Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation*

Research Review Citation: Ip S, Terasawa T, Balk EM, Chung M, Alsheikh-Ali AA, Garlitski AC, Lau J. Comparative Effectiveness of Radiofrequency Catheter Ablation for Atrial Fibrillation. Comparative Effectiveness Review No. 15. (Prepared by Tufts Medical Center Evidence-based Practice Center under Contract No. 290-02-0022.) Rockville, MD: Agency for Healthcare Research and Quality. July 2009. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each comparative effectiveness research review is posted to the EHC Program Web site in draft form for public comment for a 4-week period. Comments can be submitted via the EHC Program Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft comparative effectiveness research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. The tables below include the responses by the authors of the review to each comment that was submitted for this draft review.

Section	Comment	Response
Executive Summary	No additional comments submitted.	
Introduction	Page 2, paragraph 5: Style Issue: "These linear lesions include a roof line, posterior line, mitral line…" Although these lesions are comprehensively defined in subsequent sections, at this point a reader unfamiliar with ablation techniques will not understand what these lesions are. Perhaps: "These linear lesions are placed in different regions in the left atrium and may include the posterior left atrium, the roof of the left atrium, the interatrial septum, and the isthmus formed between the mitral annulus and the pulmonary veins/left atrial appendage."	Thank you for the suggestion. It has been incorporated.
Introduction	Some comment on the difficulty of pharmacologic rate control should be mentioned. Perhaps: "…calcium channel blockers, and digoxin. In some cases adequate rate control requires AV nodal ablation and implantation of a permanent pacemaker."	Thank you for the suggestion. A statement to that effect has been added to the introduction.
Introduction	Page 6, Key Question 4, lines 36-40: "Major adverse events associated with RFA are relatively uncommon, overall occurring in less than 5% of patients in most studies. However, it is difficult to compare the rates of adverse events across studies as the descriptions of the various adverse events were not always comparable." I think it is necessary here (and probably elsewhere, as in the discussion about efficacy of catheter ablation) to discuss the time dependent nature of this data. I was thinking about this specifically in terms of PV stenosis, which is essentially impossible in experienced labs, but probably more likely than the quoted statistic in non-experienced labs. The data for safety and efficacy in the future will depend on what kinds of labs are doing the majority of the procedures.	Limitations of evaluation of adverse events have been added to Discussion section
Introduction	Page 8, lines 15,16 "However, implementation of recent guidelines to more aggressively treat hypertension and dyslipidemia in high risk patients may somewhat alleviate the rising prevalence of AF." There is no compelling evidence to support this assertion. It is true that specific medications (ACE inhibitors, statins, beta blockers) may prevent AF onset and/or recurrence in short term follow up, there is no data to suggest that this effect will be sufficiently strong to reduce the population incidence.	This sentence has been deleted.

Section	Comment	Response
Introduction	page 9 refers to "chronic AF" - it would be preferable to clarify that this is now referred to as "long standing persistent AF" as noted later in the document	This has now been clarified by a footnote.
Introduction	Key point #3 could potentially have been addressed by including studies that used 4 mm electrode catheters and studies of techniques that did not include pulmonary vein isolation. I agree that for brevity and clarity with where the field is at present, these can be omitted from this document. But it should be noted that future developments may change AF approaches to some types of AF in the future.	No response necessary.
Methods	Although the investigators' search strategy yielded numerous studies, we question why they did not tap into databases other than the Medline database. One possible database is the Cochrane database. In addition, it is unclear as to whether the investigators considered studies cited in the bibliography of other studies they identified through their search.	We have updated our search including the Cochrane database.
Methods	The collection of data appears to have been guided by the authors themselves, not judged by the independent technical expert panel (TEP). It is unclear whether the investigators decided a priori to exclude prospective or retrospective studies with < 10 subjects per arm, prospective cohort studies with < 50 patients receiving RFA, and retrospective cohort studies reviewed for adverse events with < 100 patients.	It was an a priori decision. It has now been clarified.
Methods	The statistical methods used for combining data on the endpoint of stroke are incorrect. Given the small number of events, the investigators need to either use a Bayesian analysis or the method of exact likelihoods. We refer the investigators to the following citation: A survey of current problems in meta-analysis. Discussion from the Agency for Health Care Policy and Research inter-PORT Work Group on Literature Review/Meta-Analysis. Hasselblad V, Mosteller F, Littenberg B, Chalmers TC, Hunink MG, Turner JA, Morton SC, Diehr P, Wong JB, Powe NR. Med Care. 1995 Feb;33(2):202-20. This report includes best practices regarding the choice of method. We were also confused by the use of risk ratios for other clinical outcomes, when the odds ratios for AF as a predictor of AF recurrence, were also used.	The method of exact likelihoods is no longer considered valid for this particular problem. While Bayesian analysis is acceptable, we chose to use the method suggested by the EPC Guide for Comparative Effectiveness Review. We acknowledge that using both RR and OR in the review might be unclear. However, we felt obliged to report the metrics that were originally reported by the primary studies. We used RR for our own meta-analyses because of relatively high control event rates.

Section	Comment	Response
Methods	The authors need to clarify their statement that "we assigned an overall grade describing the strength of evidence for each key question …" under Rating the Body of Evidence. Additional information on how ratings were obtained and how they were performed should be included. Who performed the ratings? Was the TEP involved? Did all members of the EPC participate? Was consensus reached by vote or other tool?	TEP did not participate in the evaluation of the evidence. Authors responsible for the respective key questions rated the strength of evidence. Differences were resolved by consensus. These points have now been clarified in the text.
Methods	Many important data related to ablation results, adverse effects, and comparison studies were not included in this analysis. Here are some examples of missing data: Example #1 – Missing Data: The A4 study. Here is the citation: Jais P, Cauchemez B, Macle L, et al. Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation: The A4 Study. Circulation. December 9, 2008 2008;118(24):2498-2505.	This study was not yet published in the period of the draft report. This study has been included in the updated search in the final report.
Methods	Example #2 – Missing Data: Very late recurrence was not mentioned in this manuscript. This is an important issue, as indicated in the Heart Rhythm Society's Consensus Document. The original article about this issue was published 2003, by Hsieh MH and Chen SA et al: Clinical outcome of very late recurrence of atrial fibrillation after catheter ablation of paroxysmal atrial fibrillation. Hsieh MH, Tai CT, Tsai CF, Lin WS, Lin YK, Tsao HM, Huang JL, Ueng KC, Yu WC, Chan P, Ding YA, Chang MS, Chen SA. J Cardiovasc Electrophysiol. 2003 Jun;14(6):598-601.	This article was rejected because 4 mm catheter was used.
Methods	Another important article on this issue was published 2007 by Mainigi SK and Marchlinski FE et al: Incidence and predictors of very late recurrence of atrial fibrillation after ablation. Mainigi SK, Sauer WH, Cooper JM, Dixit S, Gerstenfeld EP, Callans DJ, Russo AM, Verdino RJ, Lin D, Zado ES, Marchlinski FE. J Cardiovasc Electrophysiol. 2007 Jan;18(1):69-74.	This article is included in our report.
Methods	Example #3 – Missing Data: According to the most updated analysis from a world-wide survey that included more than 20,000 patients, the 4-mm has almost equal efficacy to the irrigated catheter. This is not reflected in the current analysis.	4-mm studies did not meet our inclusion criteria.
Methods	Example #4 – Missing Data: A February 2008 report with very detailed analysis of the recurrence and adverse rate of the complex fractionated atrial electrogram (CFAE) ablation should be included.	Studies that exclusively targeted CFAE did not meet our inclusion criteria.

