Evidence report for pulmonary vein isolation (catheter ablation) in atrial fibrillation

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Content

Part 1 - Scoping

Methods

Using an established, structured template that delineates key elements for scoping (i.e., the population, interventions, and key outcomes to consider), we collaboratively agreed with UKSH on the scope of the present evidence report. Initial scoping was completed on September 11, 2018 and refined January 15, 2019 following feedback discussions with UKSH on structured templates for evidence review reports. Revised scoping upon initial evidence review was shared with UKSH on January 31, 2019, and UKSH agreed to scoping revisions on February 4, 2019.

Results – Criteria Selection for Critical Appraisal

Population

Inclusion criteria

Patients with symptomatic, recurrent, nonvalvular atrial fibrillation. The nonvalvular atrial fibrillation may be paroxysmal or persistent and may occur with or without comorbid heart failure.

Exclusion criteria

Permanent atrial fibrillation (specifically decision to stop attempts to restore and maintain normal sinus rhythm)

Relevant note about population in consideration

As part of the evidence review, we will include a clear statement that consideration of PVI should be preceded by a thorough investigation to rule out atrial fibrillation secondary to correctable underlying pathology (e.g., hyperthyroidism), and that this evidence review and associated decision aid do not pertain to patients who have not had a thorough investigation to exclude such secondary causes.

Intervention and Comparator

Catheter ablation/pulmonary vein isolation ablation

The intervention is pulmonary vein isolation ablation (a type of catheter ablation, also called pulmonary vein ablation or pulmonary vein antrum isolation), which will hereafter be abbreviated *PVI*.

Medical management (no ablation)

The comparator is medication for rate or rhythm control. This may be abbreviated “No PVI” but is not absence of intervention. The comparator state will not include ablation procedures or invasive procedures.

Outcomes

FAQ 1: What does the treatment involve?

We will include a description of the treatment or procedure, including use of anesthesia, length or frequency of intervention, recovery time, length of stay, and need for post-PVI medication as relevant.

Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

It was requested to advise generally on the importance of regular physical activity, attaining a healthy weight, and being evaluated for sleep apnea if clinically appropriate. A summary of treatment involvement for an option (PVI or no PVI) may include general descriptions of not being a treatment for stroke prevention, treatment of the underlying cause, or overall cardiovascular risk reduction and the importance of other aspects of clinical care (that is, PVI or medication management for rate or rhythm control is not complete clinical care). Although a detailed review of these concepts is beyond the scope of this evidence review, this evidence review will include clear statements capturing the considerations in the previous sentence.

FAQ 2: Will I live longer?

We will report absolute and relative effect estimates for the outcome of all-cause and/or cause-specific mortality as appropriate based on available evidence. Results may be reported separately for those with and without comorbid heart failure with reduced systolic function/ejection fraction.

FAQ 3: Will my symptoms get better?

The outcome of interest is resolution or improvement of symptoms attributable to the nonvalvular atrial fibrillation. The outcome to assess this question will be quality of life measures. Results may be reported separately for those with and without comorbid heart failure with reduced systolic function/ejection fraction.

FAQ 4: What is my risk of being hospitalized later?

The outcome of interest is cardiac hospitalization. Results may be reported separately for those with and without comorbid heart failure with reduced systolic function/ejection fraction. The FAQ language appears as above for the sake of brevity, but in reporting on the outcome of interest, we will make it clear that this concerns cardiac hospitalization only, not all-cause hospitalization (including addressing this for patient-facing content).

FAQ 5: What are the risks?

Outcomes of interest are long-term adverse effects, irreversible adverse effects, and procedure-related serious adverse effects such as mortality or perforated vessels.

FAQ 6: What are the side effects?

Outcomes of interest are common procedural or drug-related side effects. Descriptive responses are acceptable, and this does not involve systematic evidence searches, critical appraisal, or evidence synthesis.

FAQ 7: Will I need additional treatment?

Outcomes of interest include repeat ablation and the need to increase medication use. In the absence of clinical outcomes, surrogate measures to consider may include recurrence of atrial fibrillation. If recurrence of atrial fibrillation is used, it may be further separated into early ("blank period") recurrence within 3 months following PVI and "late" recurrence.

Part 2 - Search and Selection

Methods

First-round searching will consist of searching DynaMed Plus summaries pertinent to the topic. The search starts with DynaMed Plus because DynaMed Plus content is based on a thorough, systematic search and active literature surveillance system.

> Systematic literature surveillance (SLS) has been a cornerstone of creating DynaMed content since its inception. Currently, the SLS team works closely with members of McMaster University's Department of Health Research Methods, Evidence, and Impact to define and refine optimal search strategies, utilizing search terms for methodology and for clinical concepts (especially diagnosis and treatment) for each journal. These filters for PubMed searches are derived from PubMed Clinical Queries, McMaster University Hedges system, and DynaMed search filters and were found to capture >95% of relevant valid articles for use in DynaMed.[1]
>
> [1]Alper BS, Iorio A. Optimising search filters for active literature surveillance: a concordance study. Global Evidence Summit. Cape Town, South Africa; September 2017.
>
> The SLS team, in collaboration with McMaster University, continually evaluates and improves these filters to keep abreast of the ever-changing medical literature landscape. PubMed searches are performed daily. Each article is assessed by an external screener for clinical relevance, then reviewed by internal staff for both clinical relevance and validity. Any disagreements are settled by the Deputy Editor of the SLS team.
>
> In addition, the SLS team continually monitors the Journal source list against the list of journals catalogued in MEDLINE and existing DynaMed content to determine the set of journals that provide the highest yield for valid, clinically relevant content. As of November 2018, 507 Journals are systematically searched (see http://dynamed.com/home/content/content-sources). The journal selection threshold leads to routine adjustments to the number of journals selected.

