PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Ranolazine for the Treatment of Chronic Stable Angina: A Cost-Effectiveness Analysis from the United Kingdom Perspective
AUTHORS	Coleman, Craig; Freemantle, Nick; Kohn, Christine

VERSION 1 - REVIEW

REVIEWER	Olivia Phung Western University of Health Sciences, Pomona, CA, USA
REVIEW RETURNED	25-Jun-2015

GENERAL COMMENTS	This paper is a well-conducted cost-effectiveness analysis on the use of ranolazine in a specific angina population. The Introduction section could benefit from a brief description of the standard of care for patients in this stage of disease severity, citing the appropriate clinical guidelines. The Introduction section could also benefit from a brief statement regarding the place in therapy that ranolazine holds in the current treatment guidelines. The Discussion section could benefit from a comparison of ranolazine's role in the current guidelines and the benefits shown in this analysis.

REVIEWER	Udho Thadani, MD, FACC, FAHA Professor Emeritus of Medicine,University of Oklahoma HSC; Staff Cardiologist VA Medical Center, Oklahoma City, Oklahoma, USA Have acted as a consultant to Gilead Sciences in the past and currently on Speakers program for Gillead Sciences and CME Speakers program funded by Gilead Sciences. Speaker for Amgen. Several Research studies funded by pharmaceutical companies .
REVIEW RETURNED	17-Jul-2015

GENERAL COMMENTS	This manuscript is Titled " Ranolazine for the Treatment of chronic stable Angina: Cost-Effectiveness Analysis from the United Kingdom Perspective" The data presented is from the ERICA trial, a well conducted multicenter study, with accurate accounting of angina frequency and quality of life measurements. However, the majority of the patients who took part in the trial were not from the UK. Overall results show that the ranolazine will be cost effective in the

	UK, but this assumes that the response rate and quality of life improvement experienced was similar in the patients from the UK compared to the rest of the patients from other parts of the word. If authors have this data, it needs to included or at least mentioned in the results section of the manuscript. Also in the ERICA tria,l beta-blockers were not used to treat angina. Many of the chronic stable angina patients respond to beta-blockes, and these drugs are cheaper and generic. Therefore cost analysis incorporating back ground therapy with betablockers, in addition to amlodipne, and or nitrates is needed, to be certain whether addition of ranolazine will indeed be cost effective in treating patients with angina, experiencing either daily or weekly angina attacks. Erica was a short term study and one can not be certain if the effectiveness of ranolazine will persisit over time.

REVIEWER	Peter D Sozou London School of Economics and Political Science, UK
REVIEW RETURNED	17-Aug-2015

GENERAL COMMENTS	This manuscript presents a cost-benefit analysis of the use of ranolazine for the treatment of stable angina. It is based on a comparison of ranolazine + standard care with standard care alone, over a 1-year period, with ranolazine applied over the year to those patients who respond positively to it in the first month of treatment, and otherwise discontinued. At the heart of the study is a Markov model of transition between different angina states. I have some serious concerns about the assumptions underlying the model. If I have understood the study correctly, the observed transition frequencies for those patients who improve in the first month are then assumed to apply to all patients who have improved over the year. This does not seem plausible to me, for several reasons. First, the model is likely to be making very optimistic assumptions about ranolazine, because of the way responders are identified. In a chronic condition, it is possible that some patients could improve or deteriorate from one month to another due to chance events. So some patients who have taken ranolazine could see an improvement over a month due to chance. Those who have improved due to chance should not be expected to necessarily keep improving. But the model seems to assume that those patients who improved in the first month and are classified as responders can only ever improve. This seems to lead to the conclusion that all patients who improved in the first month and who stay on ranolazine will be free of angina attacks within three months! Is this plausible? The model's assumptions seem to be introducing a bias, of the same character as that described in the literature on "regression towards the mean". Second, even if we ignore the first point, can it be assumed that all patients who respond to ranolazine, with a given frequency of angina attacks, are a homogeneous group? For example, it was found that it the first month, 13.7% of responders with weekly angina attacks transitioned to no angina attacks. It is then assumed that 13.7% of responders with weekly angina attacks will transition to no attacks every month. But those people who initially had daily attacks, and transitioned after one month of ranolazine to weekly attacks are likely to have different characteristics from those who initially had