Section	Comment	Response
	The relevant citation is: Clinical outcomes of catheter substrate ablation for high-risk patients with AF. Nademanee K, Schwab MC, Kosar EM, Karwecki M, Moran MD, Visessook N, Michael AD, Ngarmukos T. J Am Coll Cardiol. 2008 Feb 26;51(8):843-9.	
Methods	Example #5 – Missing Data: No study compares RFA to an open surgical procedure (limited or otherwise) this is certainly an important question. We think it is necessary to use studies comparing surgical procedure with medications; this will offer us insights into RFA vs. medical therapy for AF. The increased risks/complications involved with a surgical approach are also important to review. This supports the HRS/EHRA/ECAS consensus statement for the limited use of stand-alone AF surgery.	The key questions did not address surgery vs. medications.
Methods	Example #6 - Another concern relates to the misuse of data. Here are some examples: Inaccurate use of two studies used in text and tables: Ref #26: Oral H, Pappone C, Chugh A et al. Circumferential pulmonary-vein ablation for chronic AF. New England Journal of Medicine. 2006;354:934-941. This study was not referenced for the right purpose. This study did not compare the benefits and risks of catheter ablation with those of amiodarone therapy; instead, it reviewed the use of cardioversion therapy. Oral H. et al, concluded that sinus rhythm can be maintained long term in the majority of patients with chronic AF by means of circumferential pulmonary-vein ablation independently of the effects of antiarrhythmic-drug therapy, cardioversion, or both.	We only used those study results that addressed our key research questions and our analytic frameworks. Although we are aware of those data, we did not include them in our analysis on rhythm control because the way the authors analyzed the data did not fit the framework. We agree that this study could be seen as an RCT comparing ablation to observation after cardioversion (i.e., no treatment) since amiodarone was prescribed for only three months in both arms; thus, we have added a sentence detailing the design of this study to highlight this issue.
Methods	Ref #33: Cheema A, Vasamreddy CR, Dalal D et al. Long-term single procedure efficacy of catheter ablation of atrial fibrillation. Journal of Interventional Cardiac Electrophysiology. 2006;15:145-155. There is a poor discussion of recurrence rates of AF. In fact, there is no discussion of asymptomatic versus symptomatic AF recurrences and there are incorrect statements such as the one below: “Cheema et al. reported an atypically high recurrence rate of 63%. (33).” The recently published Thermocool study reported symptomatic AF recurrence rates at 9 months in excess of 45% at most of the centers except one. In fact, more surveillance has unearthed more recurrences; a fact well recognized and not commented upon and with significant bearing on the need to continue anticoagulation in these patients. This may also bear on the quality of life impact	The sentence in Key Question 2 about the “atypically high recurrence rate” was further clarified to state that among the eligible studies (that mostly had recurrence rates of 13-37%), Cheema was atypically high (at 67%).

Section	Comment	Response
Methods	Outcomes of Interest - Pages 14 – 16: Typographical error: consistent style for the bullet points is required. Perhaps all with the first letter capitalized?	We adopted your suggestion. Thank you.
Methods	The methodological decisions to exclusively compare outcomes of catheter ablation for AF with antiarrhythmic drugs, and to only examine outcomes obtained in randomized clinical trials, are not clearly justified.	Please see Methods section. We also included non-randomized comparative studies.
Methods	Nonrandomized study inclusion: The bulk of the evidence demonstrating the effectiveness of RFA for AF, and its effects on cardiac function, atrial size, and quality of life has been published in nonrandomized studies. While we recognize that nonrandomized studies are typically less rigorous than RCTs and generally considered lower in the hierarchy of evidence, it does not follow that nonrandomized studies are completely uninformative. In fact, the data from numerous nonrandomized studies of AF ablation were sufficiently consistent and compelling that many leading centers around the country began to offer AF ablation prior to the completion of any RCTs, and this in turn made recruitment of patients for RCTs quite challenging.	Please see Methods section. We also included non-randomized comparative studies.
Methods	The AHRQ authors report identifying 99 studies that met the criteria of their literature search. Additional studies of potential interest for key question 1 were excluded due to small sample size or use of 4 mm tipped ablation catheters, which were the only RF catheters available in the United States until the early 2000 timeframe. Most if not all of the 99 studies analyzed by the AHRQ authors reported rhythm control as their primary end point, and a number of these reported additional outcomes of interest as defined by question one. The decision, for all of the outcomes in key question 1, to analyze only data reported in 5 RCTs (as well as 2 nonrandomized comparative cohort studies), thus effectively ignores the vast majority of available evidence on these topics. While we have no objection to placing extra emphasis on evidence obtained from the highest quality RCTs, we believe the data reported in many nonrandomized studies are robust and remarkably consistent, and their exclusion from the assessment of procedural efficacy unwarranted.	Please see Methods section. We also included non-randomized comparative studies.

Section	Comment	Response
Methods	High evidence rating if 2 RCTs were graded as Good: As only 1 of the 5 RCTs was graded as good in quality, and evidence was required from 2 good RCTs in order to rate the overall evidence as high, the AHRQ authors conclude that only ?a moderate level of evidence? shows that RFA is superior to medical therapy as a second-line therapy for the maintenance of sinus rhythm. It is possibly noteworthy that the designation of an RCT as good in quality required the reporting of single procedure efficacy in the absence of AADs. Thus, any study that intentionally and transparently used AADs for some period of time following ablation would be rated as less than good	The use of AADs for some restricted period of time after the procedure was not a reason for rating the study less than good, but the outcome measure needed to report the recurrence rate while the subject was off AAD.
Methods	While we agree that more uniform reporting of ablation outcomes is desirable for future studies, we do not believe that a strategy of using AADs and ablation as concomitant therapy is inappropriate or biased, particularly in the setting of a randomized study. In fact, emerging evidence suggests that some period of continued AAD use early after ablation may be desirable, both because some arrhythmias occurring early after ablation subside after inflammation from the ablation itself resolves, and possibly because maintenance of sinus rhythm in this timeframe facilitates electrical remodeling. (1,2) The reasons why 4 of the 5 RCTs were graded as fair or poor in quality were not enumerated in the report.	Please see above response. Details regarding quality rating can be found in the evidence tables. A sentence has been added to explain the quality ratings of the studies.
Methods	April 2008 search cut-off date: Since the authors literature search in April 2008, at least 3 additional RCTs of RFA for AF have been published or presented in a public setting - 2 RCTs published in the peer reviewed literature (3,4) and another presented at a public FDA advisory meeting on November 20th, 2008.(5) Incorporation of data from these 3 randomized studies between RFA and AAD therapy as second-line therapy for paroxysmal AF could significantly alter the conclusions of this comparative assessment on several aspects of the report conclusions, in particular those cited for key question 1. Specifically, we believe the rating of the overall evidence showing the superiority of RFA, as compared with AAD, for the maintenance of sinus rhythm as a second-line therapy for AF would be upgraded to high, and that this is the more appropriate conclusion based on the published literature. We recognize that the AHRQ authors had to select a cut-off date for their systematic literature review; however, because there is	This study has been rejected because it used 4 mm standard catheter tip, which is one of our exclusion criteria.

Section	Comment	Response
	significant ongoing research on the topic, the authors should include the important data that has been recently published or presented publicly subsequent to the April 2008 cut-off date to present a more accurate picture of the current knowledge regarding RFA for AF. References: 1. Oral H, Knight BP, Ozaydin M, et al. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. Journal American College of Cardiology 2002; 40:100-4.	
Methods	2. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. Heart Rhythm 2007; 4:816-861.	The consensus statement is referenced in the report.
Methods	3. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: The A4 Study. Circulation 2008; 118:2498-2505.	This study is included in our update search.
Methods	4. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. New England Journal of Medicine 2008; 359:1778-85.	This study has been excluded since it compared PV ablation to AV nodal ablation followed by pacemaker placement, which is not addressed in our key research question
Methods	5. U.S. Food and Drug Administration. Circulatory Devices Panel Meeting: Briefing Information. 2008. Available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-00-Index.html. Accessed December 11, 2008.	We only included studies published in peer-reviewed journals.
Methods	Note that the search criteria were restricted to RF ablation. There will be increasing information regarding other energy sources in the future.	No response needed.
Methods	page 14: Arrhythmia outcomes were excluded during the blanking period. However, there are important events that may occcur during this period that might influene cost benefit of the technique, such as hospitalizaitons and cardioversions; these should presumably be included - this also applies to page 21, table 7.	We did not exclude information on hospitalizations and cardioversions during the blanking period. The arrhythmia outcomes that were not excluded in the studies were related specifically to AF or atrial tachyarrhythmia recurrence.
Methods	Mortality should be included in the key questions – although it can not be answered at present. I am not qualified to judge the statistical methods.	Even though the term “mortality” was not included in the key questions, results included “mortality” if such data were reported.

