Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Treatment of Atrial Fibrillation*

Draft review available for public comment from July 27, 2012 to August 24, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General: Quality of the Report	Superior	Thank you.
Peer Reviewer #2	General: Quality of the Report	Superior	Thank you.
Peer Reviewer #3	General: Quality of the Report	Superior	Thank you.
Peer Reviewer #4	General: Quality of the Report	Good	Thank you.
TEP #1	General: Quality of the Report	Good	Thank you.
TEP #2	General: Quality of the Report	Superior	Thank you.
TEP #3	General: Quality of the Report	Superior	Thank you.
TEP #4	General: Quality of the Report	Good	Thank you.
TEP #5	General: Quality of the Report	Good	Thank you.
TEP #6	General: Quality of the Report	Superior	Thank you.
TEP #7	General: Quality of the Report	Good	Thank you.
Peer Reviewer #1	General: Clarity and usability	The report is well structured and organized. The main points are clearly presented. The conclusions can be used to inform policy and/or practice decisions.	Thank you.
Peer Reviewer #2	General: Clarity and usability	The executive summary is well prepared, clear and quite usable. The references at the end of the ES are incomplete (obviously do not include all the papers referenced in the ES). This should be mentioned and the reader of the ES should be referred to the complete reference list for the full paper.	We have added a sentence to the Executive Summary referring the reader to the full report for complete lists of included and excluded articles.

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Peer Reviewer #3	General: Clarity and usability	Page 108. The Discussion of findings in relationship to what is already know would benefit from headings. In particular it would be good to highlight any findings that are not consistent with current guidelines.	We have reviewed the discussion of findings and feel that the section would not benefit from headings related to consistency with current guidelines and so have left it as is.
Peer Reviewer #4	General: Clarity and usability	Manuscript is well-structured and well-organized. Main points are presented clearly. Conclusions generally seem justified by data presented	Thank you.
TEP#1	General: Clarity and usability	The report is well organized, although rather lengthy. The main points are clear except as noted above [now below—see comments on ES]. The clinical impact of the report will likely be limited, primarily due to the fact that there was insufficient evidence to provide definitive answers to most of the KQs (as reflected in the fact that the questions posed in the research gaps section are essentially the same as the original KQs). The principal value of the report will be in calling attention to those areas where additional research is needed. Most importantly, in the opinion of this reviewer, the report highlights the almost complete lack of long-term studies (i.e. more than 5 years in duration) and studies that address quality of life outcomes.	We thank the reviewer for their comments and agree that long-term studies and studies that address quality of life outcomes are needed as future research.
TEP #2	General: Clarity and usability	The organization of the report is good. The report follows a logical sequence of a detailed “Executive Summary” followed by the full report in a well structured manner. Key points are clearly presented. Within the limits of the available literature that was reviewed, the conclusions are valid and can be applied to decisions in clinical practice or inform policy.	Thank you.
TEP #3	General: Clarity and usability	Well done.	Thank you.
TEP #4	General: Clarity and usability	The report covers many comparisons and interventions and therefore will be difficult for many readers to work through. Any time spent condensing and summarizing text will be useful to readers I think. The Conclusions/Discussion are quite long and I think some sections can be shortened quite a bit, e.g. Findings in Relationship to What is Already Known. and especially the Research Gaps section.	Where possible we have condensed this report, as well as made sure that navigation through the report is easy for the reader. Because these CERs are targeted to serve a diverse set of stakeholders there is information included in the report which may not be useful to a specific stakeholder but is highly relevant to another stakeholder; this necessitates a large amount of information (and length).
TEP #5	General: Clarity and usability	As stated before, the report is well-written and accomplished what was originally stated with some difficulties and limitations in collecting the data and these limitations are clearly stated by the authors. Nevertheless, this report is valuable work for practicing clinicians who deal with Afib patients daily and open the door for the need for more research needed for the future.	Thank you.
TEP #6	General: Clarity and usability	The manuscript is very well structured and presented, and the conclusions will be very useful to both clinicians and policymakers.	Thank you.

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Peer Reviewer #1	General	The report is clinically meaningful. Detailed data between subgroups such as elderly versus young and women versus men could be better.	We agree that additional evidence focusing on subgroups of interest is needed as an area of future research.
Peer Reviewer #1	General	Key questions are appropriate and explicitly stated.	Thank you.
Peer Reviewer #1	General	Although this review does not cover prevention of stroke, it should be mentioned that whether a rate control or rhythm control strategy is used in patients with either paroxysmal, persistent, or permanent atrial fibrillation (AF), those at increased risk for stroke according to a CHADS2 score or CHA2DSVASc score should be treated with antithrombotic therapy.	Within the Executive Summary and Introduction we clarify that "management of AF involves three distinct areas, namely, rate control, rhythm control, and prevention of thromboembolic events. This comparative effectiveness review (CER) covers the first two areas. A separate CER focusing on the prevention of thromboembolic events is being conducted in parallel, also commissioned through the Agency for Healthcare Research and Quality's (AHRQ's) Evidence-based Practice Center (EPC) Program." Given the overall size and scope of the treatment of atrial fibrillation report we have left the discussion of stroke prevention the parallel report.
Peer Reviewer #2	General	This is a well-prepared, exhaustive review of the treatment of AF. It is clinically meaningful and I like the key questions. Many of my comments relate to the Executive Summary but likewise apply to the main text.	Thank you.
Peer Reviewer #3	General	The questions chosen for this topic are highly relevant to clinical practice and clearly stated. The list is quite comprehensive and the only weakness is that value is not considered. I realise this is not in the scope of the project but should be part of future AHRQ reports (if allowed by congress).	We agree that assessing the comparative value of the various treatment options would be useful to many stakeholders. However, as the reviewer assumes, this was outside of the scope of the current report.
Peer Reviewer #3	General	If more funds were availabe would also examine those with postpoperative afib as this is a common problem with a fair amount of literature that could be anayzezd.	We thank the reviewer for their suggestion and agree that the topic although out of scope of this project would be interesting and timely. Note that additional information on how to officially nominate a topic can be found at: www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/how-to-suggest-a-topic-for-research.
Peer Reviewer #3	General	Another common clinical question is whether to attempt cardioversion (DC or medical) after a period of anticoagulation or after imaging with transesophageal echocardiography. I realize the literature may be limited here.	We thank the reviewer for their suggestion and agree that the topic although out of scope of this project would be interesting and timely. Note that additional information on how to officially nominate a topic can be found at: www.effectivehealthcare.ahrq.gov/index.cfm/submit-a-suggestion-for-research/how-to-suggest-a-topic-for-research.

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Peer Reviewer #4	General	Page 9 [=ES-1], Background - should make it clear somewhere early on that this review excludes all forms of post-operative AF and AF from other reversible causes	We now include these specific exclusion criteria in the inclusion/exclusion section of the Executive Summary.
Peer Reviewer #4	General	Page 10 [=ES-2], lines 51-52 - I have not seen this recommendation before, regarding rhythm control strategies in the absence of symptoms. Where does this come from? Please cite a reference for this statement.	Some physicians implement this in their practice because AF begets AF and more AF worsens atrial remodeling. Their rationale is if one prevents AF, one can prevent or slow down remodeling. This has not been shown to have an effect on patient outcomes and all the recommendations base rhythm control strategy on the presence of symptoms. Therefore, we have deleted this sentence from the final report and Executive Summary.
Peer Reviewer #4	General	Page 45 [=1], Background - I suggest adding a brief discussion on patterns of AF (first detected episode, paroxysmal, persistent, and permanent) as described in current AF guidelines, as patterns of AF guide treatment in many ways	We agree with the reviewer. We have added this discussion to the first paragraph in the Background section of the Executive Summary and main report.
Peer Reviewer #4	General	Page 45 [=1], lines 51&52 - why are you citing the 2006 guidelines, when more recent guidelines were published in 2011?	The 2006 guidelines are the most recent full guideline publication related to atrial fibrillation – the 2011 version, which we cite in the following paragraph, was a focused update and so we felt both versions were still applicable to be included.
TEP #2	General	This report is a near exhaustive review of the topic “Treatment of Atrial Fibrillation”. At the outset the goals of the review have been well defined. The Key Questions (KQ) are appropriate as it relates to the topic of review and have been explicitly stated by the authors in full detail. The Executive Summary provides a relatively detailed summary of the entire report in 36 pages in which one can find an overall answer to each KQ question. Interested individuals can find further detailed information on such questions in the body of the report. All six Key Questions are well detailed. For each KQ bullet points provide a brief conclusion of the studies reviewed followed by a more detailed yet, concise description of the included studies under multiple subheadings pertaining to specific questions. . The report is well written and easy to follow.	Thank you.
TEP #3	General	Target population and key questions are explicit. It is implicit that the target audience includes all clinicians who care for patients with atrial fibrillation, though not explicitly stated.	The reviewer is correct that the target audience includes both providers for patient with atrial fibrillation and relevant policymakers as well.

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TEP #4	General	The report represents a lot of work. Because there are so many comparisons and studies it is in some cases difficult for readers to glean key points. There are some cases in which the SOE ratings appear to be applied inconsistently or there are discrepancies between the tables and the text. In some cases the results are based on very short-term studies (e.g. 1 day or less) but it is not clear when the results are presented that this is the case. This is very important as many clinicians will be interested in longer-term outcomes.	We have revised the report to correct any inconsistencies. We also highlight in the limitations section of the report how the evidence supporting long-term outcomes is limited.
TEP #5	General	This is a well-written report and not an easy task as the authors acknowledged in their writing. The authors have taken an extensive research in a very important patient-population who suffer from Afib, but as they discovered the difficulty in comparing the 2 most common strategies (rate- and rhythm-control) in managing Afib. This is a valuable work for clinicians, however more future works need to be done.	Thank you. We agree that there remain many areas of needed future research.
TEP #5	General	The authors used OR to measure benefit (or lack of), why not using RR (relative risk) instead of OR?	Although relative risks are a sometimes a bit easier to understand than ORs, when rates are low, ORs approximate RRs, making the odds ratios and relative risks nearly the same. We have maintained ORs throughout our meta-analyses.
TEP #5	General	Knowing not all studies provided the type of Afib, however, for those studies did, does the authors know percent of patients with paroxysmal, persistent and permanent?	This information is provided in the study characteristics tables included as part of Appendix F.
TEP #6	General	The manuscript provides a comprehensive and systematic review of the relevant English language literature addressing each of the Key Questions targeted by the project. The questions are largely quite relevant, the searches were well described and presented, and the findings were clearly presented enough for a general audience and generally nuanced enough for a more technical electrophysiology audience. On the whole, I found the overall document to be a quite impressive achievement that accomplished the project's stated goals.	Thank you.
TEP #7	General	This is a very well done and comprehensive review. There are some substantial revisions that are needed. In particular, the rate control sections should mention the effective rate control and exercise tolerance in quality of life and not only on rate. The assertion that "strict" rate control is indicated is highly debatable, and goes against the guidelines both European and Canadian.	The reviewer brings up good points. We have modified the rate control section in the Introduction and the Executive Summary.
TEP #7	General	There is no mention of the largest single blinded placebo controlled study of antiarrhythmic drugs, the ATHENA Trial.	Because the ATHENA trial was placebo-controlled it did not meet our inclusion criteria.