	weekly attacks. A third potential concern concerns for how long it is reasonable to assume that a given patient has a constant transition probability to another state. If we ignore the first two points above, there remains the question a given patient in a given state can be assumed to have a constant intrinsic transition probability per month over the course of a year. By analogy, a couple's intrinsic chance of conception per month will decline, due to the effects of ageing; this is, for younger women, a relatively small effect over a year, though not a zero effect. I would like to see some discussion explaining the assumption that a person with a given frequency of angina attacks could be assumed to maintain steady transition probabilities. I am not saying that this is necessarily an unreasonable assumption, only that it would be good to have some explicit justification. An angina specialist would need to judge that the assumption is reasonable. (NB in practice this would not be a concern for ranolazine responders in the model if my understanding is correct – as explained in the first point – that ranolazine responders who stay on ranolazine would be free of angina within three months.) I have not had time to check the cost-benefit analysis, but it seems to me that these points above, particularly the first two, raise fundamental concerns about the model. If they can be addressed in a reasonable way with plausible assumptions, the manuscript could be revised and resubmitted. Or if I have misunderstood something, the ms should be resubmitted with a fuller account of the model, and the background assumptions. On the presentation of the model, I did not find Fig. 1 itself useful, though the caption was informative.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name Olivia Phung
Institution and Country Western University of Health Sciences, Pomona, CA, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below:

This paper is a well-conducted cost-effectiveness analysis on the use of ranolazine in a specific angina population.

Thank you.

The Introduction section could benefit from a brief description of the standard of care for patients in this stage of disease severity, citing the appropriate clinical guidelines. The Introduction section could also benefit from a brief statement regarding the place in therapy that ranolazine holds in the current treatment guidelines.

We have added into the introduction section a brief description of the standard of care for stable angina patients and the role of ranolazine according to NICE guidance.

The Discussion section could benefit from a comparison of ranolazine's role in the current guidelines

and the benefits shown in this analysis.

We feel our results are supportibe of the current NICE recommendation for ranolazine in stable angina (use in persons with stable angina whom cannot tolerate or have contraindications to the first line therapies of beta-blockers or calcium channel blockers, or for persons whom symptoms are not controlled after optimal use of beta-blockers and calcium channel blockers). Per the reviewer's request, we briefly state this in our discussion section.

Reviewer: 2

Reviewer Name Udho Thadani, MD, FACC, FAHA
Institution and Country Professor Emeritus of Medicine,University of Oklahoma HSC; Staff Cardiologist VA Medical Center, Oklahoma City, Oklahoma, USA
Please state any competing interests or state 'None declared': have acted as a consultant to Gilead Sciences in the past and currently on Speakers program for Gilead Sciences and CME Speakers program funded by Gilead Sciences.
Speaker for Amgen.
Several Research studies funded by pharmaceutical companies.

Please leave your comments for the authors below:

This manuscript is Titled " Ranolazine for the Treatment of chronic stable Angina: Cost-Effectiveness Analysis from the United Kingdom Perspective". The data presented is from the ERICA trial, a well conducted multicenter study, with accurate accounting of angina frequency and quality of life measurements. However, the majority of the patients who took part in the trial were not from the UK. Overall results show that the ranolazine will be cost effective in the UK, but this assumes that the response rate and quality of life improvement experienced was similar in the patients from the UK compared to the rest of the patients from other parts of the world. If authors have this data, it needs to included or at least mentioned in the results section of the manuscript.

UK specific data from the ERICA trial is not available. However, 97% of patients were recruited from Eastern Europe. We now provide this data in the results and discuss the assumption in the limitations section.

Also in the ERICA trial beta-blockers were not used to treat angina. Many of the chronic stable angina patients respond to beta-blockes, and these drugs are cheaper and generic. Therefore cost analysis incorporating back ground therapy with betablockers, in addition to amlodipne, and or nitrates is needed, to be certain whether addition of ranolazine will indeed be cost effective in treating patients with angina, experiencing either daily or weekly angina attacks.