Section	Comment	Response
Results	RFA versus medical/surgical therapy (Table 1) Page 19, para 4: "The methodological quality of one study was good, three studies were fair, and one study was poor." This sentence needs references. In addition, information on methodological quality should be placed in Table 1 rather than Table 2 or alternatively, methodological quality should be discussed in the next section where Table 2 is reviewed. Since these seven studies form the cornerstone for data on AF ablation, a separate Table on the specifics of how the Quality Ratings were obtained would be very useful to the reader.	A sentence has been added to explain the quality ratings of the studies. Details regarding quality rating can be found in the evidence tables in the appendix. In our opinion, quality rating is better juxtaposed in the Results section.
Results	The tables need to be formatted appropriately; For example, center "Results" over (Interv, control, and P between) in all tables. The tables need to be reviewed: Table 10: What study does the * refer to? "Error, bookmark not defined" in Table 17.	Thank you for pointing out. These errors have been corrected.
Results	We believe inclusion of the nonrandomized studies examining sinus rhythm maintenance with RFA is warranted in the AHRQ report. For illustration, we will summarize the results of a meta-analysis presented at the AHA 2008 meeting, which included both randomized and non-randomized studies.(1) Using different search criteria, this study identified 63 ablation studies involving nearly 8800 patients. The meta-analyzed single procedure success rate of RFA off AAD was 57% (95% CI 50%-64%), the multiple procedure success rate off AAD was 71% (95% CI 65%-77%), and the multiple procedure success rate on AAD or with unknown AAD usage was 77% (95% CI 73%-81%). These success rates agree with those in the RCTs reviewed by the authors, and appear to be substantially higher than what would be expected with AADs in a second-line setting.	Please see response to this comment in previous section.
Results	At least 3 additional RCTs of RFA for AF have been published or presented since the AHRQ literature search. Two of these studies randomized RFA and AADs as second-line therapy for paroxysmal AF. One study included 112 patients.(2) Using a strict definition of AF recurrence ? any episode lasting >3 min. after up to 3 ablation procedures or changes in drug therapy within the first 3 months ? the reported success free of recurrent AF between months 3 and 12 was 89% and 23% with RFA and AADs, respectively. The rate of crossover (after AF recurrence) in patients initially randomized to AADs was 63%. In November, results from a randomized trial of a similar patient population were presented at the AHA meeting, and to an FDA	We included only studies published in peer-reviewed journals. The Jais article was published after the draft report and has been added to the update.

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	advisory panel. Although these data have not yet been published in peer-reviewed form, it is noteworthy that the FDA advisory panel unanimously recommended the THERMOCOOL study catheter for approval. In this study, which allowed for concomitant AAD use with a previously ineffective drug after RFA, the reported freedom from symptomatic AF was 75% in the RFA group and 21% in the AAD group. We recommend that the results from both of these studies be included in the assessment. If this is done, we believe the rating of the overall evidence showing the superiority of RFA, as compared with AAD, for the maintenance of sinus rhythm as a second-line therapy for AF would be upgraded to ?high?, and that this is the more appropriate conclusion based on the published literature.	
Results	Rates of congestive heart failure: We agree that there is limited evidence on the use of RFA in patients with CHF; however, we believe the authors failed to review pertinent nonrandomized evidence regarding potentially beneficial effects of RFA in patients with structural heart disease and/or established heart failure (HF). At least 2 nonrandomized studies, each including >50 ablation subjects, have assessed the impact of RFA in the setting of HF and/or reduced LV systolic function. Hsu et al.(4) reported results following RFA in 58 patients with HF symptoms and reduced LV systolic function (LVEF).	Non-comparative single-arm studies did not meet our inclusion criteria for this question
Results	Most recently, the Pulmonary Vein Antrum Isolation vs. AV Node Ablation with Bi-Ventricular Pacing for Treatment of AF in Patients with Congestive Heart Failure (PABA-CHF) trial randomized 81 patients to RFA with the intent of sinus rhythm maintenance or implantation of a biventricular pacing device following RFA of the AV junction.(6) Of the patients randomized to ablation, 78% and 88% were in sinus rhythm with or without the use of AADs at 3 and 6 months, while all of the patients randomized to biventricular pacing remained in AF. At 6 months, patients assigned to ablation, compared with those assigned to biventricular pacing, had higher EFs	We have excluded studies on AV nodal ablation.

Section	Comment	Response
Results	Left atrial and ventricular size: The authors report that no RCT compared LAD or LVEF in patients treated with RFA vs. medical therapy. They do discuss changes in LAD and LVEF reported from 1 RCT based on comparison between ablation patients who did and did not maintain sinus rhythm.(7) Very few patients in that study maintained sinus rhythm with medical therapy alone. Similar findings from a nonrandomized cohort study were also reviewed.(8) The authors conclude that there is insufficient evidence to compare changes in left atrial or left ventricular size between RFA and medical treatment. One randomized and at least 4 nonrandomized studies have reported reductions in chamber dimension and/or improvements in LVEF following RFA in patients with pre-existing LV systolic dysfunction. The studies by Hsu et al. and Chen et al. both assessed LVEF before and after ablation.(4,5) In the Hsu series, the LVEF and fractional shortening increased by 21±13% and 11±7% (absolute changes), respectively, from baseline to 12 months (P In the recently published A4 trial, ablation patients had minimal changes from baseline to 12 months in mean LAD (39.5 to 38.7 mm), LV end-diastolic dimension (51.9 vs. 50.0 mm) or LVEF (63.1 vs. 65.4%).(2) Based on the above we believe there is moderate evidence that RFA, particularly when sinus rhythm is successfully maintained, is associated with reduced LAD and improved LVEF in patients with pre-existing chamber dilation and reduced LVEF.	We described the results from the Oral 2006 in that section because this is the only available data from RCT regarding this issue acknowledging that it is not a direct comparison between RFA and medical treatment but before-after comparison within RFA arm. Now that we have included the A4 study (Jais et al. 2008), which has the relevant direct comparison, we deleted the Oral 2006 from both text and Table. Non-comparative single-arm studies did not meet our inclusion criteria for this question.
Results	In response to Key Question 1, the Draft Review described the analysis based on five RCTs and two retrospective cohort studies of patients with AF that compared RFA with medical treatment. Since this analysis was conducted, an additional study has been released that would be relevant to include by Jais et al., published in Circulation earlier this month. It concluded that AF ablation was superior to anti-arrhythmic drugs in paroxysmal AF patients, helping them maintain sinus rhythm, improve symptoms, exercise capacity, and quality of life.	This study is included in our update search.