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TEP #7	General	The failure to discuss the limitations of “atrial fibrillation recurrence” as an endpoint is a major omission.	We now discuss the limitations of this outcome in our Discussion section under the “Limitations of the Evidence Base and the Comparative Effectiveness Review Process” section.
TEP #7	General	The literature search, listing of studies and description is very well done and comprehensive.	Thank you.
TEP #7	General	A discussion of the meaning of “effectiveness” Although not mentioned explicitly, the implicit suggestion is that effectiveness relates to the ability of rhythm control drugs to restore and maintain sinus rhythm, and the ability of rate control drugs to reduce heart rate below a predetermined value. Another, probably clinically more relevant definition of effectiveness would be “the ability to make patients think better, keep them out of hospital, and keep them from dying” pererferally mentioned, but not in sufficient detail, are studies that indeed show improvement in exercise tolerance with rate control for example most studies of calcium channel blockers, or studies that suggest that beta blockers lead to worse rate control (summarized by Boriani et al and Segal et al); the single largest placebo controlled blinded randomized trial of antiarrhythmic drugs, the ATHENA trial, the only study to show a reduction in the hard endpoints of cardiovascular hospitalization and cardiovascular mortality.	Effectiveness is defined to be a positive impact on outcomes of interest, which as the reviewer suggested varies both across the key questions and also may differ for specific intermediate or final outcomes. Because what constitutes effectiveness may vary based on the perspective of a decisionmaker—and how to balance the different risks and benefits depends on how a decisionmaker values these specific outcomes—we do not strictly define effectiveness as impact on one specific outcome but instead present the comparative impact of the available interventions on the available outcomes of interest.
TEP #7	General	I disagree with the author that the RACE Trial was not adequately powered to permit definitive conclusions. Guidelines indicate, and I personally agree, that there is no evidence to support more “aggressive” ie: “strict” rate control beyond approximately 100 into 110 beats per minute at rest in patients with atrial fibrillation, unless there are ongoing symptoms felt to be due to rapid rate. I agree with the authors that this contention that lenient rate control is not necessarily as good as “strict” rate control is not completely proven, but surly the default should be less toxic drug therapy resulting in fewer side effects if the outcome is unknown.	We have modified the rate control section in the Introduction and the Executive Summary to reflect the reviewers concerns regarding strict versus lenient rate control given uncertain evidence.

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TEP #7	General	Although I agree in principle that evidence gaps are present and are compare to safety and effectiveness of antiarrhythmic drugs are required, I believe very importantly comparative effectiveness should concentrate on patient wellbeing, quality of life, adverse effects, hospitalization, and morbidity and mortality rather than simply "ability to achieve and maintain sinus rhythm".	We agree that outcomes of interest are much broader than just the ability to achieve and maintain sinus rhythm. As such the outcomes which we looked to include in our comparative effectiveness review included: Intermediate outcomes: o Restoration of sinus rhythm (conversion) o Maintenance of sinus rhythm o Recurrence of AF at 12 months o Development of cardiomyopathy Final outcomes: o Mortality (all-cause, cardiac) o Myocardial infarction o Cardiovascular hospitalizations o Heart failure symptoms o Control of AF symptoms (e.g., palpitations, exercise capacity) o Quality of life o Functional status o Stroke and other embolic events o Bleeding events Adverse events: o Adverse events from drug therapies (e.g., hypotension, hypothyroidism and hyperthyroidism, arrhythmias [bradyarrhythmias, tachyarrhythmias, or proarrhythmias], allergic reactions, hepatotoxicity, neurotoxicity, pulmonary toxicity, ophthalmological toxicity, dermatological toxicity) o Procedural complications (including pulmonary vein stenosis, left atrial esophageal fistula, phrenic nerve palsy, tamponade, and other)

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TEP #7	General	With respect to a CRT device in patients with atrial fibrillation, there are no randomized studies exclusively focusing on AF patients, but sub analysis of the RAFT Trial suggests that there is no proven benefit for CRT in patients with heart failure and coexisting atrial fibrillation (Healy et al).	We agree with the reviewer that there are no randomized studies of CRT exclusively focusing on patients with AF, but only secondary analyses of major trials. In this analysis, we are only interested in studies that reported on the effect of CRT on atrial fibrillation burden for patients with AF. Unfortunately, we did not find any studies which met our inclusion criteria. The secondary analyses of major trials that although not meeting our inclusion criteria of being a population of interest, do discuss outcomes of interest are the analysis of CARE-HF and the analysis of MADIT-CRT. Those showed conflicting findings. These points have been added to the paragraph on CRT in the Introduction.
TEP #8	General (Tables)	Appreciate the different types/formats of tables based on data being presented.	Thank you.
Public Reviewer #1 – Edward Greissing, Sanofi	General	Overall, we think that the AHRQ draft report has many strengths, but there are some critical gaps, which have the potential to lead to better understanding of important treatment issues if properly addressed.	We thank the reviewer for their comment and hope that the revised final report is found to fill some of these identified critical gaps.
Public Reviewer #2 – Alice M. Mascette	General	Despite these minor editorial comments, the document is excellent and the product of a well-conducted analysis and will serve as a useful document for practicing clinicians.	Thank you.
Peer Reviewer #2	ES (Introduction)	Page 9 [=ES-1], line 43: The risk of stroke is as low as 1% in some low-risk patients. To say the risk ranges from 3-8% is incorrect.	We have modified this sentence to indicate that the risk may range up to 8% but do not include a lower limit.
Peer Reviewer #2	ES (Introduction)	Page 11 [=ES-3], line 56: Persistent AF also includes AF that requires termination, even if less than 7 days in duration.	We do not think that the suggested change is supported by the 2006 AF guidelines that provide a definition for all types of AF. In that document, the following is stated: “If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained beyond 7 d, it is termed persistent. Termination with pharmacological therapy or direct-current cardioversion does not alter the designation.”
Peer Reviewer #2	ES (Introduction)	Page 13 [=ES-5], figure: among the procedure complications I would include tamponade specifically.	We have added in tamponade as a specific adverse event in the figure as suggested.
Peer Reviewer #2	ES (Methods)	Page 16 [=ES-8], line 4: all calcium channel blockers are non-dihydropyridine (verapamil and diltiazem). This should be specified since the dihydropyridine CCBs are not effective in rate control but rather are used for hypertension. Also elsewhere, such as figure on page 66 [=22?] of PDF.	We have clarified that the calcium channel blockers included in our analysis are non-dihydropyridine calcium channel blockers.

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Peer Reviewer #2	ES (Results)	Page 21 [=ES-13], line 29 (also p 70 [=25], line 52): It should be specified that the rates of 80 and 110 are at rest.	This clarification has been added as suggested.
Peer Reviewer #2	ES (Results)	Page 34 [=ES-26], Table F and elsewhere: The authors conclude that amiodarone is no different, as opposed to a lack of evidence that it is superior to propafenone (as opposed to the low SOE data that suggest superiority of amiodarone over dronedarone and sotalol. My read of the literature would suggest that propafenone is similar to sotalol in efficacy and as such would be less effective than amiodarone. The discussion (page 38 [=ES-30]) should also be softened in this regard.	We agree with the reviewer that the language required softening and clarification. In Table F and elsewhere, the text was modified to indicate the SOE for maintenance of SR was insufficient rather than low. Because this review separates outcomes of "maintenance of SR" from "recurrence of AF", our approach was to use the outcome as stated in the published paper. Only 3 of the 9 studies assessing "maintenance of SR" provided statistical comparisons and because the 3 reported comparisons were of different drugs, no conclusions could be reached. In looking only at studies that reported an outcome of "recurrence of AF" two studies found no difference between amiodarone and propafenone and there were no studies that provided conflicting results to these findings. In looking at studies that reported an outcome of recurrence of AF or adverse drug event, once again no difference was found between amiodarone and propafenone and no other study reported conflicting results. Unfortunately, other comparisons of amiodarone and propafenone or amiodarone and sotalol, or sotalol and propafenone were done in only 1 study or there were conflicting findings across studies. We also explored combining the three outcomes listed above (maintenance of SR, recurrence of AF, and recurrence of AF or ADE) and came to the same conclusions. There was insufficient evidence for the comparison of amiodarone and dronedarone. There was conflicting results in the comparisons between propafenone with sotalol, and between amiodarone with sotalol. Based upon two fair quality studies, there was a low level of evidence supporting no difference between amiodarone and propafenone.