We agree this is a limitation and have noted so in the discussion section (Page 16-17). Of note, the TERISA trial demonstrated the efficacy of ranolazine when used in a heavily (~90%) beta-blocker treated population. We have added this discussion to the manuscript.

Erica was a short term study and one cannot be certain if the effectiveness of ranolazine will persisit over time.

We agree, this is a common concern/limitation with most Markov models. We now acknowledge it in the discussion section as a limitation and point out that we restricted our analysis' time horizon to 1-year. We also now provide data from ROLE to support the 1-year time horizon of our model.

Reviewer: 3

Reviewer Name Peter D Sozou
Institution and Country London School of Economics and Political Science, UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below:

This manuscript presents a cost-benefit analysis of the use of ranolazine for the treatment of stable angina. It is based on a comparison of ranolazine + standard care with standard care alone, over a 1-year period, with ranolazine applied over the year to those patients who respond positively to it in the first month of treatment, and otherwise discontinued. At the heart of the study is a Markov model of transition between different angina states.

I have some serious concerns about the assumptions underlying the model. If I have understood the study correctly, the observed transition frequencies for those patients who improve in the first month are then assumed to apply to all patients who have improved over the year. This does not seem plausible to me, for several reasons.

We believe the reviewer has mis-interpreted our model. A very important point of our model is that starting in the second month (cycle 2) and onward, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Thus, no loss or additional efficacy in either treatment group could occur.

We have re-written some of the methods section and the legend of Figure 1 to try and make this clearer.

First, the model is likely to be making very optimistic assumptions about ranolazine, because of the way responders are identified. In a chronic condition, it is possible that some patients could improve or deteriorate from one month to another due to chance events. So some patients who have taken ranolazine could see an improvement over a month due to chance. Those who have improved due to chance should not be expected to necessarily keep improving. But the model seems to assume that those patients who improved in the first month and are classified as responders can only ever improve. This seems to lead to the conclusion that all patients who improved in the first month and who stay on ranolazine will be free of angina attacks within three months! Is this plausible? The model's assumptions seem to be introducing a bias, of the same character as that described in the literature on "regression towards the mean".

We believe the reviewer has mis-interpreted our model. A very important point of our model is that starting in the second month (cycle 2) and onward, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Thus, no loss or additional efficacy in either treatment group could occur.

We have re-written some of the methods section and the legend of Figure 1 to try and make this clearer.

Second, even if we ignore the first point, can it be assumed that all patients who respond to ranolazine, with a given frequency of angina attacks, are a homogeneous group? For example, it was found that it the first month, 13.7% of responders with weekly angina attacks transitioned to no angina attacks. It is then assumed that 13.7% of responders with weekly angina attacks will transition to no attacks every month. But those people who initially had daily attacks, and transitioned after one month of ranolazine to weekly attacks are likely to have different characteristics from those who initially had weekly attacks.

We believe the reviewer has mis-interpreted our model. A very important point of our model is that starting in the second month (cycle 2) and onward, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Thus, no loss or additional efficacy in either treatment group could occur.

We have re-written some of the methods section and the legend of Figure 1 to try and make this clearer.

A third potential concern concerns for how long it is reasonable to assume that a given patient has a constant transition probability to another state. If we ignore the first two points above, there remains the question a given patient in a given state can be assumed to have a constant intrinsic transition probability per month over the course of a year. By analogy, a couple's intrinsic chance of conception per month will decline, due to the effects of ageing; this is, for younger women, a relatively small effect over a year, though not a zero effect. I would like to see some discussion explaining the assumption that a person with a given frequency of angina attacks could be assumed to maintain steady transition probabilities. I am not saying that this is necessarily an unreasonable assumption, only that it would be good to have some explicit justification. An angina specialist would need to judge that the assumption is reasonable. (NB in practice this would not be a concern for ranolazine responders in the model if my understanding is correct – as explained in the first point – that ranolazine responders who stay on ranolazine would be free of angina within three months.)