Section	Comment	Response
Results	We agreed with the majority of the conclusions reached in Key Question 1, but disagreed with two of them. First, we believe there is sufficient evidence regarding the impact of catheter ablation on left atrial and ventricular function and dimensions. Second, while there are insufficient data on anticoagulation therapy, we recommend the Draft Review acknowledge the standard of care that has been established and recognized globally. Four studies, included in the list of references of the Draft Review but perhaps not examined for this particular question, examined left atrial size prior to and following catheter ablation for the treatment of atrial fibrillation. These studies found a 10-20% decrease in LA dimensions, in patients treated with catheter ablation for the treatment of AF, although the actual mechanism of how and why this occurs is unknown. In addition, left ventricular function and dimension improvements have also been observed in several studies; approximately a 20% improvement was seen in LV ejection fraction in comparing pre- and post-ablation measurements in patients with and without LV impairment at baseline. Similar results were reported by Oral10 and Tondo11 in 2006. However it should be noted that the patient populations included in these studies referenced for cardiac chamber dimensions were treated with catheter ablation and not compared to patients treated with medical management. This may have been why the Draft Review, if they examined them for these outcomes, considered the results of them insufficient evidence.	With regard to the "standard of care" of anticoagulation post RFA, we reference the consensus document in our report. It is not the role of this comparative effectiveness review to acknowledge or endorse any professional recommendations.
Results	In addition, while we agree there are insufficient data to compare the rates of avoiding anticoagulation between RFA and medical treatment, there is an established standard of care being practiced today. We recommend the Draft Review recognize that a standard of care has been established and defined by two sources included in the Draft Review references: the American and European ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation and the 2007 global expert consensus: HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow Up.	We do not make standard of care recommendations in an evidence review.
Results	We found the list of studies reviewed in Key Questions Two, Three and Four to be quite extensive and we know of no other studies that would be relevant to add here. In addition, we found the conclusions drawn to be appropriate. We appreciate how Key Question 3 was	Thank you.

Section	Comment	Response
	phrased because we believe that by reviewing the literature based on type of technology and approach used, the authors were able to conduct a more precise analysis of the effect of RFA in different situations.	
Results	Although you allude to this in your methods section, I think it is important to emphasize the vast differences in monitoring for asymptomatic AF recurrence when efficacy is considered.	This limitation has been added to the Remaining Issues/Future Research section.
Results	Page 32. With regard to operator/hospital experience and complications, I think it is potentially misleading to focus entirely on published data (i.e. this subselects only those operators who publish, likely to be more talented and experienced than the general population). To this end, even though it is statistically flawed, it may be reasonable to compare published controlled data to survey data, which at least allows response from a greater proportion of practitioners to provide contrast.	We only used data from primary studies published in peer reviewed journals in this report.
Results	In general, the limitation of the available studies were not completely discussed (except statistically). Limitations such as lack of monitoring, inconsistent treatment of repeat procedures and use of medications were not always discussed.	These limitations have been added to the Remaining Issues/Future Research section.
Results	pg 23 - patient level characteristics. You note that all studies found no relation of age to AF recurrence. I believe this points out a potential recruitment bias that is present in AF studies. Specifically that older patients who are selected or agree to participate in these relatively small trials are generally at the healthy end of the spectrum. They are by no means a consecutive series of patients. This is an important issue since the majority of the AF population is elderly. In Key question 2 - patient level factors - age has very important implications. This comment also applies to page 34: Key Question 2.	The reviewer makes an important point. We have looked at the ranges of age, ejection fraction, and LA diameter across studies, including the threshold used in multivariable analyses when these variables were dichotomized. Based on this information we have added descriptions of these ranges that act as caveats to the findings. The conclusions have been limited to the appropriate ranges of age, EF, and LAD.
Results	page 24: The final conclusion regarding recurrence and types of AF needs to be clarified in each paragraph to indicate which of the two groups has the greater risk of recurrence	Thank you for pointing this out. We agree and have made the edits wherever the HR or RR data were reported.
Results	page 32: The statement: "rates of cerebrovascular events ..4% or less.." is accurate but is potentially misleading as the risk in many studies is now 3-4x less. This is likely related to better anticoagulation regimens in the past 5 years. You should provide a better indication of estimated risk; perhaps the overall risk from pooling all studies, or compare studies in the first 4 yrs and last 4 yrs	Newer studies appear to have reported lower adverse event rates than older studies particularly on PV stenosis and strokes; however, we respectfully disagree with the suggestion to pool all studies. There is clear heterogeneity among study design, sample size, patient characteristics, technologies and techniques of ablation, supportive interventions as well as definitions of adverse events adopted across the studies; therefore,

Section	Comment	Response
	of the data collection period.	providing pooling estimates without taking account of these factors would be even more misleading. We have described the range and median of reported rates across the studies that assessed each particular adverse event, avoiding arbitrarily selected point estimates such as 4% and less in order to provide a better risk profile.
Results	page 36 in the discussion of 8 mm vs irrigated: although there is not evidence for differences in outcomes, there is a general feeling in the EP community and animal data that the risk of thromboembolism, and perhaps esophageal injury, is greater with the 8 mm catheter and many centers have stopped using it. Consider looking at this issue.	We only examined data from studies that met our eligibility criteria.
Figures	No additional comments submitted.	
Tables	No additional comments submitted.	
References	No additional comments submitted.	
Discussion	Rhythm Control: "There is a moderate level of evidence to show that patients who received RFA as a second-line therapy had a higher chance of maintaining sinus rhythm compared with those treated with medical therapy alone" needs to be modified to reflect the duration of follow-up in the randomized clinical trials. We suggest changing it to: "there is a moderate level of evidence to show that patients who received RFA as a second-line therapy had a higher chance of maintaining sinus rhythm at 12 months compared with those treated with medical therapy alone."	Your suggestion has been adopted. Thank you.
Discussion	Rates of Stroke: "There is a moderate level of evidence to show that there was no statistically significant difference in the risk of cerebrovascular events at 12 months in patients who underwent RFA compared to those treated with medical therapy". Given the small number of patients included in the randomized clinical trials of RFA AF and the very small number of strokes that occurred during the short follow-up, those studies had no statistical power to show a significant difference in the risk of stroke. We suggest changing "moderate level" to "low level".	Your suggestion has been adopted. Thank you.

Section	Comment	Response
Discussion	Avoiding Anticoagulation: "No studies directly compared freedom from anticoagulation in patients treated with RFA versus medical therapy." Studies have evaluated the consequence of stopping anti-coagulation following conversion to sinus using medications and surgical interventions. These data should be included.	We have included the A4 study (Jais et al. 2008), the relevant results of which have been added to this section.
Discussion	Readmissions: "There is low level of evidence to suggest that findings on differences in readmission rates between patients treated with RFA and those treated with antiarrhythmic medications (AADs) are inconsistent." This is a very confusing sentence. We suggest changing it to: "There is low level of evidence on differences in readmission rates between patients treated with RFA and those treated with AADs."	Your suggestion has been adopted. Thank you.
Discussion	Ejection fraction (EF) and left atrial diameter (LAD): "There is a moderate level of evidence that EF and LAD are not independent predictors of AF recurrence." Only patients with mildly enlarged left atria were included in the randomized clinical trials of AF RFA (these patients also make up the majority of patients who undergo this procedure in routine clinical practice). Indeed, the average left atrial diameter in randomized clinical trials of AF RFA ranged from 3.9 to 4.6 cm and in 4 out of the 6 published trials, the average left atrial diameter was ≤ 4.2 cm. Likewise, these trials did not enroll patients with a low EF, and indeed an EF < 35% was an exclusion criterion in at least 2 of the 6 published randomized clinical trials. Thus, the conclusions about the LAD and EF are not supported.	The reviewer raises an important caveat. We have added descriptions of the ranges of EF and LAD across studies, and have added resultant caveats to the conclusions.
Discussion	Age, sex and the presence of structural heart disease: "There is a high level of evidence that age, sex, and the presence of structural heart disease are not associated with AF recurrence". We do not agree with this statement: First, this does not address the relationship of structural heart disease and AF progression. This issue was the focus of the following citation: Saksena S, Hettrick DA, Koehler JL, Grammatico A, Padeletti L. Progression of paroxysmal atrial fibrillation to persistent atrial fibrillation in patients with bradyarrhythmias. Am Heart J. 2007 Nov;154(5):884-92. Saksena S. et al review the epidemiological and natural history study of AF using implantable devices that are absent from the analysis. Second, the AHRQ document does not adequately convey facts about these factors and AF recurrence. The average age of patients enrolled in the six published randomized clinical trials of AF RFA ranged from 51 to 62 years of age and the % of women ranged from 12 to 41%. Although men have a 1.5x greater risk of developing AF	We have also added the ranges of ages across studies and the resultant caveats. Regarding structural heart disease and sex, however, it is important to remember that our conclusions are based on the evidence from the eligible studies. We do not stray into theoretical or indirect evidence. The studies found little or no association between presence of structural heart disease and recurrence rates. The percent of women in the studies are high enough for the findings from the studies about the effect of sex on recurrence rates to be valid. Regarding Saksena et al, this review does not attempt to review the evidence of the epidemiology of AF or its natural history. Whether structural heart disease is associated with progression to AF in theory or in fact is a moot point regarding the question of the predictors of recurrence of AF after RFA. To answer the key questions we rely on the empirical data that most closely address the question of interest. Women have been added to the list of under-represented groups ripe for