Second-round searching will involve PubMed/MEDLINE® searches for intervention-specific systematic reviews that are more recent than those identified in first-round searching.

Third-round searching will involve original study tracing from systematic reviews, guidelines or other relevant sources. This may be done to identify additional evidence sources if the results from the first two rounds of searching are insufficient.

Fourth-round searching will involve searches for original evidence reports. Such searching will be limited to areas considered insufficiently addressed by earlier searches, such as focused concepts published after search dates in systematic reviews.

Additional selective searching, such as tracing citations from articles found or seeking related articles, may be done for additional concepts discovered.

FAQ Summary

Results

First-round searching – DynaMed Plus

DynaMed Plus subsection	Relevant for FAQ(s)	Number of article citations	Number of unique references included
Ablation therapy for atrial fibrillation topic, Catheter ablation section, Efficacy subsection (January 29, 2019)	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	2	1 (Ganesan 2013)
Ablation therapy for atrial fibrillation topic, Catheter ablation section, Efficacy compared to drug therapy subsection (January 29, 2019)	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	19	2 (Khan 2014, Turagam 2018)
Ablation therapy for atrial fibrillation topic, Catheter ablation section, Procedural complications subsection (January 29, 2019)	FAQ5, FAQ6	9	1 (Gupta 2013)
Ablation therapy for atrial fibrillation topic, Catheter ablation section, Follow-up after catheter ablation subsection, (January 29, 2019)	FAQ1, FAQ7	1	1 (Calkins 2012)
Ablation therapy for atrial fibrillation topic, Guidelines and resources section, Guidelines subsection, International guidelines subsection (January 30, 2019)	FAQ1, FAQ5, FAQ6, FAQ7	1	1 (Calkins 2017)

Second-round searching – searches for intervention-specific systematic reviews

Database	Search string	Relevant for FAQ(s)	Number of search results	Number of references included
PubMed January 29 and 30, 2019	(ablation OR pulmonary vein isolation OR pulmonary vein isolation ablation OR pulmonary vein ablation OR pulmonary vein antrum isolation OR pulmonary vein antrum ablation OR catheter ablation OR radiofrequency ablation OR cryoablation) AND atrial fibrillation AND ("2011/01/01"[PDAT] : "3000/12/31"[PDAT]) AND systematic[sb]	FAQ1, FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	138	9 (AlTurki 2019, Briceño 2018, Chen 2018, Clarnette 2018, Ganesan 2013*, Gupta 2013*, Khan 2014*, Khan 2018, Phan 2016)
PubMed January 30, 2019	(ablation OR pulmonary vein isolation OR pulmonary vein isolation ablation OR pulmonary vein ablation OR pulmonary vein antrum isolation OR pulmonary vein antrum ablation OR catheter ablation OR radiofrequency ablation OR cryoablation) AND atrial fibrillation AND ("2011/01/01"[PDAT] : "3000/12/31"[PDAT]) AND guideline[ptyp]	FAQ1, FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	35	2 (Calkins 2012*, 2017*)

* already identified in first-round searching

Third-round searching – original study tracing from systematic reviews

Source	Tracing	Relevant for FAQ(s)	Number of search results	Number of references included
Khan 2018	Confirmed Khan 2014 and Khan 2018 included the same 11 trials of patients without comorbid heart failure with reduced ejection fraction (thus ensuring Khan 2014 represents a current systematic review for patients without comorbid heart failure with reduced ejection)	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	N/A	
Calkins 2012	Tracing of any studies providing data on repeat ablations	FAQ7	1	0*
Calkins 2017	Tracing of any studies providing more current data on repeat ablations	FAQ7	1	1 (Al-Hijji 2016)

* reported repeat ablation rates of 20 to 40%, but this was based on data published in 2004, so we favored looking for more current data

Fourth-round searching – searches for original evidence reports

Database	Search string	Relevant for FAQ(s)	Number of search results	Number of references included
PubMed January 31, 2019	(ablation OR pulmonary vein isolation OR pulmonary vein isolation ablation OR pulmonary vein ablation OR pulmonary vein antrum isolation OR pulmonary vein antrum ablation OR catheter ablation OR radiofrequency ablation OR cryoablation) AND atrial fibrillation AND ("2018/01/01"[PDAT] : "3000/12/31"[PDAT]) AND randomized controlled trial[ptyp]	FAQ2, FAQ3, FAQ4, FAQ5, FAQ6, FAQ7	18	0*

* This search captures the CASTLE-AF trial (Marrouche 2018), but this trial is already included in the systematic reviews of Khan 2018 and Turagam 2018, so it was not counted here, as we did not summarize/address this trial separately. We are also aware of the pending publication of the CABANA trial, with top-line results announced in 2018. Based on the combination of the design and rationale and the top-line results, it is clear this trial includes patients both with and without heart failure, including a little over 33% having NYHA Class II or greater heart failure. However, the trial has not yet been published in full, and the ClinicalTrials.gov entry (NCT00911508) shows basic results were submitted on December 26, 2018 and were returned to the study sponsor/investigator after quality control review on January 15, 2019.

