National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Ivabradine for the treatment of chronic heart failure

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from BMJ Group to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, Friday 22 June using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

29 October 2009
## Issue 1  
**Relationship between treatment effect and beta-blocker dose**

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<td>There are several references to the relationship between the effect of ivabradine on outcomes given varying doses of beta-blocker, with the following statements serving as examples: p.71 “The ERG considers that there is uncertainty around the benefit of adding ivabradine to optimised standard care where patients are able to achieve at least 25% of target beta-blocker dose. Although a trend to benefit of ivabradine is observed, benefit seems to [<strong>increasing</strong>] with increasing beta-blocker dose and [****<strong>achieved for all outcomes assessed in the ERG’s exploratory analyses.</strong>**]” p.126 “the ERG considers that the beneficial effect of ivabradine could be [<strong>in patients with a resting heart rate ≥75 bpm who achieve higher doses of beta-blocker therapy”</strong>] p.127 “The ERG speculates that the results of the exploratory analyses suggest that there is uncertainty around the benefit of adding ivabradine to standard care for patients with a resting heart rate of ≥75 bpm and who are achieving higher levels of beta-blockade”</td>
<td>The manufacturer proposes that the following statement is a more accurate reflection of the facts: “The ERG has identified that there appears to be an [***in the effect of ivabradine on mortality in patients with a resting heart rate ≥75 bpm who achieve higher doses of beta-blocker therapy. However the ERG acknowledges that there is a [******in heart failure hospitalisation regardless of beta-blocker dose (albeit non-significant in the higher dose groups, possibly for reasons of low event rates). Furthermore the cost effectiveness model, robustly demonstrates that ivabradine on top of standard therapy remains cost effective regardless of beta-blocker dose”</td>
<td>The manufacturer suggests that these statements should be amended as they oversimplify the clinical data and lend the reader to conclude that there may be no benefit to adding ivabradine to patients with a heart rate ≥75 bpm receiving higher doses of beta-blockade. The manufacturer maintains that, regardless of beta-blocker dose, in patients with a resting heart rate ≥75 bpm ivabradine has been demonstrated to at least reduce the risk of hospitalisation, and this is one reason for which ivabradine remains cost effective in all beta-blocker dose subgroup analyses. In addition, as acknowledged by the ERG, care must be taken in interpreting between group differences from subgroups of subgroups within the trial. This amendment provides the reader with a more accurate description of the apparent relationship between treatment effect and beta-blocker dose.</td>
<td>No change required; not a factual error. The ERG considers that the sentences extracted by the manufacturer should be considered in the context of the full text in which they appear in the ERG report. Each sentence forms part of a narrative within the relevant sections of the ERG report and these sections draw out the points made in the manufacturer’s proposed revised text. For example, in the Executive Summary and Section 4.3.4, the ERG highlights and discusses the observed [****<strong>associated with ivabradine in the cause-specific outcomes of hospitalisation due to worsening heart failure and heart failure mortality, irrespective of beta-blockade achieved.</strong>]</td>
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These statements oversimplify the relationship between ivabradine effect and beta-blocker dose and may be interpreted incorrectly.

The manufacturer feels that further context is required in relation to the following sentence, particularly in light of the full publication of Swedberg 2012 (1) which brings further clarity to the relationship between baseline heart rate and the clinical effect of ivabradine.

p.65 “Although the ERG appreciates the manufacturer’s comment that variation in clinical effect of ivabradine is linked with baseline resting heart rate and not baseline level of beta-blockade, the ERG considers it important to note that, in the licensed population, across the groups assessed based on various thresholds of beta-blockade (Table 19)…”

The manufacturer proposes that the following statement is a more accurate reflection of the facts:

“The ERG notes the manufacturer’s comment that variation in the clinical effect of ivabradine is linked to baseline resting heart rate and is not significantly impacted by beta-blocker dose (1). It is therefore relevant to consider how resting heart rate varies across beta-blocker dose categories in the licensed population. Table 19 shows that resting heart rates are in patients on target dose beta-blockade than in patients not receiving a beta-blocker.

Furthermore, the multivariable analysis of SHIfT data by Swedberg et al. (now fully published (1)) suggests that the relationship between beta-blocker dose and treatment effect may be confounded by factors related to patient severity.”