We acknowledge the assumption of maintained efficacy for 12-month in those initially responding to ranolazine (as noted above, this is not assuming they will continue to improve each cycle, but rather that what every efficacy they realized in the first month will continue at that same level for the remaining months of the model). As noted in our response to reviewer 2, this is a common assumption required of Markov models as they attempt to extrapolate out outcomes to longer time horizons. We now note this as a limitation of our analysis and provide some data from the ROLE program to justify our use of a 1-year time horizon and this assumption of maintained efficacy.

I have not had time to check the cost-benefit analysis, but it seems to me that these points above, particularly the first two, raise fundamental concerns about the model. If they can be addressed in a reasonable way with plausible assumptions, the manuscript could be revised and resubmitted. Or if I have misunderstood something, the ms should be resubmitted with a fuller account of the model, and the background assumptions.

We believe the reviewer has mis-interpreted our model. A very important point of our model is that starting in the second month (cycle 2) and onward, all patients were assumed to stay in the same angina frequency health state for the remainder of the model's time horizon or until death. Thus, no loss or additional efficacy in either treatment group could occur.

We have re-written some of the methods section and the legend of Figure 1 to try and make this clearer.

On the presentation of the model, I did not find Fig. 1 itself useful, though the caption was informative.

The CHEERS reporting guidance (too which BMJ journals utilize) calls for the inclusion of such a model schematic. If the editor wishes for us to remove it, we would be happy to do so.

VERSION 2 – REVIEW

REVIEWER	UdhoThadani University of Oklahoma HSC, and VA medical Centre, Oklahoma City, OK, USA Speaker for Gilead Science and past consultant to the same company. Principal Investigator for research studies for which the university and VAMC receive grant support to conduct the studies.
REVIEW RETURNED	07-Sep-2015

GENERAL COMMENTS	Authors have addressed concerns raised in my original review. The wording lack of objective data in UK patients to support the conclusion should be added to the abstract conclusion.

REVIEWER	Peter D Sozou, Research Associate London School of Economics and Political Science UK
REVIEW RETURNED	07-Sep-2015

GENERAL COMMENTS	I thank the authors for providing clarification: I had previously not understood the model correctly. I now understand that all patients are assumed to stay in the same health state from cycle 2 until the end of the modelled period, apart from those patients who die. [I am however puzzled by the last sentence on p9, beginning “For those patients discontinuing…”. If my new understanding is correct, then those patients discontinuing ranolazine will remain in the same health state for the remainder of the modelled period, so why the reference to “transition probabilities” in this sentence?] I have two major concerns with the revised ms as it is at present. First, it seems to me that the assumption that angina frequency states remain constant for 11 months is not likely to be accurate, given the evidence in Table 2 that a non-trivial proportion of standard-of-care plus placebo patients improve and deteriorate over a 1-month period. (In their covering letter the authors mention the ROLE program: while this does provide evidence that ranolazine can be tolerated and apparently effective over a year, that study did not appear to record angina frequency data.) For this reason, I do not think the study can claim to provide high quality evidence on the cost-effectiveness of ranolazine over a 1-year period. To provide high-quality evidence would require that patients are observed (and their angina frequency recorded) over a year. A separate question is: given that the requisite data are not available over a year, if one nevertheless wishes to estimate cost-effectiveness over a year, making the most of the limited data, have the authors adopted a reasonable modelling approach? Clearly some gross simplifying assumptions must be made. It seems to me that what the authors have assumed is equivalent to assuming that the overall health gains are made in the first cycle are retained for the rest of the year. This does not seem unreasonable to me. But if this study is accepted for publication on this basis, its limitations must be made clearer.