Fifth-round searching – addition of studies based on external review

After Universitätsklinikum Schleswig-Holstein (UKSH) reviewed the original Evidence Report, they requested summarization of Hakalahti 2015 based on an interest in the outcome of symptomatic recurrence of atrial fibrillation reported in this systematic review. We summarized Hakalahti 2015, and as an additional response to this request, we also checked a 2012 Cochrane review on catheter ablation for paroxysmal and persistent AF (CD007101) and a 2016 Cochrane review on ablation for non-paroxysmal AF (CD012088) to see if either included symptomatic recurrence of atrial fibrillation as an outcome, and neither did.

Part 3 - Critical Appraisal of Evidence Reports

Methods

For each study selected for critical appraisal, we assessed for criteria needed for Level 1 [likely reliable] evidence ratings in DynaMed's Levels of Evidence criteria in which evidence quality is labeled in 1 of 3 levels:

- **(level 1 [likely reliable] evidence)** for studies with clinical outcomes and minimal risk of bias;
- **(level 2 [mid-level] evidence)** for studies with clinical outcomes and significant methodological or statistical limitations; and
- **(level 3 [lacking direct] evidence)** for reports that do not include scientific analysis of clinical outcomes or for study types that do not include comparisons between groups.

The specific concepts we critically assessed are fully mapped to cover all the criteria used in GRADE. We summarized key concerns identified that reduce the certainty of evidence in categories used for GRADE methods (i.e., risks of bias, indirectness, imprecision, inconsistency, and other considerations if relevant). In the study-level summaries inconsistency assessment was applied to consistency of within-study results – this applies to consistency across related outcomes for both original studies and for systematic reviews, and also applies to consistency across studies when applied to systematic reviews.

Characteristics and Results of Critically Appraised Studies/ Sources

AL-HIJJI 2016

Al-Hijji MA, Deshmukh AJ, Yao X, Mwangi R, Sangaralingham LR, Friedman PA, Asirvatham SJ, Packer DL, Shah ND, Noseworthy PA. Trends and predictors of repeat catheter ablation for atrial fibrillation. Am Heart J. 2016 Jan;171(1):48-55. Epub 2015 Oct 24. PubMed

Relevant for FAQ7

- **Study design:** retrospective analysis of administrative claims data
- **Population:** patients receiving catheter ablation for atrial fibrillation
    - 8,468 patients from the Optum Labs Data Warehouse database (details below)
        - median age was 61 years (IQR 54 to 68 years), 70.9% male, 83.2% white, left ventricular ejection fraction not reported
    - Included: privately-insured and Medicare Advantage patients in the United States who are in the Optum Labs Data Warehouse database and underwent catheter ablation for atrial fibrillation between January 1, 2004 and September 30, 2014 (also had to be enrolled in continuous medical and pharmacy health plan coverage at the time of and for at least 12 months prior to the ablation)
    - excluded: patients with ablation in 12 months prior to study period; patients with secondary diagnoses of WPW, nonparoxysmal AV nodal tachycardia, paroxysmal ventricular tachycardia, and ventricular premature beats; and patients with pacemakers or ICDs implanted during the index procedure (to avoid including patients receiving AV nodal ablation and pacemaker implantation for atrial fibrillation)
    - database reported to have “longitudinal health information on >100 million enrollees over the last 20 years from geographically diverse regions across the United States with greatest representation from the South and Midwest”
- **Intervention:** catheter ablation
- **Comparison:** not applicable
- **Outcome:** primary outcome of interest was repeat ablation
- **Duration of follow-up:** median follow-up was 1.1 (IQR 0.5 to 2.3) years; total of 14,280.6 person-years of follow-up for repeat ablation outcome
- **Certainty: Moderate**
    - **Risk of bias:** retrospective studies carry potential weaknesses, but use of claims data may ameliorate that to a certain extent, and no serious concerns otherwise, particularly considering the outcome of interest
    - **Precision:** no serious concerns
    - **Directness:** no serious concerns, aside from not having clear data on proportion of patients included with heart failure with reduced ejection fraction/reduced systolic function; however, authors noted no clear difference in rate of repeat ablation among those with versus those without congestive heart failure
    - **Consistency:** no serious concerns
    - **Other considerations:** cited by Calkins 2017 as providing contemporary data on repeat ablation rates
- **Results:**
    - a total of 1,263/8,648 (14.6%; 95% CI 13.9% to 15.4%) underwent repeat ablation