Baseline heart rate has been shown to be a significant modifier of treatment effect. Although heart rate changes across the subgroups may appear similar, patient groups on higher beta-blocker doses do have lower heart rates. In addition, lower heart rates are a marker of less severe patients which confound a simple interpretation of these tables.

Swedberg et al. have conducted an analysis of the relationship between beta-blocker dose and heart rate in the SHIFT trial which has not been referenced in the ERG report. This study (now fully published (1)) concludes,

“The present analysis indicates that the effects of ivabradine on the primary clinical outcome of SHIfT, and its components, were not significantly impacted by beta-blocker dose. Any borderline non-significant trends were significantly weakened by adjustment for the previously identified interaction between baseline heart rate and…”

Baseline heart rate has been shown to be a significant modifier of treatment effect. Although heart rate changes across the subgroups may appear similar, patient groups on higher beta-blocker doses do have lower heart rates. In addition, lower heart rates are a marker of less severe patients which confound a simple interpretation of these tables.

Swedberg et al. have conducted an analysis of the relationship between beta-blocker dose and heart rate in the SHIFT trial which has not been referenced in the ERG report. This study (now fully published (1)) concludes,

“The present analysis indicates that the effects of ivabradine on the primary clinical outcome of SHIfT, and its components, were not significantly impacted by beta-blocker dose. Any borderline non-significant trends were significantly weakened by adjustment for the previously identified interaction between baseline heart rate and…”

No change required; not a factual error

The ERG considers that the data presented in Table 19 indicate that, in the licensed population, the across subgroups; range of mean (SD) baseline resting heart rate is to bpm, with considerable variation around the mean values. As the manufacturer highlights the highest resting heart rate is seen in the subgroup of patients receiving no beta-blocker (bpm in the ivabradine group and bpm in the placebo group). The ERG considered the baseline resting heart rates to be across subgroups as the variation in resting heart rate fluctuates in the ivabradine arm across subgroups achieving some level of beta-blockade rather than steadily declining across subgroups of increasing...
### ivabradine treatment

Other confounding factors associated with a less severe patient may also be contributing to the effect, for example younger age, less COPD, lower NYHA class and higher left-ventricular ejection fraction. As is seen in the analysis of the full population of the SHiFT trial (presented by Swedberg et al. in the recent publication), albeit with minor differences between some subgroups in both populations.

The ERG has noted in its report the importance of the link between baseline resting heart rate and outcome. The ERG agrees that the recent publication by Swedberg suggests that borderline significant trends were weakened by adjustment for interaction between baseline resting heart rate and ivabradine treatment effect but argues that a similar analysis has not been carried out for the results generated from the licensed population. As the variation in baseline resting heart rate across subgroups in the licensed population does not mirror the trend observed in the full population of the SHiFT trial, the ERG maintains that it cannot be assumed that there is no association between variation in clinical effect and level of beta-blockade in the licensed population of the
The ERG reports a linear regression showing a correlation between beta-blocker dose and the benefit of ivabradine on cardiovascular mortality.

p.64 “The ERG also carried out a simple linear regression analysis. Results of this analysis identified a correlation between increasing level of beta-blockade and a reduction in benefit with ivabradine use for the endpoint of cardiovascular mortality; plot presented in Appendix 7”. The manufacturer proposes that it should be clarified that this analysis is not adjusted for confounding factors.

The manufacturer proposes that the following is a more complete description of the analysis:

“The ERG also carried out a simple linear regression analysis which was unadjusted for confounding factors. Results of this analysis identified a correlation between increasing level of beta-blockade and a reduction in benefit with ivabradine use for the endpoint of cardiovascular mortality; plot presented in Appendix 7”.

In the interests of accuracy, the manufacturer feels it should be recognised that this analysis does not take the role of confounding factors into account.