Section	Comment	Response
	than women, overall, women account for 53% of patients with this arrhythmia in the U.S. Thus, older patients, women and patients with structural heart disease need to be well-represented in future studies.	future research, including the elderly, those with low EF or large LAD, and people with multiple comorbidities.
Discussion	Adverse effects: "There is a moderate level of evidence to show that adverse events associated with RFA are relatively uncommon….based on the study description, we surmised that most of the adverse events either took place in a peri-procedural time frame or shortly after being discharged home post-procedure." While this statement is true during short-term follow-up, one could argue that data on long-term adverse effects of this procedure are lacking. Not only were the randomized clinical trials of AF RFA limited to 12 months, but data on some important endpoints, such as the effects of prolonged radiation exposure, remain unknown. These long-term adverse events need to be explored in future studies. In addition, we were surprised that retroperitoneal bleed, pulmonary embolus, pulmonary damage, and LA thrombus on echo (not causing thromboembolic events) are not listed, did they just not occur in these studies?	The issue raised has been incorporated into the Discussion section. In consultation with TEP, we only collected the most common major adverse events in our evidence tables.
Discussion	Regarding Key Question 1: The AHRQ authors conclude that there is a low level of evidence to suggest that RFA improves quality of life (QoL) compared to medical treatment. Presumably this conclusion is based on the fact that none of these studies were graded as good in quality. The AHRQ authors also elected not to review any nonrandomized evidence on the subject. Nonrandomized studies of AF ablation that measured QoL outcomes were reviewed earlier this year.(1) This review article, which did not follow formal search criteria, identified 7 nonrandomized studies of AF ablation that reported QoL outcomes. Two of these were not studies of pulmonary vein isolation and will not be discussed further.(2,3) Two of the remaining 7 studies examined QoL specifically in patients with heart failure as discussed previously.(4,5) Both of these studies showed quite large improvements in SF-36 scores, with physical and mental summary scores increasing by over 20 points in one study (6), and many individual subscale scores more than doubling in the other.(7) In addition, the study by Hsu et al. also showed significant reductions (improvement) in AF Symptom Checklist scores. Of the 3 remaining nonrandomized studies described in the review article by Reynolds et al., one was the same cohort study discussed	We do not use results from review articles in this systematic review. We have now included the A4 study (Jais et al. 2008) identified from our update search, the relevant results of which have been added to this section. The other two studies did not meet our inclusion criteria.

Section	Comment	Response
	in the draft AHRQ report (8), one was a study included in the assessment of safety outcomes (key question 4) but not otherwise discussed, (5) and the other was excluded from the AHRQ systematic review because it enrolled fewer than 100 patients.(9) The latter two studies enrolled 63 and 105 patients, respectively, and both measured quality of life before and after ablation using the SF-36. One of the studies also used the AF symptom checklist questionnaire. Both studies reported large and statistically significant improvements in SF-36 scores (over 30 point changes for both role physical and bodily pain scales in one) following ablation. It is worth noting that the changes in QoL scores described in Table 6 of the draft report as well as in the studies reviewed above were easily large enough to be considered clinically meaningful, and in general were 2-3 times larger than QoL changes seen in several randomized AAD trials.(10,11,12) We believe the nonrandomized evidence showing large and consistent improvements in QoL following RFA for AF in the 4 studies discussed above (5,6,7,9) should be added to this AHRQ assessment. There have been 3 RCTs published or reported since April 2008 that included QoL end points.(13,14,15) In the ablation group of the randomized A4 study (13), the physical and mental component scores of the SF-36 improved by 7.2 and 9.7 points, respectively, from baseline to 12 months. At 12 months, the physical and mental summary scores were statistically significantly higher in the RFA group than the AAD group (p=0.01), as were 6 of the 8 SF-36 subscales ? this despite the fact that an intention to treat analysis was reported and 63% of the patients randomized to drugs later crossed over to ablation. The randomized trial recently reported to the FDA measured the same QoL endpoints, and produced similar results where in subjects treated with the NAVISTAR THERMOCOOL Catheter (open irrigation), the SF-36 mental summary scores increased from 7.7 ? 9.8 points 3, 6, and 9 months after the study?s blanking period, and physical summary scores increased by 5.2 ? 6.7 points.(15) Finally, the PABA-CHF trial assessed QoL using the Minnesota Living with Heart Failure.(14) In the PVI group, mean scores improved from 89±12 at baseline to 60±8 at 6 months (lower scores better on this survey). Based on our review of currently available evidence, we believe there	

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	is at least a moderate, and possibly a high level of evidence to indicate that QoL improved to a greater extent after RFA than with AADs (or AV junction ablation and biventricular pacing) in the context of second line therapy.	
Discussion	References: 1. Reynolds MR, Ellis E, Zimetbaum P. Quality of life in atrial fibrillation: measurement tools and impact of interventions. Journal Cardiovascular Electrophysiology 2008; 19:762-768. 2. Erdogan A, Carlsson J, Neumann T, et al. Quality-of-life in patients with paroxysmal atrial fibrillation after catheter ablation: results of long-term follow-up. Pacing Clinical Electrophysiology 2003; 26:678-84. 3. Goldberg A, Menen M, Mickelsen S, et al. Atrial fibrillation ablation leads to long-term improvement of quality of life and reduced utilization of healthcare resources. Journal Interventional Cardiovascular Electrophysiology 2003; 8:59-64. 4. Gentlesk PJ, Sauer WH, Gerstenfeld EP, et al. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. Journal of Cardiovascular Electrophysiology 2007; 18:9-14. 5. Tondo C, Mantica M, Russo G, et al. Pulmonary vein vestibule ablation for the control of atrial fibrillation in patients with impaired left ventricular function. Pacing Clinical Electrophysiology 2006; 29:962-970. 6. Hsu L-F, Jais P, Sanders P, et al. Catheter ablation for atrial fibrillation in congestive heart failure. New England Journal of Medicine 2004; 351:2373-2383. 7. Chen MS, Marrouche NF, Khaykin Y, et al. Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. Journal American College of Cardiology 2004; 43:1004-1009. 8. Pappone C, Rosanio S, Augello G, et al. Mortality, morbidity, and quality of life after circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long-term study. Journal American College of Cardiology 2003; 42:185-97. 9. Weerasooriya R, Jais P, Hocini M, et al. Effect of catheter ablation on quality of life of patients with paroxysmal atrial fibrillation. Heart Rhythm 2005; 2:619-623. 10. Dorian P, Paquette M, Newman D, et al. Quality of life improves with treatment in the Canadian Trial of Atrial Fibrillation. American Heart Journal 2002; 143:984-90.	We have checked the references provided above with our included and excluded list of studies. References #4-8 were included in our draft report, and references #13-14 have been included in our final report through update literature search. The following are the reasons for exclusion for other references: Reference #1 is a review article summarized studies presenting quality of life outcomes in patients received various AF intervention. We do not include review article in our report. References #2-3 were excluded from our report due to the sample size less than 50. Reference #9 was excluded from our report because it was a cohort study with a sample size less than 100. References #10-12 were not included in our report because the AF interventions were not RFA. Reference #15 was not included in our report because it is an unpublished study.