        - of those who underwent repeat ablation (1,263) timing of repeat ablation was:
            - within 1 month, 49/1,263 (3.9%)
            - 1 to 3 months, 119/1,263 (9.4%)
            - within 3 months, 168/1,263 (13.3%)
            - 3 to 12 months, 647/1,263 (51.2%)
            - within 12 months, 815/1,263 (64.5%)
            - >12 months, 448/1,263 (35.5%)
        - median time to repeat ablation
            - 0.7 (IQR 0.4 to 1.4) years
    - considering only those who underwent repeat ablation beyond the 3-month period (due to the first 3 months typically being considered a "blanking"/stabilization period):
        - total of 1,095/8,648 (12.7%; 95% CI 12.0% to 13.4%) underwent repeat ablation
            - 647/1,095 (59.1%) of these were between 3 and 12 months
            - 448/1,095 (40.9%) of these were >12 months
    - no clear difference in rates of repeat ablation between those with and those without congestive heart failure (HR 0.94, 95% CI 0.82 to 1.09)
    - because sleep apnea is known to be associated with atrial fibrillation, authors also conducted an exploratory secondary analysis of rates of sleep apnea among those who did and did not undergo repeat ablation, finding comparable rates (25.5% versus vs 24.9%, respectively)
    - they note certain demographic factors may be associated with higher rates of repeat ablation (e.g., younger age, higher household income, being in the Southern United States), but we note interpretation of such subgroup analyses must be carried out with considerable caution (e.g., these findings could be a byproduct of multiple subgroup testing), but full consideration of this matter is beyond the scope of this evidence review

ALTURKI 2019

AlTurki A, Proietti R, Dawas A, Alturki H, Huynh T, Essebag V. Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. BMC Cardiovasc Disord. 2019 Jan 15;19(1):18. PubMed

Full-text for this systematic review and meta-analysis (SRMA) was obtained to assess eligibility/appropriateness for inclusion in this evidence report. However, AlTurki 2019 has odd/atypical inclusion criteria for the intended comparison of catheter ablation versus medical management, namely specifying that medical management could include either rate or rhythm control (further specifying that rhythm control had to be amiodarone) or atrioventricular (AV) nodal ablation with biventricular (BiV) pacing. The latter aspect is not consistent with either our specified inclusion criteria for medical management or the more broadly-understood clinical definition of what constitutes medical management for atrial fibrillation. The allowance of AV nodal ablation with BiV pacing made the PABA-CHF trial (Khan 2008, PMID 18946063) eligible for inclusion, and it was used in meta-analytic estimates. We therefore did not consider this SRMA any further, especially since we found 3 other SRMAs addressing the scoped question with a more appropriate/representative body of evidence (Khan 2014, Khan 2018, Turagam 2018).

BRICEÑO 2018

Briceño DF, Markman TM, Lupercio F, Romero J, Liang JJ, Villablanca PA, Birati EY, Garcia FC, Di Biase L, Natale A, Marchlinski FE, Santangeli P. Catheter ablation versus conventional treatment of atrial fibrillation in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials. J Interv Card Electrophysiol. 2018 Oct;53(1):19-29. Epub 2018 Jul 31. PubMed

> Full-text for this systematic review and meta-analysis (SRMA) was obtained to assess eligibility/appropriateness for inclusion in this evidence report. However, much like with AlTurki 2019, the inclusion/exclusion criteria led us to exclude this SRMA from further consideration. See AlTurki 2019 for details, but briefly, Briceño 2018 specified an intent to compare catheter ablation to "conventional therapy for AF", and like AlTurki 2019, this also resulted in the inclusion of the PABA-CHF trial (Khan 2008, PMID 18946063).

CALKINS 2012

Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano RJ Jr, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. Europace. 2012 Apr;14(4):528-606. PubMed

Relevant to FAQ1, FAQ7

> This reference was used for study tracing to find evidence on repeat ablations and as part of answering the question of what the treatment involves. It reported repeat ablation rates of 20 to 40%, but this was based on data published in 2004. We desired more current information if available (and were able to find such), so we did not review this reference.

CALKINS 2017

Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, Akar JG, Badhwar V, Brugada J, Camm J, Chen PS, Chen SA, Chung MK, Nielsen JC, Curtis AB, Davies DW, Day JD, d'Avila A, de Groot NMSN, Di Biase L, Duytschaever M, Edgerton JR, Ellenbogen KA, Ellinor PT, Ernst S, Fenelon G, Gerstenfeld EP, Haines DE, Haissaguerre M, Helm RH, Hylek E, Jackman WM, Jalife J, Kalman JM, Kautzner J, Kottkamp H, Kuck KH, Kumagai K, Lee R, Lewalter T, Lindsay BD, Macle L, Mansour M, Marchlinski FE, Michaud GF, Nakagawa H, Natale A, Nattel S, Okumura K, Packer D, Pokushalov E, Reynolds MR, Sanders P, Scanavacca M, Schilling R, Tondo C, Tsao HM, Verma A, Wilber DJ, Yamane T. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017 Oct;14(10):e275-e444. PubMed

Relevant to FAQ1, FAQ5, FAQ7

This reference was used for data on complication rates, study tracing to find evidence on repeat ablations, and as part of answering the question of what the treatment involves. It provides incidence, and suggested prevention strategies, diagnostic approach, and management strategies for "selected" complications. We provide below the data for incidence (preventative strategies, diagnosis, and management of potential complications are beyond the intended scope of this work). We also note that, although this reference provides numerous references for its report on "selected" complication rates, it does not explicitly state a systematic review for complication rate data, and it does not indicate the sample size in consideration for each complication.