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Peer Reviewer #2	ES (Discussion/ Conclusion)	Page 37 [=ES-29], line 51: I strongly disagree with the conclusion that there is a "continued need to achieve strict rate control until more definitive date emerge". This is not supported by the data we have in RACE-II. While there may still be questions, the lack of superiority, and trend toward worse outcomes, in strict rate control make it clear that there may be problems with strict rate control. The current recommendation also flies in the face of the recent guideline update. This conclusion is not repeated in the main paper, page 160 [=116?] of the PDF.	We have modified the rate control section in the Introduction and the Executive Summary to reflect the reviewer's concerns regarding strict versus lenient rate control given uncertain evidence.
Peer Reviewer #2	ES (Discussion/ Conclusion)	Page 38 [=ES-30], line 3: While "paddle" placement (in fact should use the term, "electrode" since most use adhesive electrical patches) is not significantly better with AP or AL, anecdotal experience favors trying an alternate placement when one vector fails. This should be mentioned, and is supported by Joglar et al, where 3 pts (5%) converted only after repositioning the electrodes.	The use of the term "paddle or pad" can be confusing or misleading and we have taken the reviewer's suggestion to change the terms to "electrode." However, when the term "electrode" is first used in the main text we have added a break down of whether the "electrodes" were paddles, pads, etc. in case the reader wishes to have this more detailed information. With regard to use of an alternative placement when the initial placement fails, we have added data from two studies (Alps et al and Kirchhof et al) as these two studies included a crossover within their study protocol or allowed for the crossover. In the study by Joglar et.al, the alternative placement occurred only at the end of a pre-specified sequence. For example, patients randomized to an initial 100J shock would be required to receive subsequent treatments in this order: 200J, 360J, 360J with pressure on pads, then 360 J with alternative position. The results from alternative position are more challenging to interpret given the study procedures and would not necessarily be supportive of trying the alternative approach, but rather trying the alternative approach after numerous other procedures have failed.

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TEP #1	ES (General)	(Note: Due to the length of the full document, I only had time to review the Abstract and Executive Summary (i.e. through page ES-36). Therefore, it is possible that some of the issues I have raised are addressed in the Main Report.) It is abundantly clear that a considerable amount of time and energy was devoted to researching and developing this document. In addition, the document addresses several questions that frequently arise in routine clinical practice. Unfortunately, the usefulness of the document is limited to some extent by the relative paucity of available studies that focused specifically on some of the issues raised in the key questions (KQs).	We thank the reviewer for their feedback.
TEP #1	ES (General)	Additional concerns include: 1. While the rationale for limiting the search to articles published after January 1, 2000 is clear, the study findings still need to be placed in context of relevant investigations conducted prior to 2000. This is particularly true for KQ1 and KQ4, i.e., the questions that address pharmacologic agents for rate control (KQ1) and rhythm control (KQ4). In my opinion, failure to discuss earlier studies greatly limits the validity of the authors' conclusions with respect to KQ1 and KQ4. For example, if studies published prior to 2000 clearly established that beta-blockers are the most effective agents for controlling heart rate in patients with atrial fibrillation (AF), then the value of additional studies addressing this question would be limited. As a result, the conclusion in Table A that there is insufficient evidence comparing beta-blockers and calcium channel blockers (CCBs) for ventricular rate control could be misleading and could adversely affect evidence-based clinical decision-making (i.e., selection of a CCB rather than a beta-blocker, even though the totality of evidence demonstrates superiority of beta-blockers). The issue of including (or at least summarizing) earlier studies is less important for the KQs addressing the comparative effectiveness of procedure-based interventions, for which limited published data are available prior to 2000.	We appreciate the reviewer's concerns about the need to put the findings of our review into the larger context of investigations conducted prior to 2000. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000. We now cite in the Methods chapter the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation (www.ncbi.nlm.nih.gov/books/NBK33108) as an additional reason for our concentration on the evidence published in 2000 or later. In addition, in the Discussion section where we summarize the findings in relation to what was already known we summarize the findings of this prior systematic review and specifically what was known concerning rate- and rhythm-control pharmacological therapies.

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TEP #1	ES (General)	2. The statements of KQ3 and KQ4 lack clarity. Specifically, KQ3 seeks to compare non-pharmacologic rate-control therapies with pharmacologic rate control therapies in patients who have ALREADY FAILED INITIAL PHARMACOTHERAPY. Thus, it seems that the question, as framed, is almost guaranteed to produce the result that non-pharmacological approaches are more effective than failed pharmacological approaches for controlling heart rate, which is indeed exactly what the data showed. And for KQ4, comparing anti-arrhythmic drugs (AADs) with electrical cardioversion for restoration of sinus rhythm is not a clinically relevant question because electrical cardioversion is clearly more effective; the real key question is the comparative effectiveness and safety of the available AADs.	These key questions were nominated through a topic triage process and then further refined through the topic refinement process involving key informants and then the systematic review process involving the technical expert panel. As such the key questions were seen to be important by the stakeholder groups as stated. The reviewer is, however, correct that within the individual key question that specific comparisons are most timely or of clinical interest and are therefore supported by the evidence.
TEP #1	ES (Introduction)	Page ES-3, lines 32-36: A reference is needed to support the potential role of CRT as a therapy for AF. (I am not aware of any studies that have addressed this.)	We agree. We now provide citations.
TEP #1	ES (Introduction)	Page ES-4: See above re: clarity and relevance of KQ3 and KQ4.	As above.
TEP #1	ES (Methods)	All aspects of the Methods, including inclusion/exclusion criteria, search strategy, outcome measures, and statistical analyses, appear to be appropriate. The only concern, as noted above, is the decision to exclude studies prior to 2000 in situations where earlier studies may have informed the analyses and potentially altered the conclusions.	We appreciate the reviewer's concerns about the need to put the findings of our review into the larger context of investigations conducted prior to 2000. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000. We now cite in the Methods chapter the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation (www.ncbi.nlm.nih.gov/books/NBK33108) as an additional reason for our concentration on the evidence published in 2000 or later. In addition, in the Discussion section where we summarize the findings in relation to what was already known we summarize the findings of this prior systematic review and specifically what was known concerning rate- and rhythm-control pharmacological therapies.
TEP #1	ES (Results)	The presentation of the Results is clear and the Tables and Figures are useful. The key findings are accurately summarized in bullet points.	Thank you.

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TEP #1	ES (Results)	Specific comments: 1. Pages ES-11 to ES-12: See comments above about the limitation of not incorporating earlier studies, at least in summary form, into the analyses and discussion. This deficiency is perhaps most germaine regarding the comparison of beta-blockers and CCBs for rate-control.	We appreciate the reviewer's concerns about the need to put the findings of our review into the larger context of investigations conducted prior to 2000. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000. We now cite in the Methods chapter the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation (www.ncbi.nlm.nih.gov/books/NBK33108) as an additional reason for our concentration on the evidence published in 2000 or later. In addition, in the Discussion section where we summarize the findings in relation to what was already known we summarize the findings of this prior systematic review and specifically what was known concerning rate- and rhythm-control pharmacological therapies.
TEP #1	ES (Results)	2. KQ4, page ES-18: It is unclear whether the amiodarone studies refer to IV amiodarone for acute phase cardioversion during hospitalization, out-patient oral amiodarone for cardioversion, or a combination of both. Please clarify.	The focus in our CER is on acute phase cardioversion, but because the therapeutic effects of oral antiarrhythmic drugs may take days to weeks to achieve, the time frame for "acute phase cardioversion" in this review is 6 weeks (this is described in the summary of findings for KQ4). We have added additional information about whether the drugs were given IV, orally, or a combination of both and have added information about the number of studies done in the ED, inpatient, or outpatient setting.
TEP #1	ES (Results)	3. Page ES-28, Table G: In the quality of life section, it is unclear why 9 studies involving 5806 subjects were insufficient to provide insight into this issue.	Although there were 9 studies which assessed quality of life the instruments and metrics used as well as the findings were inconsistent and imprecise. We therefore were not able to come to a conclusion about the comparative effectiveness of rate versus rhythm strategies on quality of life. We describe the findings and inconsistency in the main report results section and more detailed SOE tables in the Discussion

Commentator & Affiliation	Section	Comment	Response
TEP #1	ES (Discussion/ Conclusion)	The implications are clearly stated and the limitations with respect to the paucity of data are acknowledged. As noted above, studies published prior to 2000 are relevant to at least 2 of the KQs, and some discussion of this issue is needed.	We appreciate the reviewer's concerns about the need to put the findings of our review into the larger context of investigations conducted prior to 2000. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000. We now cite in the Methods chapter the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation (www.ncbi.nlm.nih.gov/books/NBK33108) as an additional reason for our concentration on the evidence published in 2000 or later. In addition, in the Discussion section where we summarize the findings in relation to what was already known we summarize the findings of this prior systematic review and specifically what was known concerning rate- and rhythm-control pharmacological therapies.
TEP #1	ES (Discussion/ Conclusion)	The Research Gaps section is disappointing in that it is little more than a restatement of the original KQs. Taken at face value, the implication of this is that despite all of the work that went into this effort, the results provide little in the way of new insights that will help guide therapy, particularly in subgroups of interest, such as older adults, women, minorities, etc.	Although there is substantial evidence within this CER, there are also substantial gaps in the evidence specifically targeting subgroups of interest (elderly, women, minorities) and longer term outcomes. We therefore think that emphasis on these uncertainties is warranted.
TEP #1	ES (Discussion/ Conclusion)	Specific comments: 1. Page ES-29, lines 45-49: Based on the data presented, the comparative effectiveness of beta-blockers vs. CCBs for rate control remains uncertain and warrants either further investigation or inclusion of older studies in the analysis.	We have modified these sentences to include calcium channel blockers as well.
TEP #1	ES (Discussion/ Conclusion)	2. Page ES-29, lines 51-53: The call for a "continued need to achieve strict rate control" is not supported by the data presented. Indeed, lenient rate control was associated with fewer strokes (mechanism unknown) and was non-inferior with respect to all other outcomes. In addition, lenient rate control is easier to achieve and requires less medication, thereby reducing side effects and costs while potentially improving adherence. A more appropriate conclusion is that lenient rate control appears to be an acceptable alternative to strict rate control, but that additional studies are needed, especially the evaluation of outcomes over a longer period of time.	We have modified the rate control section in the Introduction and the Executive Summary to reflect the reviewer's concerns given strict versus lentient rate control given uncertain evidence.