Section	Comment	Response
	11. Singh SN, Tang XC, Singh BN, et al. Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation. Journal American College of Cardiology 2006; 48:721-730. 12. The AFFIRM Investigators. Quality of life in atrial fibrillation: the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. American Heart Journal 2005; 149:112-120. 13. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: The A4 Study. Circulation 2008; 118:2498-2505. 14. Khan MN, Jais P, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. New England Journal of Medicine 2008; 359:1778-85. 15. U.S. Food and Drug Administration. Circulatory Devices Panel Meeting: Briefing Information. 2008. Available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-00-Index.html. Accessed December 11, 2008.	
Discussion	As stated previously, results from a trial randomizing RFA and AAD therapy for paroxysmal AF patients were presented in November at the AHA 2008 meeting, and to an FDA advisory panel.(1) Biosense Webster conducted a prospective clinical study of the NAVISTAR THERMOCOOL Catheter (open irrigation) for the treatment of the drug refractory symptomatic paroxysmal AF. The study met its primary effectiveness endpoint, namely superior effectiveness of AF ablation with the THERMOCOOL Catheter compared to AAD treatment, with a 95% probability that the treatment difference is 31% - 58% in favor of THERMOCOOL Catheter ablation. Using Bayesian methodology, the posterior mean probability of success is 0.627 ± 0.048 for the NAVISTAR THERMOCOOL group and 0.172 ± 0.049 for the AAD (Control) group. The 95% credible interval for the difference between the THERMOCOOL and AAD (Control) probabilities of success is 0.313 to 0.584, with a median difference of 0.457. - The effectiveness evaluation in this study utilized a conservative definition for the chronic effectiveness endpoint, in which more than freedom from documented symptomatic AF recurrence was required to be adjudicated a chronic success. - For the THERMOCOOL group, any of the following resulted in the subject being adjudicated as a chronic effectiveness	We only included studies published in peer-reviewed journals.

Section	Comment	Response
	failure, irrespective of symptomatic AF recurrence: AAD failure (the addition/increased dose of AADs, including Class I and Class III antiarrhythmic drugs, beta blockers, and ACE inhibitors), repeat ablation after day 80, or acute procedural failure. - It is important to note that AV nodal blocking agents were formally considered AADs when prescribed for AF, even though recent ACC/AHA/ESC guidelines have clarified that their principal role in the treatment of atrial fibrillation is to achieve ventricular rate control, and not for AF prevention. This adjudication rule was added at the time the protocol was amended to permit enrollment of subjects who had only failed AV nodal agents as Class II/IV agents may affect symptoms (e.g., palpitations). In fact, 9% (9/103) of the THERMOCOOL subjects were adjudicated as chronic failures solely due to use of an AV nodal blocking agent/ACE inhibitor, or late repeat ablation in the blanking period, in the absence of symptomatic AF recurrence. - Symptomatic AF recurrence was assessed via transtelephonic monitoring (TTM). TTMs were collected, analyzed and adjudicated using a 3-step review process that helped to ensure the highest possible rigor for detection of AF recurrence. TTM compliance was excellent in the study (88.8% ±16.0). The full proceedings of the advisory committee meeting and study sponsor slide presentation including a summary of the safety and effectiveness data are available at http://www.fda.gov/ohrms/dockets/ac/cdrh08.html#circulatory. A copy of the study sponsor's FDA executive summary and panel pack provided to the committee including the clinical trial data are available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-00-Index.html. References: 1. U.S. Food and Drug Administration. Circulatory Devices Panel Meeting: Briefing Information. 2008. Available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-00-Index.html. Accessed December 11, 2008.	

Section	Comment	Response
Discussion	Regarding Key Question 2: The AHRQ authors stated that there is a low level of evidence that AF type, namely non-paroxysmal AF, is predictive of a higher rate of AF recurrence. To add to the evidence in this regard, most randomized trials of ablation for treatment of atrial fibrillation primarily enrolled patients with the paroxysmal form of this condition. As a result this statement is based largely on non-randomized studies. Most studies used multivariate logistic regression as opposed to time to event analysis in drawing their conclusions. While valid, this analysis makes it difficult to assess whether duration of freedom from atrial fibrillation and arrhythmia burden following ablation differ in patients presenting with various subtypes of AF. That said, non-paroxysmal atrial fibrillation was significantly associated with AF recurrence.	The conclusions are clearly and explicitly based on the evaluated studies. Patients cannot be randomized to AF type, so RCT data is not necessarily more pertinent to answer this question. Most studies reported hazard ratios, implying at least a time to event analysis, though granted studies often failed to adequately report their methods. We would have used stricter criteria if we were trying to answer whether the duration of AF-free survival differed. True, nonparoxysmal AF was significantly associated with recurrence in crude analyses that completely ignored time to events, but these were not sufficiently supported by the multivariable analyses. This section has been partly rewritten to further clarify our logic in reaching our conclusions.
Discussion	The AHRQ authors stated that there is a moderate level of evidence that ejection fraction (EF) and left atrial diameter (LAD) are not independent predictors of AF recurrence. While this finding is generally supported in the literature, one must be cautious about the data used in the analysis. Few if any studies contributing data to this assessment used MUGA/RNA testing to estimate ejection fraction, tests considered by many to represent the gold standard in estimating EF. Most studies relied on semi quantitative analysis of echocardiographic data, typically without a core lab used to verify accuracy of the data. Finally, estimation of EF may have been made difficult by the virtue that many patients may have had atrial fibrillation at the time of EF assessment, a factor known to interfere with an accurate EF estimate. The same concerns apply to LA dimensions. Most studies would have used LAD from parasternal short axis ECHO-images as opposed to a more precise LA volume index. A recently published RCT found higher EF associated with better outcomes (OR 1.1, p=0.02).(2) References: 1. Khaykin Y, et al. Factors Predicting Success And Failure Of Catheter Ablation For Atrial Fibrillation: A Multivariate Analysis. Presented at the 60th Annual Meeting of the Canadian Cardiovascular Society, October 2007, Quebec City, Canada 2. Jais P, et al. Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation: The A4 Study. Circulation 2008;	Since Doppler EF is the standard method to clinically measure EF and this is the method that was used in all or almost all relevant studies, we consider this a moot point. Jais 2008 has been added to the analysis. Its weak association between EF and recurrence did not alter conclusions. We included only peer reviewed published studies; therefore the Khaykin presentation was not included.