- **Certainty: Very low**
  - **Risk of bias:** approach to finding evidence for and synthesizing complication rates unclear (no clear systematic review process or methods stated)
  - **Precision:** ranges given for some outcomes, but for others, no range and no indication of precision
  - **Directness:** unclear representation of patients with comorbid heart failure with reduced ejection fraction/reduced systolic function, so unclear whether results apply as readily to such patients
  - **Consistency:** unable to assess within this body of evidence
  - **Other considerations:**

Complications of catheter ablation: incidence and prevention Complication	**Incidence**	**No. of studies***
Air embolism	<1%	7
Asymptomatic cerebral emboli (ACE)	2% to 15%	18
Atrial esophageal fistula	0.02% to 0.11%	66
Cardiac tamponade	0.2% to 5%	14
Coronary artery stenosis/occlusion	<0.1%	9
Death	<0.1% to 0.4%	5
Gastric hypomotility	0% to 17%	13
Mitral valve entrapment	<0.1%	8
Pericarditis†	0% to 50%	8
Permanent phrenic nerve paralysis	0% to 0.4%	35
Pulmonary vein stenosis	<1%	27
Radiation injury	<0.1%	20
Stiff left atrial syndrome	<1.5%	8

Stroke and TIA	0% to 2%	15
Vascular complications	0.2% to 1.5%	18

CMAP, compound motor action potentials; PV, pulmonary vein; RF, radiofrequency; TEE, transesophageal echocardiogram
* This is number of studies *referenced*. Calkins 2017 did not clearly specify either the number of participants from the studies cited, nor did they clearly indicate a systematic review for the generation of their complication estimates.
† This is listed in their table as a complication, so we include it here as well. However, as they note, "when transmural lesions are generated during catheter ablation for AF [atrial fibrillation], some epicardial inflammation, and therefore some pericarditis, is inevitable." Consequently, it is very common for patients to experience "some pleuritic chest pain in the first several days following their procedure" or for there to be "'trace' pericardial effusion following AF ablation". However, "[t]hese largely self-limited manifestations of AF ablation-induced pericarditis are so common and of so little consequence that they are considered as part of the standard clinical course for patients who undergo AF ablation rather than as a complication of the procedure. A small subset of these patients will go on to develop more severe and clinically significant manifestations of pericarditis [such as Dressler syndrome, pericarditis leading to cardiac tamponade, and constrictive pericarditis]."

CHEN 2018

Chen C, Zhou X, Zhu M, Chen S, Chen J, Cai H, Dai J, Xu X, Mao W. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. J Interv Card Electrophysiol. 2018 Jun;52(1):9-18. Epub 2018 Mar 16. PubMed

We anticipated this systematic review and meta-analysis would be excluded from the title and abstract, but we obtained full-text to ensure this. This systematic review and meta-analysis focuses solely on persistent atrial fibrillation, excluding trials if separate data were not available for patients with persistent versus paroxysmal atrial fibrillation or including trial data for the subgroup with persistent atrial fibrillation if such data were available. They did not restrict trials based on presence/absence of comorbid heart failure with reduced ejection fraction. This resulted in them including 8 trials totaling 809 patients, which we note is substantially less than the 17 trials totaling 2,272 patients included by Khan 2018 (Khan 2018 did not restrict based on the type of non-permanent atrial fibrillation, included trials of patients both with and without comorbid heart failure with reduced ejection fraction/reduced systolic function, and provided separate estimates for these trials). We specified interest in catheter ablation vs. medical management in patients with non-permanent (i.e., paroxysmal or persistent) atrial fibrillation, so a focus solely on persistent atrial fibrillation as provided by Chen 2018 would exclude trial data from patients with paroxysmal atrial fibrillation and thus be less meaningful for the intended question when better evidence is available that does not exclude patients based on what type of non-permanent atrial fibrillation they have (Khan 2014, Khan 2018, Turagam 2018). Furthermore, although they assessed certain outcomes specific to the trials in patients with comorbid heart failure with reduced ejection fraction/reduced systolic function (e.g., change in left ventricular ejection fraction), this was not always the case (e.g., hospitalization), thereby also making use of these results complicated – if useable at all – compared to assessing trials separately for those with and without comorbid heart failure with reduced ejection fraction/reduced systolic function (which is provided by the data in the Khan 2014, Khan 2018, and Turagam 2018 systematic reviews and meta-analyses).