No change required; not a factual error

The ERG considers that when taken in the context of the full ERG report it is clear from the results presented that the simple linear regression analysis is based on the absolute data presented in Appendix 8 (data for licensed population based on percentage target beta-blocker dose at randomisation), and as such has not been adjusted for confounding factors.
### Issue 2  National Heart Failure Audit referencing error

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<td>p.49 Table 11 “Note: The ERG was unable to validate the data reported from the National Heart Failure Audit&lt;sup&gt;(1)&lt;/sup&gt; as the ERG believes that the reference cited does not report on beta-blocker prescription on discharge from hospital.” The manufacturer wishes to identify that the National HF Audit data referenced in this table was incorrectly referenced in the manufacturer submission (MS).</td>
<td>The correct reference for this data is an analysis which was commissioned by the manufacturer. The analysis is unpublished and a preliminary report (which was submitted with the MS in March) has been submitted again with this response (2).</td>
<td>Although this amendment relates to a referencing error in the MS it was considered important to identify the source of the data concerned.</td>
<td>The ERG thanks the manufacturer for the clarification. Table 11 has been amended; data from the unpublished reference have been deleted. Due to the unpublished nature of the data, the ERG has deleted the data from the Heart Failure Audit presented in Table 11. The ERG has added a footnote to the Table to highlight that the manufacturer presented data from a second source. In drafting the original report, the ERG decided against reporting unpublished data, where possible, as such data will not have been subjected to peer review.</td>
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### Issue 3  Half-cycle correction

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<td>p.77 Table 23: The ERG states, “Half-cycle correction was included for only on-going costs.” However, a half-cycle correction</td>
<td>Please can the ERG amend this statement to read, “Half-cycle correction was included for both on-going costs and effects.”</td>
<td>Factually incorrect. A half-cycle correction was included for effects.</td>
<td>The ERG agrees that the current text is inaccurate. The text has been amended to</td>
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was included for both costs and effects.

p.77 Table 23: The ERG states, “A half cycle correction was not included because of the short cycle length (one month) used”

Please can the ERG amend this statement to read, “A half-cycle correction was included for health benefits despite the short cycle length.”

Factually incorrect. A half-cycle correction was included for effects

The ERG agrees that the current text is inaccurate. The text has been amended to reflect that the half-cycle correction factor was included for both costs and benefits.

### Issue 4  Clarification on generalised ordered logistic regression

| p.82 The ERG states, “Logistic regression models (proportional odds models) are a technique used to assess the impact of covariates on categorical data. Essentially, a separate regression equation is developed assessing the impact of covariates on each category and the results of each analysis pooled to give the overall result. This model relies on the assumption that the relationship between any two outcome categorisations is the same (the proportional odds assumption).” Text is factually incorrect and could potentially mislead the reader. | Please can the ERG amend this statement to clarify that a generalised ordered regression model is a special type of ordered logistic regression which relaxes the proportional odds assumption and allows the odds ratios to vary across different categories. | It should be noted that the generalised ordered logistic regression model is an extension of a standard proportional odds model (relaxes the proportional odds assumptions and allows the odds ratios to vary across categories). The manufacturer wishes to acknowledge that this was not made sufficiently clear in the original STA submission. | The ERG agrees that the current text requires clarification. The ERG has added the following text: “The manufacturer uses the generalised ordered logistic regression, which is a special type of logistic regression model that relaxes the assumption of proportional odds.” |
**Issue 5  Clarification regarding Kaplan-Meier data in the within-trial model**