Section	Comment	Response
	118;2498-2505	
Discussion	Regarding Key Question 3: Although this review concluded that the outcomes of AF ablation are similar when using an 8 mm ablation catheter compared to an irrigated ablation catheter, it is important to recognize that most centers throughout the world now employ open irrigated ablation catheters for ablation of AF. The use of 8 mm ablation catheters has fallen dramatically because of two factors. First, most of the esophageal fistulas, which have been reported in the literature, employed 8 mm catheters and second, the small electrode size used in irrigated ablation catheters allows for more precise electrogram mapping. This is reflected in the HRS Consensus document, which stated, ?the majority of the members of the Task Force now employ irrigated tip catheters?.(1) The authors of the AHRQ assessment concluded that ablation outcomes with an 8 mm tip catheter were similar to an irrigated tip catheter based on their examination of data from three pilot studies, which compared the outcomes of 8 mm catheters to trials, which used irrigated tip catheters.(2,3,4) It is important to note that the studies differed in the types of irrigated catheters employed or power output used. Dixit et al compared the outcomes of an 8 mm ablation catheter to ablation with a closed loop ablation catheter, with no difference in outcome noted.(2) One patient who underwent ablation with an 8 mm catheter developed an esophageal fistula. Kanj et al compared the outcomes of ablation with an open irrigated catheter with high and lower power output to ablation with an 8 mm ablation catheter. (3) No difference in efficacy was observed with an open irrigated catheter using high power compared with an 8 mm tipped ablation catheter. Marrouche et al. compared high-energy ablation with an open irrigated catheter with an 8 mm ablation catheter with no difference in efficacy noted.(4) References: 1.) 1. Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. Heart Rhythm 2007; 4:816-861.	In an evidence report, we only summarized data from published studies that met our eligibility criteria. The type of catheter (open or closed irrigated) and power settings used in the trials mentioned above are described in the results section of the comparative effectiveness review.

Section	Comment	Response
	2.) Dixit S, Gertensfeld EP, Callans DJ et al. Comparison of cool tip versus 8mm tip catheter in achieving isolation of pulmonary veins for long-term control of atrial fibrillation: a prospective randomized pilot study. Journal Cardiovascular Electrophysiology, 2006; 17:1074-1079. 3.) Kanj MH, Wazni O, Fahmy T et al. Pulmonary Vein antral isolation using an open irrigation ablation catheter for the treatment of atrial fibrillation: a randomized pilot study. Journal American College of Cardiology, 2007; 49:1934-1641. 4.) Marrouche NF, Guenther J, Segerson NM et al. Randomized comparison between open irrigation technology and intracardiac-echo-guided energy delivery for pulmonary vein antrum isolation: procedural parameters, outcomes and the effect on esophageal injury. Journal Cardiovascular Electrophysiology, 2007; 18:583-588.	
Discussion	Regarding Key Question 4: We agree with the majority of conclusions on short and long-term safety of RFA made by the AHRQ authors. However, because the methodology used for the assessment did not include publications after April 2008 nor consider retrospective cohort studies of less than 100 subjects, important additional safety data was not considered. The following papers that provide excellent information on adverse events following RFA have been published since April 2008 and should be added to the AHRQ review: 1. Spragg DD, Dalal D, Cheema A, et al. Complications of catheter ablation for atrial fibrillation: incidence and predictors. Journal Cardiovascular Electrophysiology 2008; 19:627. • This paper reported on 517 patients and identified the effect of operator training on complication rates ? complications were higher during the first 100 cases (9%) than during the subsequent 541 cases (4.3%). • There were 7 CVA/TIA, 11 vascular injuries, 1 PV stenosis, 1 mitral valve injury, and 1 complete heart block reported. • Patients were routinely seen at three months.	This study has been included through our update search.

Section	Comment	Response
Discussion	2. Cha YM, Friedman PA, Asirvatham SJ, et al. Catheter ablation for atrial fibrillation in patients with obesity. Circulation 2008; 117:2583. • This paper reports on 523 obese patients following clinical outcomes and quality of life. The minimum follow-up was three months at which time a CT scan was obtained to assess for PV stenosis. • The average follow-up was 17 months. • There were 4 CVA/TIA, 7 PV stenosis, and 12 tamponade reported. • Patients demonstrated an improved QoL.	This study has been included through our update search.
Discussion	3. Corrado A, Patel D, Riedlbauchova L, et al. Efficacy, safety, and outcome of atrial fibrillation ablation in septuagenarians. Journal Cardiovascular Electrophysiology 2008; 19:807. • This paper reports on 174 patients of age greater than 75 years followed for 20 months and provides important information on RFA in Medicare age patients. • There were 4 CVA and 2 hemothorax reported.	This study has been included through our update search.
Discussion	4. Matiello M, Mont L, Tamborero D, et al. Cooled tip versus 8 mm tip catheter for circumferential pulmonary vein ablation: comparison of efficacy, safety, and lesion extension. Europace 2008; 10:955. • This paper reported on 221 patients evaluating cool tip versus 8 mm tip RFA. Patients were followed an average of 12 months. • There were 4 TIA, 1 tamponade, and no PV stenosis reported.	This study has been included through our update search.
Discussion	5. Zado E, Callans DJ, Riley M, et al. Long-term clinical efficacy and risk of catheter ablation for atrial fibrillation in the elderly. Journal Cardiovascular Electrophysiology 2008; 19:621. • This paper provides important information on Medicare aged patients who undergo RFA for AF. Of the 1,165 patients undergoing 1,506 procedures, 185 patients were age 65-74 and 32 patients were aged 75 or older. • Patients were followed an average of 27 months. • There were 6 CVA/TIA, 12 tamponade, 1 atrioesophageal fistula, 6 pulmonary vein stenosis, and 14 vascular complications reported.	This study has been included through our update search.

Section	Comment	Response
Discussion	6. Dixit F, Gerstenfeld ED, Ratcliffe SJ, et al. Single procedure efficacy of isolating all versus arrhythmogenic pulmonary veins on long term control of atrial fibrillation, a prospective randomized study. Heart Rhythm 2008; 5:182. • This study evaluated 105 patients followed for one year. • There were 0 PV stenosis, 0 tamponade, 1 CVA, 1 death, 1 atrio-esophageal perforation reported.	This study has been included through our update search.
Discussion	In November, results from a randomized trial on the use of the NAVISTAR THERMOCOOL Catheter (open irrigation) for the treatment of drug refractory symptomatic paroxysmal AF were presented at the American Heart Association's 2008 Scientific Sessions, as well as to an FDA advisory committee. Although these data have not yet been published in peer-reviewed form, important safety data from this study, which may represent the most rigorously conducted and thoroughly vetted RCT performed to date, should be considered: Pre-market approval application for the Biosense Webster NAVISTAR THERMOCOOL Catheter (open irrigation) for the radiofrequency ablation of symptomatic paroxysmal AF reviewed by the FDA Circulatory System Devices Panel Meeting, November 20, 2008. - The IDE clinical study reported on 167 patients with 106 in the catheter PVI group. - The primary safety cohort for the study included 139 patients. - All 15 subjects observed with a primary AE experienced either improvement or complete resolution of the adverse event. One subject with pericarditis was improved at the time of hospital discharge. No primary AE was adjudicated as device-related. - Additional safety analyses were performed to characterize the early-onset (? 90 days) adverse events by severity, comparing the AAD (Control) group and the NAVISTAR THERMOCOOL group subjects. It is often challenging to compare adverse events between such different treatment modalities, and the types of adverse events were different between groups, as would be expected. Nevertheless, an analysis of the number of early onset serious adverse events (SAEs)	We only included studies published in peer-reviewed journals.

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	showed that the rate was significantly lower in the NAVISTAR THERMOCOOL (18.4%; 19/103) vs. AAD (Control) group (35.1%; 20/57; p= 0.022; unpowered secondary endpoint without multiplicity adjustment). - No severe adverse events such as death, atrio-esophageal fistula, stroke, cerebrovascular accident, atrial perforation, myocardial infarction, thromboembolism, TIA, diaphragmatic paralysis, pneumothorax, heart block or severe pulmonary vein stenosis occurred within 7 days of the ablation procedure. - No pulmonary vein (PV) stenosis, defined in the study protocol as ?70% reduction in the diameter of the pulmonary vein from baseline, has been reported to date in this study. The PV stenosis rates observed in this clinical trial compare favorably to the results found in the literature, in which the overall incidence of symptomatic or asymptomatic PV stenosis (?70% reduction in PV diameter) was 1.6%. - Overall, the primary and secondary safety analyses performed to date represent an excellent safety profile for NAVISTAR THERMOCOOL Catheter ablation in this AF population, with NAVISTAR THERMOCOOL group subjects experiencing approximately one-half the serious adverse events of their AAD (Control) arm counterparts. It is noteworthy that the FDA advisory committee unanimously recommended the study catheter (an open irrigated RF catheter with three-dimensional mapping capability) for approval. The full proceedings of the advisory committee meeting and study sponsor slide presentation including a summary of the safety and effectiveness data are available at http://www.fda.gov/ohrms/dockets/ac/cdrh08.html#circulatory. A copy of the study sponsor's FDA executive summary and panel pack provided to the committee including the clinical trial data are available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4393b1-00-Index.html.	