Commentator & Affiliation	Section	Comment	Response
TEP #1	ES (Discussion/ Conclusion)	3. Page ES-30, lines 17-20: PVI plus CFAE also causes more scarring, as a result of which longer term outcomes could be less favorable in part due to greater reduction in mechanical atrial function.	We thank the reviewer. We have modified that section within the Executive Summary and discussion of the main report to include this point.
TEP #1	ES (Discussion/ Conclusion)	4. For virtually all of the KQs, additional studies are needed evaluating longer-term outcomes and quality of life outcomes.	We agree that long-term and quality-of-life outcomes are lacking throughout the available evidence. This is highlighted in our research gaps section.
TEP #4	ES (Introduction)	I think the intro can be tightened up quite a bit. Some of the sentences don't seem necessary (e.g., page ES-1, "AF is a major public health problem in the United States." when the actual numbers are presented and more meaningful I think) and some of the statements seem a little self-congratulatory and I think can be taken out (e.g., p ES-2, "Thus, an updated review of published studies... are very timely") or repetitive (e.g, p ES-2, "It is importnat to synthesize the evidence that has been published since then to better define the role of this procedure", then "It is important to examine all available evidence on strict versus lenient rate control...", etc)	Where possible we have tightened up the Executive Summary introduction. Note, however, that because the Executive Summary is for many stakeholders the only part of the document that is read, and because these stakeholders have diverse backgrounds/familiarity with the topic, there is substantial details in the Executive Summary targeting this diverse readership.
TEP #4	ES (Introduction)	In some places need to define terms a little better, for example rate control is never defined when it's first introduced nor is rhythm control, or what it means to be a Class I ACC recommendation etc.	As suggested we have added in definitions for these key terms.
TEP #4	ES (Introduction)	Some parts of the Intro seem to present results e.g. p ES-3 "The relatively small number of patients in each trial makes definitive conclusions...difficult."; "Comparative long-term risks and benefits of rate-control versus rhythm control strategies...remains unclear."	We have modified these sentences to clarify that they refer to our ability to reach conclusions prior to our systematic review.
TEP #4	ES (Results)	p ES-9: The conclusions about unpublished trials are only based on a search of ClinicalTrials.gov. The blanket statement that "we don't think there's publication bias" seems overstated as there are numerous other potential sources of unpublished trials and clinicaltrials.gov is far from comprehensive.	As stated in our protocol for this CER, ClinicalTrials.gov is the main source we used for searching for unpublished trials. We now have included an acknowledgment that there are other sources for publication bias which are not assessed in our review.
TEP #4	ES (Results)	Throughout the results, there is inconsistency in how the bullet summary points are presented. In general I think it is helpful to be more consistent and try to provide # of studies, some indication of quality/type of study, and perhaps something about sample size, but this is done inconsistently.	We have modified the key points to consistently provide this information.

Commentator & Affiliation	Section	Comment	Response
TEP #4	ES (Results)	As noted before some of the results are based on follow-up just lasting hours, and this is not reflected in the summary bullets (which just say that one treatment is better than another).	The reviewer is correct that many of the outcomes of interest are short-term or vary in terms of their length. Although we do not present this in the key points we provide this information throughout the report when discussing the outcomes and then also in the discussion when describing limitations of the evidence base and need for future research in to longer-term outcomes.
TEP #4	ES (Results)	Some of the SOE ratings don't seem to jibe with the evidence, e.g., Table A in the ES, Amidoarone vs. Ca-challenel blockers rated as insufficient despite 3 studies with 271 patients.	Although there were three studies which explored this comparison, their findings were inconsistent and imprecise and did not allow conclusions to be reached. Additional details about these studies and the limitation of the evidence are found in the main report KQ 1 and Discussion sections.
TEP #4	ES (Results)	One of the bullets for KQ 4 (drug pretreatment) seems inconsistent with the abstract (it found moderate evidence of enhanced electrical cardioversion, the abstract says inconclusive).	We have corrected the abstract.
TEP #4	ES (Results)	ES Table D: In some cases OR's are presented but others not (Drug enhancement of Ext Electrical Cardioversion); if OR's aren't provided then it seems that p values at least should be given. Also in this Table, if the CI is provided there is no reason to say that difference is statistically significant, it should be evidence from the CI.	We have added in the p values as suggested. Because the readership of the report varies in terms of the statistical familiarity we have left in text describing the direction and statistical significance of listed ORs.
TEP #4	ES (Results)	Also in ES Table E there are some places where the OR's are interpreted e.g. "demonstrating large and significant benefit of Maze" when again if the estimate and CI is presented there is no need for this.	Although the interpretation of the estimate and CI is clear to many readers of the CER, it is not universally understood, and therefore we provide this additional language to help our readership in the synthesis and understanding of the evidence review.
TEP #4	ES (Discussion/ Conclusion)	Some of the Discussion also sounds a little self-congratulatory, I would avoid saying things like "we provide important information" and "will inform clinical decisionmaking" and funders etc. Rather try to discuss the findings and how they may effect these stakeholders.	As suggested we have modified the discussion (in both the Executive Summary and main report) to remove some of these judgments.
TEP #4	ES (Discussion/ Conclusion)	This sentence needs some re-working or perhaps deletion (ES-30): "This information is important and should help inform clinical decision regarding what antiarrhythmic medication to use in a particular patient among all the medications that are considered appropriate for that particular patient by practice guidelines."	The cited sentence has been deleted.

Commentator & Affiliation	Section	Comment	Response
TEP #4	ES (Discussion/ Conclusion)	The Research Gaps section is very detailed but I think pretty long, especially for the ES. I would try to summarize into a few key bullets in the ES and try to condense down in the main report as well.	We have shortened the research gaps section slightly in the Executive Summary. Although this section is long we think that it represents important needed direction for future research. Given that many stakeholders may not read the full main report we felt that keeping this information in the Executive Summary was important.
TEP #4	ES (Discussion/ Conclusion)	Suggest delete the last sentence of the Conclusions in the ES.	We have deleted this sentence as suggested.
TEP #6	ES (General)	With regard to key question 3, both the Executive Summary and the primary document should make it more clear that AV node ablation is a drastic and irreversible procedure that essentially results in pacemaker dependence for the patient, and the decision to undergo this procedure is irrevocable and not to be undertaken lightly. Merely presenting the degree to which medications or "a newer procedure" controls the heart rate fails to express the gravitas of such a decision.	Thank you for this important comment and we agree with your statement that AVN ablation with pacemaker placement is a treatment of last resort. We have added new language in the Executive Summary and the main document to reflect this fact and the fact that use of the procedure should be viewed as an opportunity to continue to investigate new drugs or interventions that preclude the need for this procedure.
TEP #6	ES (General)	I had several concerns with regard to key question 5. While much of the clinical research has focused on pulmonary vein isolation, it is important to recognize that the overarching categorization should be "AF ablation" and PVI is mere one (albeit the dominant and most studied) technique for accomplishing AF ablation. The fact that the writers acknowledged some of the different techniques for ablating AF, there is, actually even more heterogeneity of techniques that are employed even among those considered to be "PVI"; these can include wide-area circumferential ablation, formal venous antral PVI, focal PV ablation (generally not performed any more due to risk of PV stenosis), and each of these may or may not include formal testing to determine the integrity of the isolation procedure, which, in turn can be performed by a variety of techniques (testing for entrance block, exit block, both, etc.). In addition, any of these procedures can be performed with accompanying ablation of complex fractionated electrograms, SVC isolation, CTI ablation, ablation of the ligament/vein of Marshall, CS ablation, ablation of atrial ganglionic plexi, left atrial roof lines, a mitral isthmus line, left atrial appendage isolation, etc., some of which were acknowledged in the analysis, and some of which were not. When considering the pragmatic realities that all of these are in use to varying degrees with multiple types of catheters, 4mm, 8mm, internally irrigated, and a variety of externally irrigated catheters, there is a real-world morass that will make it difficult to apply the findings practically for most clinicians.	The reviewer brings up several good points. In this analysis, we had to rely on the description of the authors of the main papers regarding what procedure they did, what areas they ablated, etc. We had no way to ascertain whether what they reported was perfectly accurate and captured the entirety of what was done. We have acknowledged our dependence on the descriptions provided in the literature in the Discussion chapter under the Limitations of the Evidence base section.