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<td>p.84 “The ERG notes that the ICER obtained using the observed Kaplan-Meier data for the “within-trial” period was £794 more than the base case ICER. Therefore the ERG considers the use of the parametric equations for the “within-trial” period to favour the ivabradine model arm.” This is not technically correct.</td>
<td>Can the ERG please include a statement to clarify that the data used for the Kaplan-Meier estimates is from all patients in SHIfT (patients with heart rate ≥70 bpm) rather than the licensed indication (with heart rate ≥75 bpm), and this has driven a higher ICER for a within-trial model which uses Kaplan-Meier data rather than a parametric model.</td>
<td>The ERG’s conclusion does not take into account the differences in population heart rate between the estimates derived from Kaplan-Meier data and the parametric model (which adjusts to consider a population with a higher baseline heart rate). The model has been developed using data from the whole patient cohort i.e. patients with a heart rate ≥70 bpm. The data used for the Kaplan-Meier estimates is consequently derived from the entire dataset rather than from the licensed indication (heart rate ≥75 bpm). It is the use of data from the whole cohort which has driven the higher ICER rather than the use of the parametric model. An analysis which used observed data from patients with heart ≥75 bpm has been undertaken and the results showed a more favourable ICER (rather than less favourable), indicating that the parametric modelling approach is conservative and biased against ivabradine. It is also noted that a more favourable result from observed data is not consistent with the ERG’s conclusion.</td>
<td>The ERG agrees that the current text is inaccurate. The text has been updated to: “The ERG notes that the incremental cost-effectiveness ratio (ICER) obtained using the observed Kaplan-Meier data for the “within trial” period was £794 more than the base case ICER. However, the ERG notes that Kaplan-Meier data from the full population of SHIfT (heart rate ≥ 70 bpm) are used and that these data are unadjusted for heart rate; estimates based on Kaplan-Meier data for the full population of SHIfT may underestimate the effect of ivabradine in the licensed population.”</td>
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Kaplan-Meier data (in patients with heart rate $\geq 75$ bpm) would be consistent with the slight under-prediction of CV mortality and under-prediction of the ivabradine treatment effect which the ERG has observed to result from the final parametric models (p.113, 122).

**Issue 6  CV mortality risk equation: contextualising statistical non-significance**

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<td>p.90 The ERG states that, “contrary to the clinical analysis of SHIfT the manufacturer’s regression analysis suggests that treatment with ivabradine is associated with a non-significant reduction in the risk of cardiovascular mortality.”</td>
<td>Can the ERG please clarify that the risk equations were developed from the entire SHIfT cohort (heart rate $\geq 70$bpm) and that the non-significant treatment effect on CV mortality in this regression model is consistent with the findings of the clinical analyses in this population (heart rate $\geq 70$bpm). Can the ERG also clarify that the treatment interaction term distorts the value of the treatment coefficient and the associated statistical significance in the regression model, which therefore means that estimates of the primary coefficient cannot be interpreted in isolation from the interaction term. Lastly, can the ERG please further clarify and evidence the statement that the absence of a significant treatment effect for ivabradine may also be because the regression equation is likely to under-predict the risk of cardiovascular mortality, and discuss the plausibility of this hypothesis in the context of the issues outlined</td>
<td>Firstly the risk equations have been developed from data from the whole SHIfT cohort (patients with a heart rate $\geq 70$bpm). A non-significant treatment effect in this population would be consistent with the clinical analyses undertaken on the overall SHIfT dataset. The economic analysis does not therefore contrast with the clinical results as the ERG have suggested. Secondly, the statistical significance of the treatment covariate should not be interpreted in isolation due to the presence of the interaction effect in the regression model. The inclusion of treatment interaction with heart rate changes the value of the regression coefficient and distorts the statistical significance of the coefficient term. This explains</td>
<td>The ERG agrees that aspects of the current text require clarification. The ERG has updated the text on pages 90 and 91 to clarify that the regression analysis was based on the full population of SHIfT and that the under-prediction of treatment effect (rather than the difference in the significance of treatment effect) may be a result of the under-prediction of cardiovascular mortality risk (or baseline characteristics adjusted for). Similar amendments have also been made on page 93 in the discussion of the regression analysis for heart failure mortality.</td>
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why the statistical significance of the treatment effect differs substantially from the clinical data. The ERG may have misinterpreted this finding.

Finally the treatment effect of ivabradine is potentially underestimated since the relationship between treatment and heart rate is not strictly linear. The risk equations may under-predict CV mortality because, for example, a clinical factor that predicts outcomes has not been considered (e.g. some form of disease severity indicator). However, there is no evidence to suggest that the statistical significance of ivabradine would have been unduly affected by this. The SHiFT trial provides a large, robust clinical dataset and it is unclear how the ERG expects a non-significant treatment effect for ivabradine to be driven by an under-prediction of cardiovascular mortality in the risk equation. We do not believe this hypothesis has been sufficiently clarified and would perhaps like the ERG to clarify this issue further, particularly in the context of the alternative rationale discussed above.