Section	Comment	Response
Discussion	We agree with the Draft Review's conclusion, that RFA was superior to medical treatments at maintaining sinus rhythm in patients with PAF over one year of follow up.? We also agree that adverse events should be uniformly defined so that meaningful comparative analyses can be performed? As technology and approaches advance over time. We have included a list of ongoing trials which were not listed in the Draft Review's references, but that should be reviewed and included as this comparative effectiveness review is finalized. Please see Table 1 for details. In addition, while not listed in the table, the Health Technology Assessment Program, part of the UK's National Institute for Health Research (NIHR), just released a systematic review of the evidence on atrial fibrillation and typical atrial flutter. It found that the evidence suggests that RFCA is a relatively safe and efficacious procedure for the therapeutic treatment of AF and typical atrial flutter.	We did not find Table 1 in this document, but we noticed some ongoing studies were mentioned in the following section.
Discussion	I did not understand the discussion section, as all of the material presented had already been presented and "discussed" in the conclusions section.	Discussion expands on the conclusions a bit more; we are also conforming to the CER format requirement.
Discussion	See comment in results regarding recruitment bias: (pg 23 - patient level characteristics. You note that all studies found no relation of age to AF recurrence. I believe this points out a potential recruitment bias that is present in AF studies. Specifically that older patients who are selected or agree to participate in these relatively small trials are generally at the healthy end of the spectrum. They are by no means a consecutive series of patients. This is an important issue since the majority of the AF population is elderly. In Key question 2 - patient level factors - age has very important implications. This comment also applies to page 34: Key Question 2.)	We also note under "Remaining Issues and Future Research" that "Further investigations on the efficacy of RFA of RFA for AF should also be targeted at patient population under-represented in the current literature but often encountered in clinical practice (e.g., the elderly, patients with multiple comorbidities)."
General	Although we agree with the investigator's list of remaining issues, some critical issues not mentioned by them are suggested below: 1) Follow-up is one of the most important differences among the studies. The authors may want to comment on this in more detail. It has been shown that patients with symptomatic AF have asymptomatic recurrences of AF. Some patients may be more likely to develop asymptomatic AF post-ablation, and they may be considered "cured" if asymptomatic episodes are not captured. Whether a patient has recurrent AF or not, is partly determined by	These relevant issues regarding followup and post RFA monitoring are now specifically mentioned under "Remaining Issue and Future Research".

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	how much their physicians look for recurrent AF. Therefore, we think it is crucial that post-procedure monitoring of patients in clinical trials becomes standardized and that studies follow frequent asymptomatic monitoring (e.g., event monitors or perhaps insertable loops, in future studies) to evaluate recurrences. We would like to suggest that the pacemaker population is a good model for future baseline review; this population includes mode-switching episodes, which can be definitively monitored.	
General	2) We believe the authors need to highlight the need for future studies to examine the effect of this procedure on patient quality of life.	The issue is now specifically mentioned under "Remaining Issue and Future Research".
General	We would like to commend AHRQ and the Effective Health Care Program in particular, for the very thorough and comprehensive analysis they have performed on the effectiveness of radiofrequency ablation for atrial fibrillation. The report appropriately indicates the need for further research to gather additional information on a number of topics including but not limited to predictors of AF, the value of RFA as a first-line therapy for PAF, and the effect of catheter ablation on the risk of stroke or death. On-going research will continue to strengthen the evidence-base for this procedure. A primary focus of current research is on refining ablation techniques, defining methods and intervals of follow-up, and establishing a consistent approach to achieving and reporting success rates. A number of trials intended to demonstrate the safety and effectiveness of specific ablation catheters for AF treatment are nearing completion. This includes an Investigational Device Exemption (IDE) study sponsored by Biosense Webster, that was reviewed by the FDA Circulatory System Devices Panel Meeting on November, 20, 2008 and resulted in the recommendation that the NAVISTAR THERMOCOOL Catheter (open irrigation) be approved for use in a symptomatic drug-refractory paroxysmal patient population. Additionally, the Catheter Ablation versus Antiarrhythmic Drug for Atrial Fibrillation (CABANA) Trial will compare pharmacologic rate and rhythm control to catheter ablation to study the mortality benefit of ablation and gather information on the therapeutic impact to patient quality of life and healthcare resource utilization. The study will also	The relative grading of observational studies versus RCTs is not inconsistent with the fact that non-randomized studies can provide unique insights, and should be considered (as we did include such studies in this review). Despite being of a "lesser" quality, a well-designed registry with uniformly defined outcomes can add significant insights into the effectiveness and safety of this procedure outside the selective settings of clinical trials.

Section	Comment	Response
	investigate other outcomes of AF ablation and drug therapy including cardiovascular death, occurrence of disabling stroke, serious bleeding and cardiac arrest. This study has completed pilot phase enrollment, and funding for the pivotal phase is under review at the National Institutes of Health (NIH). The AHRQ authors have suggested that in order to address whether the AF type is predictive of the rate of AF recurrence after RFA, a patient registry should be considered. However, we are uncertain that a registry would be of significant help in answering this question, as suggested. The absence of a uniform approach to the RFA procedure and dissimilar assessment of AF recurrence may introduce substantial variation. We agree fully that the recommendations made for clinical trial design for AF ablation studies proposed in the HRS Consensus document should be adhered to so that there is more uniformity in the reporting of outcomes of future clinical trials.(1) Well-designed interventional trials with prescribed monitoring regimens and data vetted through peer review and/or regulatory audits can be expected to better identify recurrence rates in important subpopulations. Recommending a registry to elucidate questions such as this appears inconsistent with the report's stated position that non-randomized studies can be graded at best as of fair quality. References: 1. Calkins, H.; Brugada, J.; Packer, D.; Cappato, R.; Chen, S.; Crijns, H.; Damiano, R.; Davies, W.; Haines, D.; Haissaguerre, M.; Iesaka, Y.; Jackman, W.; Jais, P.; Kottkamp, H.; Kuck, K.; Lindsay, B.; Marchlinski, F.; McCarthy, P.; Mont, J.; Morady, F.; Nademanee, K.; Natale, A.; Pappone, C.; Prystowsky, E.; Raviele, A.; Ruskin, J.; Shemin, R. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-Up. Heart Rhythm. 4(6) (June 2007): 1-46.	
General	Lastly, extending the search time period beyond the April 2008 cut-off would allow the inclusion of important studies that would provide further insight into the evidence base and help direct more specific research investigations.	Our search has been updated through 12-2008.

Section	Comment	Response
General	We found the list of trials analyzed for the study to be relatively complete and the questions asked were written so as to elicit a comprehensive, well thought out response. In addition, we also found the Draft Review to be quite comprehensive in both its examination of the literature and the conclusions drawn, and we largely agree with all of it. However, because of our work and familiarity on the subject, we are aware of additional studies not included in the Draft Review. Results from these trials may not alter the Draft Review conclusions, but should further enhance the analysis, and therefore, be included in the Draft Review.	Please see our inclusion and exclusion criteria for this systematic review.
General	I think it may be important to consider suggestions on how further research may be conducted as well as funded given our current environment.	We do make recommendations for future research in this topic area. It is not our role to make funding recommendations.
Appendix	No additional comments submitted.	