Commentator & Affiliation	Section	Comment	Response
TEP #6	ES (General)	Similarly, there is great heterogeneity among the different surgical approaches, and both the Executive Summary and the primary document need to express more clearly that the historical Cox III Maze Procedure is a specific, almost never-performed entity any more (at least as Cox developed it), and that cryoablation approaches to approximate the Cox lesion set, and the proliferation of surgical approaches to antral ablation with and without formal electrophysiological confirmation of venous isolation cannot be assumed to have the same outcomes as reported by Cox and colleagues for their rigorous approach.	The reviewer brings up several good points. In this analysis, we had to rely on the description of the authors of the main papers regarding what procedure they did, what areas they ablated, etc. We had no way to ascertain whether what they reported was perfectly accurate and captured the entirety of what was done. We have acknowledged our dependence on the descriptions provided in the literature in the Discussion under the limitations of the evidence base section.
TEP #8	ES (General)	Very well written and concise. Will be very useful for upcoming guidelines.	Thank you.
Public Reviewer #1 – Edward Greissing, Sanofi	ES (Introduction)	The 2011 Focused Update on the Management of Patient with Atrial Fibrillation is alluded to in the background paragraph on Rate Control (pES-2), but is not mentioned in the Rhythm Control paragraph that follows (pES-2-3). We believe the Focused Update merits reference and potentially discussion in both sections. Per the guideline authors, the [guidelines] update focuses on several areas in which new data on management of patients with AF have become available, including a) recommendations for strict versus lenient heart rate control, b) combined use of antiplatelet and anticoagulant therapy, and c) use of dronedarone (p108, Section 8. Management). Importantly, in addition to a revised algorithm for maintenance of sinus rhythm from the 2006 ACC/AHA/ESC AF Guideline, the Focused Update gives dronedarone a separate Class IIA recommendation for decreasing the need for cardiovascular (CV) hospitalizations in paroxysmal AF or after cardioversion in persistent AF (p110, Table 4, Focused Update). Dronedarone is, in fact, the only anti-arrhythmic drug (AAD) to have established benefits in this respect based on a large controlled, randomized clinical trial (ATHENA, 2009). Since reducing CV hospitalization, amongst other outcomes, is an important consideration in AF management (AFFRIM, 2004) and one of the greater burdens of the disease, we recommend inclusion of this information should be considered in the final report for completeness and context.	The 2011 Focused Update is discussed in more detail in the main report Introduction. We did, however, add a sentence to the revised rhythm control section to highlight that this update exists and explore additional medications. Because the dronedarone trials were placebo-controlled rather than compared to active therapy they did not meet the inclusion criteria for our review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 – Alice M. Mascette	ES (Introduction)	The statement is made on pp. ES-2 and 2 that "when AF affects younger patients (<65 years of age), a rhythm-control strategy is often considered reasonable in the absence of substantial symptoms." If there is an evidence base for this practice, it should be cited here; if this practice is without an evidence base that should be so stated.	We agree. Some physicians implement this in their practice because AF begets AF and more AF worsens atrial remodeling. Their rationale is if one prevents AF, one can prevent or slow down remodeling. This has not been shown to have an effect on patient outcomes and all the recommendations base rhythm control strategy on the presence of symptoms. Therefore, we have deleted this sentence from the Executive Summary and final report.
Public Reviewer #2 – Alice M. Mascette	ES (Introduction)	This section goes on to state (pp. ES-3 and 3) that "none of the trials provides data on hard end points like mortality and stroke. These limitations underscore the importance of synthesizing the evidence on this procedure by pooling data from these studies and by exploring whether other types of studies or comparative effectiveness research would be helpful." Not mentioned is that an RCT specifically measuring these endpoints would be equally helpful. The current CABANA trial, funded by NIH, is recruiting patients to answer this question. See http://clinicaltrials.gov/ct2/show/NCT00911508?term=cabana&rank=1.	We agree that this information will be helpful to the reader and we have added this details as suggested to the text.
Public Reviewer #2 – Alice M. Mascette	ES (Introduction)	In this section (page ES-3 and 4), the statement is made "The comparative long-term risks and benefits of rate-control versus rhythm-control strategies for patients with AF remain unclear. Although several studies of rate and rhythm control strategy exist, it is still not known if maintaining patients with AF in sinus rhythm provides any long-term survival benefit." This statement seems to underplay the results of two large, well-conducted government-funded trials (AFFIRM, AF-CHF) that failed to show any difference in mortality or cardiovascular mortality, respectively, between rate-control and rhythm-control strategies. See as well comment under KQ6.	The reviewer brings up good points. We have modified those sentences.
Public Reviewer #2 – Alice M. Mascette	ES (Results)	The inclusion of amiodarone and sotalol as rate-control drugs (pp. ES 11-12, 19-23) should also include more discussion that these drugs are also potent membrane-active, type III antiarrhythmics, in addition to rate-controlling agents. For instance, the phrase "One study compared two beta blockers (metoprolol versus sotalol)" (pp. ES-11 and 22) might lead a health care provider to use these drugs interchangeably without understanding the full import of such a medication substitution.	We agree that this is an important distinction and now in KQ 1 when we discuss amiodarone and sotalol we clarify their additional rhythm-control characteristics.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 – Alice M. Mascette	ES (Results)	The first bulleted key point (pp. ES-12 and 25), "Based on one RCT, there was a significant decrease in strokes for patients on lenient rate control, although this decrease was not consistent with findings of one observational study (low strength of evidence)" seems more strongly or prominently stated than the evidence that supports it. It might be better to use the phrase or format used in the bullet that follows, e.g., "There was low strength of evidence to support."	We have modified this bullet as suggested.
Public Reviewer #2 – Alice M. Mascette	ES (Results)	The Executive Summary and final summary (p. ES-33, 116) includes the phrase "A specific area for future research would be to explore the risk for proarrhythmias especially in women." While this is a laudable and interesting research question, I could not find the supporting data in a search of the document text which includes several sections subtitled "Results in Specific Subgroups of Interest." See also comment under KQ5: this KQ4 section has a recommendation without data, the other has data with no specific summary recommendation. These should be dealt with similarly, which could include not highlighting those differences if the level of evidence is low.	Areas highlighted as needing future research are ones where the evidence is sparse but are both clinically important and timely. We think that the risk and benefits in women is such an evidence gap and the fact that we were not able to find much evidence specifically in this subgroup emphasizes it as an important evidence gap and area of future research need.
Peer Reviewer #1	Introduction	The Introduction is excellent. It should include more data on the prevalence of AF in different age groups and in men versus women.	Thank you. We provide information on the increase in the prevalence of AF with age: "The prevalence of AF increases with age and approaches 8 percent in patients older than 80 years of age." Providing data on the prevalence of AF in each age group is beyond the scope of this document. We have however added as suggested information on AF in men and women.
Peer Reviewer #3	Introduction	The introduction is well done. I found the references to the specific guidelines quite helpful and could make a useful table where each Key question was a row and relevant guideline comments were in the columns along with the date. Figure 1, I would say which guideline this is.	Because the emphasis of our report is on the state of the evidence rather than how this evidence is translated in to guideline recommendations we have not added additional focus on the specific guideline recommendations by key question as suggested. We do however now list the specific guideline reference for Figure 1 as suggested.
Peer Reviewer #4	Introduction	Scope and key questions seem quite good	Thank you.
Peer Reviewer #4	Introduction	Rationale and justification for this review are strong and convincing	Thank you.
TEP #2	Introduction	This section describes the magnitude of problem of atrial fibrillation and nicely sets the stage for the subsequent review. This section is strengthened further by accompanying figures and tables in facilitating the author's efforts to convey their message to the reader.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Introduction	As an overarching comment, I'm a little troubled that the authors do not even reference the 2001 EPC report. Limiting the search strategy to references from 2000 on is more justifiable in the context of this previous report. The apparent conclusion that there were no relevant studies published prior to 2000 is incorrect. I don't think the conclusions would be at all different, but I do believe the authors should at least acknowledge the availability of this evidence. It is of note that the previous review was not a comparative effectiveness review. Management of New Onset Atrial Fibrillation Evidence Reports/Technology Assessments, No. 12 Investigators: Robert L McNamara, MD, MHS, Principal Investigator, Eric B Bass, MD, MPH, Co-Principal Investigator, Marlene R Miller, MD, Jodi B Segal, MD, MPH, Steven N Goodman, MD, PhD, Nina L Kim, MA, Karen A Robinson, MSc, and Neil R Powe, MD, MPH, MBA. Rockville (MD): Agency for Healthcare Research and Quality (US); January 2001. Report No.: 01-E026 www.ncbi.nlm.nih.gov/books/NBK33108	We have now included discussion of the 2001 EPC report within our review and how the evidence from this report further supports our decision to restrict our included studies to those published in 2000 or later.
TEP #5	Introduction	Introduction: I do believe the authors studied the targeted population and stated the key questions for the search clearly.	Thank you.
TEP #6	Introduction	No specific concerns	Thank you.
TEP #8	Introduction	Very well written and concise. Will be very useful for upcoming guidelines.	Thank you.
Public Reviewer #1 – Edward Greissing, Sanofi	Introduction	Figure 2 of the draft report provides an extensive depiction of the key questions of the review within the context of the PICOTS. We agree with the selection of patient-centered outcomes included as the "final" outcomes within the framework (e.g., all-cause mortality, CV mortality, CV hospitalization, etc.). However, it is unclear from the Methods section in the draft document how each of these outcomes is defined within the analytic framework. Such ambiguity can significantly impact the interpretation of the CER's findings.	Final outcomes are those which a patient can feel or experience rather than something like recurrence of AF, which may be without symptoms and therefore is considered intermediate. In addition, final outcomes have a direct link to a health outcome rather than requiring multiple steps between the outcome and a health outcome. We now clarify this in our methods section.
Peer Reviewer #1	Methods	The inclusion and exclusion criteria are justifiable. The search strategies are explicitly stated and logical. The definitions or diagnostic criteria for the outcome measures are appropriate. The statistical methods used are appropriate.	Thank you.
Peer Reviewer #3	Methods	The inclusion and exclusion criteria are appropriate. I found the search strategy to be well described and and data extraction process quite detailed. The data synthesis methods and assessment of quality were standard and appropriate.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Methods	The standard meta-analysis examines superiority and thus the term insufficient strength often refers to lack of statistical significance from a small sample size. Should different wording be used when the goal is demonstrating non-inferiority (Key Question 2).	Although the trials in KQ 2 were targeting noninferiority, our comparative effectiveness review sought to evaluate the superiority of one treatment or strategy over another. We therefore think that the methods and term insufficient strength related to these outcomes are appropriate.
Peer Reviewer #4	Methods	Literature search strategy - what is the basis for the belief that only evidence published from 2000 and beyond represents the current standard of care? Doesn't this exclude some key studies, such as the "pill-in-the-pocket" propafenone and flecainide studies, and others? Many of the most important beta-blocker, digoxin and calcium channel blocker studies were conducted prior to 2000. While this strategy must have helped keep the number of studies evaluated more manageable, it's not convincing to me that only data from the last 12 years represents the current standard of care.	We appreciate the reviewer's concerns about the need to put the findings of our review into the larger context of investigations conducted prior to 2000. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000. We now cite in the Methods chapter the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation (www.ncbi.nlm.nih.gov/books/NBK33108) as an additional reason for our concentration on the evidence published in 2000 or later. In addition, in the Discussion section where we summarize the findings in relation to what was already known we summarize the findings of this prior systematic review and specifically what was known concerning rate- and rhythm-control pharmacological therapies.
Peer Reviewer #4	Methods	Does the exclusion of non-English language papers introduce publication bias? Are there no quality studies published in other languages?	The inclusion/exclusion of non-English language papers was discussed with the Technical Expert Panel. It was agreed that given the high volume of literature available in English-language publications (including the majority of known important studies), and concerns about the applicability of non-English publication studies to clinical settings in the United States, non-English articles could be excluded without introducing publication bias in our findings.
Peer Reviewer #4	Methods	Analytical methods seem rigorous	Thank you.
Peer Reviewer #4	Methods	Page 53 [=9], Inclusion and Exclusion criteria - do these also include patients with a first detected episode of AF?	Yes, patients with a first detected episode of AF are not excluded explicitly from our CER based on our inclusion/exclusion criteria. However most trials did exclude these patients and so they are not well represented among our included studies.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Methods	Authors provide a full description of the steps taken and methods used for their literature search and review. Inclusion/Exclusion criteria are outlined. Where appropriate, description of met analyses is provided. They have provided full description for grading the strength of each study. Figure 3 on page 18 outlines the Flow Diagram for the literature review.	Thank you.
TEP #3	Methods	No concerns.	Thank you.