CLARNETTE 2018

Clarnette JA, Brooks AG, Mahajan R, Elliott AD, Twomey DJ, Pathak RK, Kumar S, Munawar DA, Young GD, Kalman JM, Lau DH, Sanders P. Outcomes of persistent and long-standing persistent atrial fibrillation

ablation: a systematic review and meta-analysis. Europace. 2018 Nov 1;20(FI_3):f366-f376. doi: 10.1093/europace/eux297. PubMed

Relevant for FAQ7

- **Study design:** systematic review and meta-analysis of randomized, controlled trials and observational studies
- **Population:** patients with persistent and long-standing persistent atrial fibrillation undergoing an index ablation procedure
    - a total of 18,657 patients undergoing well-defined ablation procedures were reviewed in 123 cohorts (4 randomized, controlled trials contributing 9 cohorts and 109 observational studies contributing 114 cohorts)
        - average age 59 ± 3 years (range 50 to 67 years), 78% ± 8% men (56% to 94%), atrial fibrillation duration of 59 ± 21 months (range 17 to 101 months), left ventricular ejection fraction 58% ± 4% (range 48% to 65%)
        - 34 cohorts were persistent atrial fibrillation only, 31 were long-standing persistent atrial fibrillation only, and 58 were comprised of both (persistent atrial fibrillation defined as continuous atrial fibrillation for at least 7 days; long-standing persistent defined as continuous atrial fibrillation >12 months)
        - publication dates spanned 2001 to 2015, but 81% of the data were from 2010 onwards
    - eligibility criteria:
        - must have included a minimum of 60 index patients with persistent or long-standing persistent atrial fibrillation (per defined ablation strategy)
        - must have a defined follow-up of at least 12 months
        - could not use a cryoablation, surgical ablation, or hybrid ablation strategies
        - could not have "patient subsets that were not representative of consecutive ablation series (i.e., patients only with heart failure, specified age ranges, and/or other demographic/clinical characteristics)"
        - could not be a "stud[y] that segmented outcomes according to another interest variable or had an indeterminate ablation protocol"
- **Intervention:** catheter ablation (*not* including cryoablation strategies)
- **Comparison:** not applicable
- **Outcome:**
    - treatment "success" (defined as no recurrence), reported for:
        - the "single-procedure" cohort (those who had a single procedure performed and had no use of antidysrhythmic drugs), where "treatment success" means antidysrhythmic drug-free freedom from atrial dysrhythmia
            - note this does not necessarily mean patients were not taking rate-controlling medication
        - the "multiple-procedure" cohort (those either having multiple ablation procedures and/or using antidysrhythmic drugs for greater than 3 months after the index procedure), where the success rate was defined/reported as the highest success rate from among the 3 following groups: multiple-procedure, drug-free; single-procedure, drug-assisted; or multiple-procedure, drug-assisted
            - this outcome is difficult to employ clinically, so it is not considered further here

    - this study also reports on the mean number of procedures among the "multiple-procedure" cohort ("multiple-procedure" cohort being defined as above)
- **Duration of follow-up:** mean follow-up was 25 ± 12 months (range 12 to 59 months)
- **Certainty: Moderate** (may consider up to a full additional downgrade for patients with comorbid heart failure with reduced ejection fraction/reduced systolic function depending on concern about directness)
    - **Risk of bias:** systematic review authors did not formally assess quality of included studies; this precludes assessment of possibly-relevant factors like adequacy of follow-up
    - **Precision:** no serious concerns
    - **Directness:**
        - results may not apply as directly to patients undergoing ablation for atrial fibrillation with comorbid heart failure with reduced ejection fraction/reduced systolic function, so one might consider a downgrade for indirectness in that population
        - these data do not include patients with paroxysmal atrial fibrillation or patients who received cryoablation; however, these observations were not deemed serious enough to justify a downgrade, because the efficacy data also come exclusively from radiofrequency modalities, and patients with paroxysmal atrial fibrillation would not be expected to fare considerably worse than those with persistent or long-standing persistent atrial fibrillation (thus, if indirectness had any impact at all in this case, it would only be expected to decrease the apparent effectiveness [not increase it], thus offering a conservative estimate)
    - **Consistency:** no comment/data on heterogeneity for mean number of procedures in the "multiple-procedure" cohort; substantial heterogeneity for single-procedure, drug-free freedom from atrial dysrhythmia outcome (I^2 = 95%)
    - **Other considerations:** systematic review authors did not formally assess quality of included studies; we have noted relevant considerations for the outcome of interest above
- **Results:**
    - Single-procedure, antidysrhythmic drug-free freedom from atrial dysrhythmia (74 cohorts; each had to include at least 60 people, but total number of participants not reported):
        - 43% (95% CI 39% to 47%; I^2 = 95%) at approximately 25 months of follow-up
    - Mean number of procedures in the "multiple-procedure" cohorts (79 cohorts; each had to include at least 60 people, but total number of participants not reported): 1.37 ± 0.3 (range 1 to 2.3)

GANESAN 2013

Ganesan AN, Shipp NJ, Brooks AG, Kuklik P, Lau DH, Lim HS, Sullivan T, Roberts-Thomson KC, Sanders P. Long-term outcomes of catheter ablation of atrial fibrillation: a systematic review and meta-analysis. J Am Heart Assoc. 2013 Mar 18;2(2):e004549. PubMed