	My second major concern is about presentation. I do not think this study should be described as a Markov model, as that would imply that patients transition between different health states over several cycles, which is not the case here. (Note: a Markov model is one in which it is assumed that a system has a fixed probability of transiting from one state to another per unit time or per cycle, regardless of the history of how it got to that state. It therefore does not make sense to apply this term to a model in which such transitions can occur only over one cycle.) I would prefer the term “simple model”. In particular, the methods statement in the abstract is misleading as it does not mention that transitions between states only occur in the first month: this must be corrected to include this information. I have not gone through the QALY calculations in detail, but I the numbers look reasonable to me; I think it is very likely that the calculations are correct. In detail: MAJOR POINTS: 1. The model should not be described as a Markov model. 2. The title should be modified to include the word “preliminary” before “cost-effectiveness” 3. The methods statement in the abstract (p3, lines 20 to 38) must state explicitly that after the first month patients are assumed to remain in the same health state for the remainder of the modelled period unless they die. 4. The article summary (page 5) should add the following bullet point: “As a simplifying assumption, angina states were assumed not to change after the first month”. 5. In the longer methods description (pages 7 to 9), it must be made very clear at the outset that transitions in health state occur only in the first month. As things stand, page 7 refers to transition between states, and it is not until page 9 that it is stated that all patients from cycle 2 onwards are assumed to stay in the same angina frequency state. For example, lines 49-52 say “Our model followed patients as they transited between the 4 above-mentioned angina frequency health states and the death state”. It would be better to say “Patients transited between the 4 above-mentioned angina frequency health states and the death state during the first cycle. After this, patients were assumed to remain in the same health state, apart from those who died.” 6. Modify the last sentence on p9, beginning “For those patients discontinuing…”: it should not refer to “transition probabilities”. It seems to me that this sentence might be completely redundant. 7. The discussion section must make clear that this is a preliminary study, because data on angina states were not available over a year, necessitating simplifying modelling assumptions. It must state explicitly that this study does not provide high quality evidence on the cost-effectiveness of ranolazine over a one-year period, and that such evidence would require a proper 1-year observational study. (I am aware that the authors have listed the ‘extrapolation’ problem as a second limitation of the study, but I do not think this is prominent

	enough.) MINOR POINTS: 1. P9, line15: although the mortality rate of 5.8%/year is given in table 3, I suggest also including it here in the main text. 2. The results section (p13, lines 24-29) states that patients "accrued" QALYs. The word "accrue" can be taken in some contexts to mean gain, and so this could be taken by some readers to mean that they had gained this number of QALYs, relative to no treatment, which is not the case. I think it might be better to say "had" rather than "accrued", to remove any such ambiguity. 3. p17, line24: there is a missing right parenthesis.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Reviewer Name

UdhoThadani

Institution and Country

University of Oklahoma HSC, and VA medical Centre, Oklahoma City, OK, USA

Please state any competing interests or state 'None declared':
Speaker for Gilead Science and past consultant to the same company. Principal Investigator for research studies for which the university and VAMC receive grant support to conduct the studies.

Please leave your comments for the authors below:

Authors have addressed concerns raised in my original review.

Thank you.

The wording lack of objective data in UK patients to support the conclusion should be added to the abstract conclusion.

Similar wording has been added to the abstract conclusion.

Reviewer: 3
Reviewer Name

Peter D Sozou, Research Associate
London School of Economics and Political Science UK

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below I thank the authors for providing clarification: I had

previously not understood the model correctly. I now understand that all patients are assumed to stay in the same health state from cycle 2 until the end of the modelled period, apart from those patients who die.

Thank you.

I am however puzzled by the last sentence on p9, beginning “For those patients discontinuing…”. If my new understanding is correct, then those patients discontinuing ranolazine will remain in the same health state for the remainder of the modelled period, so why the reference to “transition probabilities” in this sentence?]

We have removed the reference to “transition probabilities” here.

I have two major concerns with the revised ms as it is at present.

First, it seems to me that the assumption that angina frequency states remain constant for 11 months is not likely to be accurate, given the evidence in Table 2 that a non-trivial proportion of standard-of-care plus placebo patients improve and deteriorate over a 1-month period. (In their covering letter the authors mention the ROLE program: while this does provide evidence that ranolazine can be tolerated and apparently effective over a year, that study did not appear to record angina frequency data.) For this reason, I do not think the study can claim to provide high quality evidence on the cost-effectiveness of ranolazine over a 1-year period. To provide high-quality evidence would require that patients are observed (and their angina frequency recorded) over a year.

We agree this is a concern of this and nearly every other economic model of pharmacologic therapy. That is, the need to assume efficacy beyond what is measured in the clinical trial. We note this as a limitation of the analysis in the discussion section.