TEP #4	Methods	The Analytic Framework seems pretty complicatedand it's not clear what all the arrows mean and floating boxes; e.g. "STrict versus more lenient rate control" and the adverse events box (which has arrows going both ways). I would suggest simplifying if possible, e.g. deleting the individual characteristics box and just saying "adverse events" instead of listing every single thing. I'm also not clear what the arrows going down or up from the Pharmacological therapies boxes mean (are these people that fail Pharmacological therapies? If so it should be stated).	Although detailed, the analytic framework represents the different populations, interventions, comparators, and outcomes evaluated in this systematic review.
TEP #4	Methods	I understand the literature was overwhelming and that may have played a role in limiting the searches to 2000, but I am not sure that studies of, say metoprolol or digoxin or other meds around for decades are invalid simply b/c they are older. At the least the authors should see if their conclusions are consistent with reviews that included older trials, or older reviews.	We appreciate the reviewer's concerns about the need to put the findings of our review into the larger context of investigations conducted prior to 2000. We believe that the evidence published from 2000 on represents the current standard of care for patients with AF and relevant comorbidities. In addition, a 2001 AHRQ report on the management of new onset AF summarized the evidence prior to 2000. We now cite in the Methods chapter the 2001 AHRQ report on the Management of New Onset Atrial Fibrillation (www.ncbi.nlm.nih.gov/books/NBK33108) as an additional reason for our concentration on the evidence published in 2000 or later. In addition, in the Discussion section where we summarize the findings in relation to what was already known we summarize the findings of this prior systematic review and specifically what was known concerning rate- and rhythm-control pharmacological therapies.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Methods	The method of selecting appropriate studies by 2 reviewers is reasonable. For the statistical analysis, they used a pre-packaged commercial software, one would have expected a more flexible software such as SAS or R so the report could have included the specific model terms used in the meta-analysis. The authors have indicated that the heterogeneity was tested using Q and I2 statistics but these values were not reported nor the significance level for heterogeneity was given. Including a statistical analysis section could have used to address these issues.	We now include discussion of the heterogeneity findings for the reported meta-analyses.
TEP #6	Methods	The methods seemed quite reasonable and appropriate to addressing the key questions.	Thank you.
Peer Reviewer #1	Results	The amount of detail presented in the results section is appropriate. I suggest more detail for age groups and gender.	Unfortunately, findings by age group or sex were limited in the evidence base. These specific subgroups of interest are therefore emphasized in our evidence gaps section.
Peer Reviewer #1	Results	The characteristics of the studies are clearly described. The key messages are explicit and applicable. Figures, tables, and appendices are adequate and descriptive.	Thank you.
Peer Reviewer #1	Results	The investigators did not overlook any studies that should have been included or include any studies that should have been excluded.	Thank you.
Peer Reviewer #2	Results	Page 83 [=39], line 3. Joglar et al (ref 58) was truly a single center study (UT Southwestern, Parkand and Zale-Lipshy Hospitals).	Per the published paper, the study was conducted at UT Southwestern and the Dallas VA. By our definitions, that constitutes more than one site and thus the study was classified as multisite.
Peer Reviewer #2	Results	Page 85 [=41], line 31 and beyond: Joglar (58) also notes cases where the electrode placement was changed from AP to AL, with conversion. This does not provide randomized data but suggests a trial of alternate electrode placement when one vector fails.	In the study by Joglar et.al, the alternative placement only occurred at the end of a prespecified sequence. For example, patients randomized to an initial 100J shock would be required to receive subsequent treatments in this order: 200J, 360J, 360J with pressure on pads, then 360 J with alternative position. The results from alternative position are more challenging to interpret given the study procedures and would not necessarily be supportive of trying the alternative approach, but rather trying the alternative approach after numerous other procedures have failed.
Peer Reviewer #3	Results	The tabular results provide a great amount of detail and the text summarizes the trials of each category of comparison succinctly. I did not find any trials that the investigators should have identified during the time frame analyzed. All of the included studies appear to be appropriate for the related Key Question.	Thank you.
Peer Reviewer #3	Results	The Forest plots are clear and well done.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results	On page 42, the N was provided for the biphasis shock group but not for the overall comparison.	We have now added the following information: 7% with 20J, 23% with 50J, 63% with 100J, and 83% with 200J.
Peer Reviewer #3	Results	Page 66, and Figure 16. The figure says an OR > 1 favors MAZE, but doesn't MAZE increase mortality?	The reviewer is correct. We have fixed the figure that showed data for survival. Now we show the reverse data; i.e., for mortality.
Peer Reviewer #3	Results	The Maze mortality findings were a surprise to me and though not quite significant may deserve more attention given the importance of the outcome.	Figure 16 was labeled incorrectly and has now been corrected.
Peer Reviewer #4	Results	Page 17 [=ES-9], line 21 - not all unpublished studies are likely registered on Clinical Trials.gov - may still have missed some studies	As stated in our protocol for this CER, ClinicalTrials.gov is the main source we used for searching for unpublished trials.
Peer Reviewer #4	Results	One aspect of the reporting of the Results in this analysis is bothersome and concerning, and must be revised. This is the practice of referring to nonsignificant "trends." This is unscientific at best, and misleading at worst. Some of the differences identified as "trends" cannot in good conscience be referred to as trends, with odds ratios or hazard ratios only a little different than 1.0 and extremely wide confidence intervals. Even those that some might reasonably think truly are trends should not be referred to as such in a scientific analysis - the term is really meaningless, and suggests bias on the part of the authors. The odds/hazard ratios and 95% confidence intervals should simply be presented as they are, and the reader can decide for himself or herself if trends truly exist. Examples of this terminology requiring revision are found in Tables D, E, G, and on pages 71, 72, 90, 102, 110, 130, 133, 145 (Table 18), 148 (Table 19), 149, and 151 (Table 20). All terminology in the manuscript referring to "nonstatistically significant trend" or "nonsignificant trend" or simply "trend" should be revised to indicate that there was no significant difference between the treatment groups.	As suggested we have modified our wording throughout the report to eliminate the use of the word "trend."
Peer Reviewer #4	Results	Throughout manuscript - when individual studies are discussed, it would be helpful for the authors to indicate the sample size of the study so that readers can have some perspective on the size and power of the study	We have included the number of patients in several tables throughout the main report, and in the summary strength of evidence tables. Other sample sizes are included in the study characteristics tables provided in Appendix F.
Peer Reviewer #4	Results	Page 66 [=22], line 43 - is this p value (<0.1) correct, or is this a typo that should read <0.01? If it is really < 0.1, then this difference is not statistically significant, and the wording "tended" should be deleted, and the sentence should clearly state that there was no significant difference in the maximum heart rates.	This was not a typo and the sentence has been modified as suggested.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Page 67 [=23], line 19 - please delete the term “numerically lowered” and clearly state that there was no significant difference in mean heart rates between diltiazem and amiodarone	We have modified this sentence as suggested.
Peer Reviewer #4	Results	Page 68 [=24], line 41 [=line 44?]: not necessary to take nonsignificant p values to three decimal places	Although we list all findings throughout our report to two decimal places, we consistently have left p values with the decimal places listed in the publication.
Peer Reviewer #4	Results	Page 71 [=27] - delete all references to “trends” and make it clear that there were no significant differences	As suggested, we have modified our wording throughout the report to eliminate the use of the word trend.
Peer Reviewer #4	Results	Tables 5, 6, 7, 8, 9 , 10, 11, 12, 13, 14 - please add a column in which you provide the sample sizes of each study	We have added in columns of the sample sizes for all the tables as requested.
Peer Reviewer #4	Results	Figures 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 - please indicate the sample sizes of each study in these figures	After discussion with our statistician he confirmed that the sample size within a forest plot can be misleading and that there are cases where a larger trial may in fact provide less information than a smaller one. The length of the confidence interval provides all the needed information. We have therefore left off the sample size in the forest plots but have instead included the number of patients in several tables throughout the main report, and in the summary strength of evidence tables. Other sample sizes are included in the study characteristics tables provided in Appendix F.
Peer Reviewer #4	Results	Page 87 [=43], line 7 and throughout manuscript - the term “statistically significant” is redundant - please just say “significant.”	We think that there is a distinction between statistically significant and clinically significant and have therefore kept this phrasing throughout the document where needed.
Peer Reviewer #4	Results	Page 92 [=48], lines 36-39 - why was it necessary to perform a meta-analysis of studies that compare amiodarone with rate-controlling drugs for restoration of sinus rhythm - one would not expect rate-controlling drugs to terminate AF, so the results of these studies seem obvious.	We agree with the reviewer that this comparison and outcome of interest seems obvious, but for completeness it is included in our review.
TEP #2	Results	Studies have been sufficiently described for each KQ along with the grading of strength. Discussion is strengthened further by accompanying tables and figures as appropriate.	Thank you.
TEP #2	Results	Page 19, line 31 [first Key Point under KQ 1]: “Block” should be changed to blocker	We have corrected the typo as suggested.
TEP #2	Results	Page 47, line 31: “and” should be changed to an [in the phrase “and antiarrythmic drug…”]	We have corrected the typo as suggested.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results	Page 51, lines 13-22: total studies identified are 80 yet, the breakdown of studies in the text totals 81?	We have corrected the number of studies (and updated with new studies found during the peer review period).
TEP #2	Results	Page 52, lines 7-12: total studies identified are 62 but, the breakdown of studies in the text totals 61?	We have corrected the number of studies (and updated with new studies found during the peer review period).
TEP #2	Results	Page 52, lines 24-26: the breakdown of the studies now is 64 rather than 62?	We have corrected the number of studies (and updated with new studies found during the peer review period).
TEP #2	Results	Page 68, line 36: delete “group” from “group maze” [now reads “in group the Maze group”]	We have corrected the typo as suggested.
TEP #3	Results	Although I reviewed the entire report, I will focus on KQ1-3 & 6 as the most primary care relevant questions. KQ1. The authors reach the justifiable conclusion that there is insufficient evidence available. They also to describe the setting in which each of the trials was conducted. That being said, I am concerned that generalizing the results from a hospital setting to the chronic management of rate in the ambulatory setting is problematic. Combining the results of studies from these different settings should be avoided. This obviously does not alter the conclusion that the evidence is insufficient.	The reviewer is correct that generalization of findings from one setting to another may not be possible. As they indicate we highlight throughout the report the setting of the included studies.
TEP #3	Results	KQ2. In more than one place in the report, the authors articulate the conclusion that clinicians should continue strict rate control pending further research. This conclusion cannot be defended with the evidence. This is clearly “expert opinion” in the context of insufficient evidence based on the wide confidence intervals for important clinical outcomes. The conclusion that the evidence is currently insufficient to demonstrate superiority of either strict or leaning and rate control is justified. I recommend avoiding expert opinion in the conclusions.	We have modified the rate control section in the Introduction and the Executive Summary.
TEP #3	Results	KQ3. No concerns.	Thank you.
TEP #3	Results	KQ6. No concerns.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP #4	Results	For the Forest plots in the Main Report: These are a little hard to read, for the final might want to spiff up a bit, also include the rates and n/N for each group.	Regarding the inclusion of the N for each group. After discussion with our statistician he confirmed that the sample size within a forest plot can be misleading and that there are cases where a larger trial may in fact provide less information than a smaller one. The length of the confidence interval provides all the needed information. We have therefore left off the sample size in the forest plots but have instead included the number of patients in several tables throughout the main report, and in the summary strength of evidence tables. Other sample sizes are included in the study characteristics tables provided in Appendix F. We have attempted to improve the quality of the forest plot images and will work with AHRQ to ensure that the final, published figures are legible.
TEP #5	Results	page 17[ES-9], line 29, look like the word 'search' is left out.	We have corrected this typo.
TEP #5	Results	page 26 [ES-18], line 20 indicates data favoring 360 J vs. 200 J based on 3 studies, 411 patients, however page 81 [=37], line 29 says 432 patients?	This has been corrected. The correct number is 432.
TEP #5	Results	page 83 [=29], line 38 first protocol-specified shock, is this any shock or appropriate shock?	These shocks are not ICD shocks but rather planned direct current electrocardioversions for atrial fibrillation. Therefore, by the nature of the disease and procedure all of these are "appropriate shocks."
TEP #5	Results	page 85 [=41], line 14 the point estimate and 95% CIs are identical for Alp, 2000 and Brazdzionyte, 2006?	We have corrected the typo within this analysis and have included the updated figure and findings.
TEP #6	Results	With the caveats I mentioned above, the findings were very clearly presented.	Thank you.
TEP #7	Results	For key question one I agree that there is no definitive data on superiority of one beta blocker over another. However, the more important questions are 1. Are beta blockers superior to calcium channel blockers? This is unsettled and there is more evidence favoring calcium channel blockers than beta blockers in patients without heart failure with respect to exercise tolerance.	We agree that the comparative effectiveness of beta blockers with calcium channel blockers is uncertain and we now highlight this in the evidence gaps for this key question.