Relevant for FAQ7

- **Study design:** systematic review and meta-analysis of randomized, controlled trials and observational studies
- **Population:** patients with atrial fibrillation undergoing catheter ablation

    - 19 studies totaling 6,167 patients met inclusion criteria (15 single-center case series, 2 multicenter case series, and 2 randomized trials; prospective recruitment in 7 studies, retrospective in 12; sample size min and max were 39 and 1,404, respectively), but only 3 studies had a total number of people receiving/who had received PVI <100
        - mean age ranged from 51 to 65 years
        - proportion of male subjects varied from 57% to 90%
        - mean left ventricular ejection fraction varied from 53% to 70%
        - 11 studies reported data for patients with paroxysmal atrial fibrillation, 6 studies reported data for patients with non-paroxysmal atrial fibrillation, 6 reported data for mixed populations, and it is unclear for 1 study what type of atrial fibrillation was investigated (Matsuo 2011)
        - pulmonary vein isolation with radiofrequency ablation was the ablation method in the majority of included studies
    - eligible studies had to have an evaluation of outcomes at 3 years or more and a mean/median follow-up duration of 2 years or more, and could include randomized, controlled trials or observational studies (excluding individual case reports)
- **Intervention:** catheter ablation
- **Comparison:** not applicable
- **Outcome:**
    - number of procedures received
    - treatment "success" (defined as freedom from atrial dysrhythmia, or, in the case of single-procedure success, also including the outcome of not needing a repeat procedure within 12 months) for the primary ablation procedure and for those receiving >1 procedure
        - freedom from atrial dysrhythmia by itself is a surrogate marker and is also perhaps more difficult to interpret meaningfully with uncontrolled data (freedom from atrial dysrhythmia is assessed via randomized, controlled trials and systematic reviews of randomized, controlled trials)
        - drug-free freedom from atrial dysrhythmia might be a more meaningful outcome in this context
        - we therefore only report outcomes data that correspond to drug-free freedom from atrial dysrhythmia
    - complications (only as tabulated counts of different complications in each study); we did not consider these data further given more robust complications data in other sources (e.g., Gupta 2013)
- **Duration of follow-up:** mean or median duration of follow-up varied from 28 to 71 months (6 studies had mean or median follow-up durations of 30 months or less; 13 had durations of at least 39 months)
- **Certainty: Moderate** (may consider up to a full additional downgrade for patients with comorbid heart failure with reduced ejection fraction/reduced systolic function depending on concern about directness)
    - **Risk of bias:** adequacy of follow-up unclear for 11 of 19 studies
    - **Precision:** no serious concerns
    - **Directness:** results may not apply as directly to patients undergoing ablation for atrial fibrillation with comorbid heart failure with reduced ejection fraction/reduced systolic function, so one might consider a downgrade for indirectness in that population; these data come predominantly from studies where radiofrequency ablation was used (as opposed to

cryoablation), but this was not considered serious enough to warrant a downgrade, as the efficacy data come exclusively from radiofrequency modalities
    - **Consistency:** no data on heterogeneity for outcomes of interest; substantial heterogeneity for freedom from atrial dysrhythmia in general (not medication-free freedom)
    - **Other considerations:**
        - also cited as a recent systematic review and meta-analysis by Calkins 2017
        - the systematic review authors used a modified version of quality assessment criteria for case series consisting of 7 domains (eligibility criteria reported, representativeness of population, follow-up method clearly defined, no loss to follow-up or explanation of such, prospective recruitment, consecutive recruitment, and reporting relevant prognostic factors). The 2 most common domains with issues were handling of loss to follow-up (not reported in 11 studies) and not having prospective recruitment (12 studies). We have noted what we deem to be relevant considerations for the outcome of interest above.

- **Results:**
    - late, single-procedure, drug-free success rate (14 studies, total number of participants not reported): 57.4% (95% CI 50.9% to 63.8%), no I^2 reported
        - they call this "drug-free success", but specify conducting this analysis to assess "the impact of antidysrhythmic drugs" (no mention of rate-control therapy elsewhere in the study)
        - "the time point of latest follow-up in a study was defined as the last time point reporting a minimum of 30 subjects at risk"
        - authors note this is similar to the overall clinical outcome, and although they may be solely referring to the rate and confidence interval, the overall outcome had substantial heterogeneity with I^2 values ranging from 79% to 94% depending on the outcome being considered
    - average number of procedures for overall cohort: 1.51 (95% CI 1.36 to 1.67)
        - those with paroxysmal atrial fibrillation (PAF): 1.45 (95% CI 1.31 to 1.59)
        - those with non-paroxysmal atrial fibrillation (NPAF): 1.67 (95% CI 1.31 to 2.06)
        - *P* for comparison of PAF to NPAF = 0.2 (no precision estimate provided)

GUPTA 2013

Gupta A, Perera T, Ganesan A, Sullivan T, Lau DH, Roberts-Thomson KC, Brooks AG, Sanders P. Complications of catheter ablation of atrial fibrillation: a systematic review. Circ Arrhythm Electrophysiol. 2013 Dec;6(6):1082-8. Epub 2013 Nov 15. PubMed