A separate question is: given that the requisite data are not available over a year, if one nevertheless wishes to estimate cost-effectiveness over a year, making the most of the limited data, have the authors adopted a reasonable modelling approach? Clearly some gross simplifying assumptions must be made. It seems to me that what the authors have assumed is equivalent to assuming that the overall health gains are made in the first cycle are retained for the rest of the year. This does not seem unreasonable to me. But if this study is accepted for publication on this basis, its limitations must be made clearer.

We agree this is not an unreasonable assumption as these patients by default have “chronic STABLE angina”. We have provided some additional support of this assumption to the discussion section of ur manuscript.

My second major concern is about presentation. I do not think this study should be described as a Markov model, as that would imply that patients transition between different health states over several cycles, which is not the case here. (Note: a Markov model is one in which it is assumed that a system has a fixed probability of transiting from one state to another per unit time or per cycle, regardless of the history of how it got to that state. It therefore does not make sense to apply this term to a model in which such transitions can occur only over one cycle.) I would prefer the term “simple model”.

We have changed Markov model to “economic decision model” thorough the manuscript.

In particular, the methods statement in the abstract is misleading as it does not mention that transitions between states only occur in the first month: this must be corrected to include this information.

We have clarification to the abstract.

I have not gone through the QALY calculations in detail, but I the numbers look reasonable to me; I think it is very likely that the calculations are correct.

Thank you.

In detail:

MAJOR POINTS:

1. The model should not be described as a Markov model.

Revised as noted above.

2. The title should be modified to include the word “preliminary” before “cost-effectiveness”

We disagree that the word preliminary adds anything and should be added. All models require assumptions. Referring to this model as a preliminary or pilot model somehow implies that it will be used as a standing stone to perform more detailed work.

3. The methods statement in the abstract (p3, lines 20 to 38) must state explicitly that after the first month patients are assumed to remain in the same health state for the remainder of the modelled period unless they die.

Revised as noted above.

4. The article summary (page 5) should add the following bullet point: “As a simplifying assumption, angina states were assumed not to change after the first month”.

Added.

5. In the longer methods description (pages 7 to 9), it must be made very clear at the outset that transitions in health state occur only in the first month. As things stand, page 7 refers to transition between states, and it is not until page 9 that it is stated that all patients from cycle 2 onwards are assumed to stay in the same angina frequency state. For example, lines 49-52 say “Our model followed patients as they transited between the 4 above-mentioned angina frequency health states and the death state”. It would be better to say “Patients transited between the 4 above-mentioned angina frequency health states and the death state during the first cycle. After this, patients were assumed to remain in the same health state, apart from those who died.”

Suggested revision made.

6. Modify the last sentence on p9, beginning “For those patients discontinuing…”: it should not refer to “transition probabilities”. It seems to me that this sentence might be completely redundant.

Revised as noted above.

7. The discussion section must make clear that this is a preliminary study, because data on angina states were not available over a year, necessitating simplifying modelling assumptions. It must state explicitly that this study does not provide high quality evidence on the cost-effectiveness of ranolazine

over a one-year period, and that such evidence would require a proper 1-year observational study. (I am aware that the authors have listed the 'extrapolation' problem as a second limitation of the study, but I do not think this is prominent enough.)

We have moved the 1-year extrapolation limitation to be the first listed in the limitations to make it more prominent. We have noted that this analysis should be viewed as hypothesis-generating. Finally, we have added discussion of further data from the MERLIN trial to support the one year time horizon used.

MINOR POINTS:

1. P9, line15: although the mortality rate of 5.8%/year is given in table 3, I suggest also including it here in the main text.

Added.

2. The results section (p13, lines 24-29) states that patients "accrued" QALYs. The word "accrue" can be taken in some contexts to mean gain, and so this could be taken by some readers to mean that they had gained this number of QALYs, relative to no treatment, which is not the case. I think it might be better to say "had" rather than "accrued", to remove any such ambiguity.

Changed "accrued" to "lived" in reference to QALYs (as one lives for x quality adjusted life years).

3. p17, line24: there is a missing right parenthesis.

Corrected.