Commentator & Affiliation	Section	Comment	Response
TEP #7	Results	For key question two, I agree that the level of evidence supporting lenient vs. strict rate control is weak. This however should not result in strict rate control, since the latter strategy is more difficult to achieve and leads to more drug adverse effects. If we suspend our pre existing biases, the preponderance of the evidence suggests that there is no proven added benefit to strict rate control over lenient rate control which should be the default.	We have modified the rate control section in the Introduction and the Executive Summary.
TEP #7	Results	For key question five, although the authors appropriately address elsewhere in the document the importance of morbidity and mortality and quality of life, in this particularly section (page 38 [ES-30]) there is insufficient attention paid to the most important endpoint in any comparative efficacy trial of any antiarrhythmic drug, which should be first mortality, second morbidity, and third quality of life, and only fourth and last the ability to keep the patients in sinus rhythm. The research gaps sections from page 39 onwards are extremely well done.	We agree with the reviewer's suggestion and we have modified the section as suggested.
TEP #8	Results	The presentation of results especially the diagrams and figures are very helpful. Guidelines are trying to be more algorithm and figure focused so these will be very useful.	Thank you.
Public Reviewer #1 – Edward Greissing, Sanofi	Results	Page 54 [p55] of the review states, "Cardiovascular hospitalization was reported in two studies[108, 113]…." However, neither of the two references cited provides a clear definition of what constitutes a "cardiovascular" event or hospitalization. Forleo et al include hospitalizations as a secondary endpoint, without providing a breakout of those due to CV events versus any other cause. Pappone et al evaluate CV hospitalization, which in their study could have been due to repeat procedures and, therefore, protocol-driven.	Unfortunately, our systematic review is limited in that we must use the information provided by authors within their published articles in terms of the description of outcomes. We therefore assumed all "cardiovascular hospitalizations" as listed by different authors could be grouped as one outcome of interest.
Public Reviewer #1 – Edward Greissing, Sanofi	Results	Our recommendation for the final report is for careful and rigorous methodology to account for and enunciate clearly differences in endpoint definitions between studies. One potential solution is to stratify studies based on a reference comparator that AHRQ feels defined the outcome in the most rigorous framework. Another potential solution is to stratify studies and comparisons by particular components of endpoints, such as "hospitalization for heart failure" or "hospitalization for atrial arrhythmias" within the CV hospitalization framework to avoid the issue of variations in how CV hospitalizations are defined. Furthermore, it would also be helpful to provide the study-specific definitions of such endpoints, and discuss if and how such variations should impact the interpretation of key findings within the CER.	Unfortunately, our systematic review is limited in that we did not have access to the primary datasets for the included studies and as such we are restricted to the information provided in the published literature. This means that categorization of outcomes in to great detail is not always possible and so instead we grouped similar outcomes of interest as appropriate and presented additional details about those outcomes definitions where possible.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 – Edward Greissing, Sanofi	Results	KQ5: We agree with AHRQ's placement of restoration and maintenance of sinus rhythm as an intermediate outcome within the analytic framework. Furthermore, various other endpoints are assessed when addressing Key Question 5. Such endpoints include: quality of life/functional status, CV hospitalizations, AF hospitalizations, all-cause mortaity, and stroke. Therefore the Key Question should present the broader scope of this CER query more accurately, rather than emphasizing only the maintenance of sinus thyrhm. Out recommendation is that Key Question 5 includes an emphasis on patient centered outcomes. Specifically we recommend the following specific text: *What are the comparative safety and effectiveness of newer procedural rhythm-control, other non pharmacological rhythm-control therapies, and pharmacological rhythm-control agents (either separately or in combination with each other) on key patient-centered outcomes for atrial fibrillation patients? Does the comparative safety and effectiveness of these therapies differ among specific patient subgroups of interest?*	The key questions were developed and refined through the topic triage and refinement processes and underwent a public comment period. As such we can not change the wording of the questions at this time. However, we agree that the outcomes of interest in this key question are broader than just maintenance of sinus rhythm and these are reflected in our methods section and in the results sections themselves.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 – Edward Greissing, Sanofi	Results	KQ6: The review states that rate control strategies are superior to rhythm control strategies in reducing CV hospitalizations (high strength of evidence (pES-27). This conclusion is based on 3 randomized controlled trials. [8, 9, 10] However, two of these studies (Petrac 2005 and Brignole 2002) were not rate vs. rhythm studies in the traditional sense (i.e. AFFIRM, RACE, PIAF, HOT CAFÉ), but rather an evaluation of pacing strategies (i.e. VVIR vs. DDDR) after AV nodal ablation (Petrac) and an evaluation of the effects of AADs on AF progression following AV nodal ablation (Brignole). These studies are not applicable to rate vs. rhythm evaluations for the general AF patient population. The third study (STAF)10 does quality as a traditional rate vs. rhythm study. However, per design of such studies, patients assigned to a rhythm strategy in STAF were often hospitalized for cardioversion or for switching to another AAD. Protocol-required adimissions/hospitalizations are quite distinct from unplanned CV hospitalizations which are common in AF management. The AFFIRM investigators addressed this issue specifically and found no difference in CV hospitalizations between rate and rhythm strategies in AFFIRM after censoring for cardioversion and medication switching hospitalizations associated with a rhythm strategy. Out recommendation is for the AHRQ Project Committee to reconsider this evaluation for Key Question 6 given the clinical context of the cited studies and the evidence of protocol-required cardiovascular hospitalizations vs. unplanned hospitalizations.	We do not agree with the reviewer. The study by Brignole et al compared patients who were assigned, after successful atrioventricular junction ablation and pacing treatment, to antiarrhythmic drug therapy with amiodarone, propafenone, flecainide or sotalol with patients assigned, after successful AV junction ablation and pacing treatment, to no antiarrhythmic drug therapy. The study by Petrac et al compared rate control only with atrioventricular node ablation and VVIR pacing with rate control and rhythm control using AVN ablation and DDDR pacing and antiarrhythmic drugs. Both studies meet our inclusion criteria, and in our opinion, should be kept in the analysis.
Public Reviewer #2 – Alice M. Mascette	Results	On p. 50, the fifth bullet (“There are insufficient data on the effect of transcatheter PVI on hard endpoints like all-cause mortality, stroke, heart failure, and LVEF.”) should head the list. If there are not yet hard data supporting the long-term benefit of maintenance of sinus rhythm (in terms of mortality or stroke), then the many examples of differences in therapies in their ability to maintain sinus rhythm should be lower on the list of key points.	The order of the key points matches the order of the outcomes which are discussed in the section (and carried throughout the report). In addition, the data is insufficient for this specific comparison/outcome. We have therefore maintained the current ordering of key points.
Public Reviewer #2 – Alice M. Mascette	Results	A gender difference in efficacy of drugs (but not proarrhythmia) is mentioned on p. 83, but not brought out for specific mention, as it was in KQ4, in the summaries. For consistency, we would suggest treating such differences similarly throughout the KQs.	We have emphasized in the discussion both the limitations of the evidence in subgroups of interest and the need for future research in these areas.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 – Alice M. Mascette	Results	The key points are stated quite well and only show an advantage for rhythm-control strategies in controlling rhythm. The results of the randomized clinical trials cited have not been translated into practice due to interpretations of the methods of the available RCTs (mitigating effects of proarrhythmic side effects of AA drugs, differential use of anticoagulants, analysis of softer endpoints). However, the document would be internally inconsistent to call the risks and benefits unclear in the background section, yet aver the evidence cited in this section.	The purpose of the background section is to highlight the scope of the review and what is known prior to the systematic review itself. As such the uncertainty expressed in the background section is not in conflict with the findings in the subsequent results sections.
Peer Reviewer #1	Summary/ Discussion/ Conclusion	The implications of the major finfdings are clearly stated. The limitations of the review/studies are adequately described. The investigators did not omit in the discussion any important studies. The future research section is clear and easily translated into new research.	Thank you.
Peer Reviewer #3	Summary/ Discussion/ Conclusion	Page 98. Since strict rate control was never evidence based in the first place I would not “alert health care providers to the continued need to achieve strict rate control”. Many clinicians had a Bayesian prior (based on clinical experience) that lenient rate control was just as good as strict rate control. Your data support that prior and appropriately call into question the optimal treatment strategy.	We have modified the rate control section in the Introduction and the Executive Summary.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Summary/ Discussion/ Conclusion	Page 100. It is likely that paddle position will translate into pad position (which is the preferred way to perform cardioversion due to ease of use. You may want to make a comment that the studeis were only using paddles (assuming that is correct).	The use of the term “paddle or pad” can be confusing or misleading and we have taken the reviewer’s suggestion to change the terms to “electrode”. However, when the term “electrode” is first used in the main text we have added a break down of whether the “electrodes” were paddles, pads, etc. in case the reader wishes to have this more detailed information. With regards to use of an alternative placement when the initial placement fails, we have added data from two studies (Alps et al and Kirchhof et al) as these two studies included a crossover within their study protocol or allowed for the crossover. In the study by Joglar et.al, the alternative placement only occurred at the end of a pre-specified sequence. For example, patients randomized to an initial 100J shock would be required to receive subsequent treatments in this order: 200J, 360J, 360J with pressure on pads, then 360 J with alternative position. The results from alternative position are more challenging to interpret given the study procedures and would not necessarily be supportive of trying the alternative approach, but rather trying the alternative approach after numerous other procedures have failed.
