exclusion for digitalis is justified.

Indicated Population QED!

- All of the following:
  - Beta blocker maxed or intolerant
  - HR ≥ 70 bpm
  - Ischemic etiology only:
    - HR ≥ 75 bpm
    - On a loop diuretic
- Benefits:
  - Death -20%
  - HF hospitalization -29%

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I believe I have justified with comprehensive analyses and hard data my criteria for an indicated population for ivabradine use in class 2 to 4 HF patients with systolic dysfunction. Applying the criteria differentiates well between patients who benefitted from ivabradine in SHIFT and those who did not. The benefits in this population are impressive: a 20% reduction in all cause mortality and 29% reduction in HF hospitalizations. I recommend approval for ivabradine as rapidly as possible.

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/s/

THOMAS A MARCINIAK

12/18/2014