However, the ERG considers that the significance of the covariate for treatment effect can be considered in isolation as an indication for the significance of ivabradine treatment effect over and above the modifying effect of heart rate.
# Issue 7  CV mortality risk equation: statistical significance of beta-blockade

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<td>p.91 The ERG notes, “the under-prediction of cardiovascular mortality risk could also be expected to affect the statistical significance of the optimisation of beta-blocker therapy.”</td>
<td>Can the ERG clarify why the under-prediction in cardiovascular mortality risk may have affected the statistical significance of beta-blockade, particularly in the context of the association between baseline heart rate and beta-blockade.</td>
<td>The statistical significance of beta-blocker therapy is affected by the inclusion of the heart rate covariate in the risk equations. We have run analyses with and without baseline heart rate as a covariates. Prior to inclusion of baseline heart rate, beta-blocker use is strongly associated with CV/HF mortality. However, the estimates for beta-blocker therapy are confounded by baseline heart rate; patients on beta-blocker therapy have a lower baseline heart rate (see for example Table 1, Swedberg 2012 (1)). Once baseline heart rate is taken into account the statistical significance of beta-blockade reduces. We believe the risk equations have captured a plausible effect and there is no evidence to suggest that the effect/statistical significance of beta-blocker use has been under-predicted in the current risk equations. We have controlled for confounding factors and once these factors are taken into consideration beta-blocker use is only weakly associated with the outcome variable.</td>
<td>The ERG agrees that the current text is inaccurate and thanks the manufacturer for highlighting this inaccuracy. The text has been updated to refer to the treatment effect of beta-blockade rather than the significance of this effect. Similar amendments have been made on page 93 in the discussion of the regression analysis for heart failure mortality.</td>
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We do not believe the hypothesis proposed by the ERG has been sufficiently clarified and would appreciate further clarification in the context of the association between beta-blockade and heart rate.
### Issue 8  NYHA extrapolation sensitivity analysis

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<td>P102 – The ERG notes, “The sensitivity analysis around NYHA extrapolation resulted in a £485 increase in the ICER, suggesting that that manufacturer’s base case assumption favours ivabradine.” The manufacturer proposes that the ERG could provide more context to the conclusion, in order to improve its accuracy.</td>
<td>Can the ERG clarify that the base case scenario only favours ivabradine if the sensitivity analysis undertaken, which is not evidenced based, is clinically plausible.</td>
<td>The manufacturer feels the ERG should also note that the base case analysis would only favour ivabradine if this sensitivity analysis was clinically expected. This is a crude non-evidence based scenario analysis which was undertaken in the absence of long term NYHA classification data. SHIfT clinical data did not reveal an increase in the distribution of patients in NYHA Class III and IV over time.</td>
<td>No change required; not a factual error. The ERG notes that the base case assumptions around NYHA distribution used do favour ivabradine, in a literal sense, as they lower the ICER compared with the assumptions used in the sensitivity analysis. Moreover, the paragraph on pg 102 of the ERG report emphasises that the data used in the sensitivity analysis were arbitrary (i.e., were not evidence based). In addition, on pg 123 of its report, the ERG discusses the rationality of the manufacturer’s base case assumptions.</td>
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### Issue 9  CV mortality: one-way sensitivity analysis

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<td>p.122 “The variation of the HR between estimated 95% confidence intervals of 0.83 and</td>
<td>Can the ERG firstly clarify that the regression models were based on the whole population (patients with heart rate ≥70 bpm);</td>
<td>It is noted that the mean estimate and the confidence interval displayed in the regression model</td>
<td>The ERG agrees that the current numbers are</td>
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1.07 (mean estimate was 0.94) resulted in ICERS of £5,655 and £40,638, respectively."

The confidence interval provided by the ERG is factually incorrect, which affects the conclusion drawn. Consequently the variability displayed in the ICER is greater than one would expect in a population with a heart rate ≥75bpm. The ICER is therefore biased against ivabradine. Can the ERG please also amend the confidence interval estimates to reflect those used in the model.

should not be interpreted in isolation due to the presence of the interaction effect with heart rate (3). The hazard ratio applied in the model is derived as the sum of the treatment coefficient plus treatment interaction multiplied by baseline heart rate. The mean estimate therefore depends on baseline heart rate and the confidence intervals cannot be derived readily from the regression model.