Peer Reviewer #3	Summary/ Discussion/ Conclusion	Regarding DC cardioversion there are other research gaps tha may or may not be mentioned. Should one start low Joules and increase as needed or start at high Joules where fewer shocks may be needed.	Note that there was no evidence found in our review to support this practice and we did not specifically target this comparison/outcome in our review. As such, although the topic is certainly of interest it is beyond the scope of our synthesis and we are unable to say whether future primary research is needed in this area versus a systematic review of existing studies. We have therefore not listed this area within the evidence gaps section.
Peer Reviewer #3	Summary/ Discussion/ Conclusion	Should one combine chest pressure with pad conversion to improve the rate of DC cardioversion (done at many centers)?	Note that there was no evidence found in our review to support this practice and we did not specifically target this comparison/outcome in our review. As such, although the topic is certainly of interest it is beyond the scope of our synthesis and we are unable to say whether future primary research is needed in this area versus a systematic review of existing studies. We have therefore not listed this area within the evidence gaps section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Summary/ Discussion/ Conclusion	Is there less post cardioversion bradycardia requiring treatment if rate control agents are held the morning of cardioversion (a common practice)?	Note that there was no evidence found in our review to support this practice and we did not specifically target this comparison/outcome in our review. As such, although the topic is certainly of interest it is beyond the scope of our synthesis and we are unable to say whether future primary research is needed in this area versus a systematic review of existing studies. We have therefore not listed this area within the evidence gaps section.
Peer Reviewer #4	Summary/ Discussion/ Conclusion	Page 37 [=ES-29], lines 45-47: I have rarely heard arguments that carvedilol is superior to metoprolol or atenolol - please cite a reference for this statement, or reword to provide a more convincing justification for KQ1.	This is an argument that comes up frequently in clinical settings, but there are no citations that we are aware of to support this. As such, we have deleted this sentence from the report.
Peer Reviewer #4	Summary/ Discussion/ Conclusion	Page 37 [=ES-29], lines 52&53 - this statement is in direct opposition to the current AHA/ACCF AF guidelines, which state that lenient rate control is acceptable. Please address and justify your difference from current guideline recommendations.	We have modified the rate control section in the Introduction and the Executive Summary.
Peer Reviewer #4	Summary/ Discussion/ Conclusion	Research Gaps section - very good	Thank you.
TEP #2	Summary/ Discussion/ Conclusion	Authors have clearly described the major findings and conclusion of each study reviewed. Additionally, they have performed met analyses of the reviewed literature, where appropriate, to provide more meaningful statistical analyses with more robust conclusions pertaining to the question at hand. Based on this review they have identified areas with gap in knowledge and in need for further research. The need is more obvious for questions pertaining to population subgroups such as old age, patients with heart failure or other associated risk factors.	Thank you.
TEP #3	Summary/ Discussion/ Conclusion	The overarching issue in this literature (aside from KQ2 and 6) is that we are still using intermediate outcomes for most studies rather than measures of health. Comparative efficacy of rate control drugs is a good example. The assumptions that tighter control is better, and that two different drugs with comparable control will produce equivalent outcomes are both bad assumptions. Although the authors do allude to this, I personally think it should be highlighted in research gaps.	We address the limitation of the use of intermediate outcomes (especially recurrence of AF) in the limitations section of the discussion.
TEP #5	Summary/ Discussion/ Conclusion	The authors clearly stated their key findings and provided research gap and limitation of their research for every key questions.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Summary/ Discussion/ Conclusion	There are a few places where the authors state “was moderate strength of evidence” for outcomes such as all-cause or cardiac mortality or stroke, when in fact the 95% CI does include unity and thus there is no conclusive evidence statistically speaking. Suggest stating there is no statistical significance between the two strategies.	We have reviewed the SOE ratings and stand by our ratings as listed. Those confidence intervals which cross unity but which have a summary estimate close to 1 and a precise confidence interval we rate having evidence indicating that “no difference” between the treatments is supported.
TEP #6	Summary/ Discussion/ Conclusion	The discussion was appropriate and the conclusions are resonable. I thought the discussion of the research gaps was reasonably well presented, and it seemed very clear that there were several excellent avenues for further research.	Thank you.
TEP #8	Summary/ Discussion/ Conclusion	The discussion of future research needs is very valuable for guideline developers.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1 – Edward Greissing, Sanofi	Summary/ Discussion/ Conclusion	It is important to consider previous literature evaluating CER in AF. For example, Sanofi recently sponsored a mixed treatment comparison analysis of AADs that was published earlier in Europace. In this analysis, the main anti-arrhythmics used for treatment of AF (amiodarone, dronedarone, flecainide, propafenone, and sotalol) were evaluated on the outcomes of all-cause mortality, stroke, prevention of AF recurrence, withdrawals (all-cause and specifically due to AE), serious adverse events (SAEs), and incidence of proarrhythmic events. Consistent with other reviews, this analysis found a difference in outcomes between anti-arrhythmic drugs, and some evidence of an increased risk of mortality with sotalol and amiodarone. Additionally, Sanofi has also sponsored a more detailed analysis from the AFFIRM trial that evaluated the impact of individual AADs on mortality and CV hospitalization, as well as several secondary endpoints including all-cause hospitalization, non-CV mortality, and length and severity of hospital stay. Using the AFFIRM data, these outcomes were compared among subgroups based on the initally selected AAD in the rhythm-control arm (amiodarone, sotalol, or class IC agent: flecainide or propafenone). Then, these subgroups were compared to propensity score matched subgroups form the rate-control arm. The analysis found that clinical outcomes, particularly CV hospitalization rates, are affected by initial AAD selection. Different AADs were associated with differential risk of nearly all outcomes relative to the rate-control arm. Of not, amiodarone, despite its known superior efficacy for maintaining sinus rhythm compared to other AADs, had a significantly higher rate of mortality plus ICU hospitalization, non-CV mortality, all-cause hospitalization comapred to rate-control and was no better than other initially selected AADs for these patient-centered outcomes. This also further underscored the need to evaluate AADs comprehensively and beyond their effects on cardioversion and maintenance of sinus rhythm. Our recommendation is for the final report to discuss these studies in the “Findings in Relationship to What is Already Known” section on page 108 of the draft report. We believe these studies provide additional context that complements the CER and helps researchers and decision makers continue to build on previously published findings.	We have expanded on the section in the Discussion related to what our findings add related to pharmacological rhythm control therapy. Although we do not specifically cite the mixed treatment comparison study as it is one of many studies emphasizing the uncertainty in the field we do cite the current ACC/AHA guidelines and their similar findings. Regarding the study by Saksena et al using the propensity scored matched subgroups. Because this analysis was not an RCT the study did not meet our inclusion criteria.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2 – Alice M. Mascette	Summary/ Discussion/ Conclusion	Concluding with the statement "This review did find substantial evidence supporting PVI versus antiarrhythmic drugs for reducing AF recurrences in a select subset of patients with AF (those with paroxysmal AF who were younger and with no more than mild structural heart disease) and for a surgical Maze procedure at time of other cardiac surgery as opposed to the cardiac surgery alone in reducing AF recurrences" places a heavy emphasis on the ability of rhythm controlling procedures to decrease recurrence of atrial fibrillation, without equally emphasizing the lack of compelling evidence currently for the benefits of doing so.	The reviewer raises an excellent point. We have modified that conclusion.
Public Reviewer #2 – Alice M. Mascette	Summary/ Discussion/ Conclusion	Although the methods sections include many markers of quality of the cited studies, they do not discuss the difficulty of using recurrence of atrial fibrillation/maintenance of sinus rhythm as an endpoint. For instance, some studies record only symptomatic atrial fibrillation as an endpoint; the degree of monitoring for asymptomatic atrial fibrillation is variable across studies; the periods of observation are often relatively short. No studies to our knowledge have used 100% monitoring devices for this endpoint. Yet studies have also shown the high prevalence of asymptomatic atrial arrhythmias, including in patients under treatment for atrial fibrillation. The endpoint of maintenance of sinus rhythm is easier to achieve the less data one collects. The difficulty with using an endpoint which often goes undetected also argues against the emphasis given in the conclusions section to the results dealing with the maintenance of sinus rhythm.	This is a very good point. We now discuss the limitations of recurrence of AF as an outcome within the limitations section of our Discussion.
TEP #8	Appendix (General)	Helpful for looking up some of the background work.	Thank you.