In the one way analyses the HR was estimated from unadjusted data from the overall patient population (heart rate ≥70bpm). This was a pragmatic approach taken to avoid a simulation exercise to derive the confidence interval around the treatment + treatment interaction with heart rate. The lower and upper values used in the one way sensitivity analyses were therefore 0.80-1.03. It is important to note that these confidence intervals reflect the whole population (heart rate ≥70 bpm) and are broader than the confidence intervals expected in a population with heart rate ≥75 bpm. To illustrate this point, the regression model for the licensed population (heart rate ≥75 bpm) shows a statistically significant hazard ratio of 0.84 (see manufacturer inaccurate.

The numbers have been amended as suggested by the manufacturer. Furthermore, the ERG agrees that the text requires clarification and has amended the text to clarify the reason for uncertainty seen in this sensitivity analysis.
This scenario analysis consequently overestimates the variability in the ICER expected for the licensed indication.

## Issue 10 Structural sensitivity analyses

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| p.123 “The ERG notes that not all of the manufacturer's structural assumptions favoured treatment with standard care alone, particularly:  
  - the absence of age adjustment beyond baseline  
  - the assumptions around the extrapolation of NYHA distribution  
  - the use of parametric regression rather than Kaplan-Meier data in the ‘within-trial’ period”  
Two of these statements are factually incorrect. | Can the ERG please clarify that the assumptions around NYHA class only favour ivabradine if the scenario analysis is clinically correct, and amend the statement that the use of the parametric regression favours ivabradine since this is factually incorrect (see also issue 5 and issue 8). | The assumptions around NYHA class only favour ivabradine if the scenario analysis is correct.  
The use of the parametric regression model does not favour ivabradine. The difference in results is due to the use of the whole trial cohort (patients with heart rate ≥70 bpm) in observed Kaplan-Meier estimates. | The ERG agrees that the statement “the use of the parametric regression favours ivabradine” is factually incorrect.  
The text has been amended by removing the bullet point.  
However, the ERG disagrees with the manufacturer with regards to the assumptions around NYHA class. The ERG notes that the manufacturer’s base case assumption does favour ivabradine, in that it reduces the ICER compared with the assumptions used in the sensitivity analysis.  
Moreover, when the ERG’s statement is taken in the context of the full text in which this argument is presented, it is clear that the ERG accepts the manufacturer’s base case |
**Issue 11 Regression models: Statistical significance of the treatment covariates**

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<td>p.123 &quot;The ERG notes that the regression analyses carried out by the manufacturer of cardiovascular (and heart failure mortality) suggest that ivabradine is associated with a statistically non-significant (or borderline significant in heart failure) risk reduction. In contrast, beta-blocker therapy of ≥50% of target dose (or any dose for heart failure mortality) is associated with a statistically significant risk reduction.&quot;</td>
<td>Can the ERG please clarify that the statistical significance of the treatment covariate should not be interpreted in isolation due to the presence of the interaction effect in both the CV and heart failure regression models. The use of the treatment interaction term with heart rate changes the value of the regression coefficient and distorts the statistical significance of the coefficient term in both models. It is consequently not possible to compare the statistical significance of the ivabradine treatment terms alone with the statistical significance of beta-blockers.</td>
<td>It is noted again that the statistical significance of the treatment covariate should not be interpreted in isolation due to the presence of the interaction effect in both the CV and heart failure regression models (3). The use of the treatment interaction term with heart rate changes the value of the regression coefficient and distorts the statistical significance of the coefficient term in both models. It is therefore technically incorrect to compare the statistical significance of the ivabradine treatment term alone with the statistical significance of beta-blockers. The conclusion of the ERG based on this comparison therefore have the potential to mislead.</td>
<td>The ERG agrees that aspects of the current text require clarification. The ERG considers that the significance of the treatment covariate can be considered in isolation to represent the significance of treatment effect over and above the modifying effect of heart rate. The ERG has amended the text to clarify that the comparison being made is between ivabradine treatment (over and above the modifying effect of heart rate) and beta-blockade.</td>
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Reference List


(3) Selvin S. Survival Analysis for Epidemiological and Medical Research. Cambridge University Press; 2008.