Relevant for FAQ5

- **Study design:** systematic review of prospective and retrospective studies
- **Population:** adults with symptomatic atrial fibrillation undergoing catheter ablation
    - mean age 57.3 years (range 51 to 77 years), 75% male (range 42% to 100%), paroxysmal atrial fibrillation in 43.6% (range 0% to 100%), mean ejection fraction 58.5% (range 48% to 70%), heart failure in 9.1% (range 0% to 24.5%), nonischemic cardiomyopathy in 5.9% (range 0% to 22.7%), hypertrophic cardiomyopathy in 5% (range 0% to 19%)
- **Intervention:** catheter ablation
- **Comparison:** no catheter ablation
- **Outcome:** complications (only studies reporting on complications were included)

- **Other considerations**
    - no more recent systematic review and meta-analysis found in a broad-based search of MEDLINE/PubMed (see Part 2)
    - excluded studies not in English or with <100 patients receiving catheter ablation, and pooled data from studies examining different techniques for catheter ablation due to specified intent to provide estimates for catheter ablation as a general procedure rather than any specific approach
        - A total of 192 studies totaling 83,236 patients met inclusion criteria, with the majority of data coming from studies published between 2007 and 2012 (n = 140 studies). The studies were mainly case series (87/192 studies), cohort studies (60/192 studies), and randomized trials (34/192 studies) and with sample size ranging from the specified minimum of 100 patients (n = 21 studies) to a maximum of 6,454 patients.
- **Duration of follow-up:** not reported
- **Certainty: Low** (may consider up to a full additional downgrade for patients with comorbid heart failure with reduced ejection fraction/reduced systolic function depending on concern about directness)
    - **Risk of bias:**
        - only 42 of the studies prospectively defined major complications (discussion says 45, but results section and Table 4 suggest 42, so we have assumed 42 is the correct number and 45 is a typographical error)
        - although this systematic review includes observational studies, these are often necessary to capture infrequent events, and moreover, the authors specified that the results from randomized, controlled trials did not substantively differ from the overall results including the entire group of studies
        - application of an 8-point quality scoring system for all study types that may not sufficiently capture all elements of critical appraisal, although this may be of lesser concern here given the question of interest (procedure-related complications)
    - **Precision:** no serious concerns
    - **Directness:** results may not apply as directly to patients undergoing ablation for atrial fibrillation with comorbid heart failure with reduced ejection fraction/reduced systolic function, so one might consider a downgrade for indirectness in that population
    - **Consistency:** prominent heterogeneity in results with no clear explanation for such; for example, I^2 for overall analysis was 83.8%, and no clear explanation in analyses examining time period (limiting to studies published between 2007 and 2012, I^2 = 82.2%), prospective definition of complications (I^2 = 89.2%), and catheter ablation strategy (I^2 values between 74.2% and 86.7% for 4 of the 7 strategies reported on, but 53.6% if using complex fractionated atrial electrogram as an adjunct, 47.7% if using a stepwise ablation strategy, and 12.2% if using complex fractionated atrial electrogram alone)
    - **Other considerations:** although this systematic review is from 2013, a broad-based search of Medline/PubMed did not uncover any more current systematic review addressing the broad question of catheter ablation in patients with atrial fibrillation (see Part 2)
- **Results:**
    - Authors note a decrease in overall complication rate from 2000 to 2006 (4.0%, no precision estimate provided) compared to 2007 to 2012 (2.6%, 95% CI 2.31% to 2.95%, I^2 82.2%). However, results from 2007 to 2012 are not clearly different from the overall

time period of 2000 to 2012 (2.9%, 95% CI 2.60% to 3.22%, I^2 = 83.8%), likely influenced by the majority of studies (140/192) being published between 2007 and 2012.

- Tabulated results are presented below for the entire study period, for the period between 2007 and 2012, and for studies that prospectively defined major complications. **Although Gupta 2013 specified the number of studies contributing to these estimates, they did not report the corresponding number of participants. However, each study had to have at least 100 participants per their inclusion criteria.**

Major complications for entire study period (2000 to 2012)

Complication	No. studies*	Complication rate, % (95% CI)	I^2 (%)
Acute complication rate	183	2.9 (2.60 to 3.22)	83.8
Type of complication			
Death	58	0.06 (0.03 to 0.09)	0
Atrioesophageal fistula	67	0.08 (0.05 to 0.11)	0
Pulmonary vein stenosis†	118	0.5 (0.34 to 0.60)	79.6
Vascular complications‡	117	1.4 (1.02 to 1.79)	94.1
Arteriovenous fistula	45	0.40 (0.28 to 0.55)	45.5
Femoral pseudoaneurysm	49	0.5 (0.34 to 0.60)	41.2
Stroke/TIA	155	0.6 (0.50 to 0.67)	46.8
Stroke	111	0.4 (0.30 to 0.44)	34.3
TIA	94	0.4 (0.28 to 0.47)	37.9
Tamponade	131	1.0 (0.83 to 1.14)	68.5
Pericardial effusion	67	0.7 (0.56 to 0.88)	55
Phrenic nerve injury	48	0.4 (0.22 to 0.54)	70.2
Diaphragmatic paralysis	21	0.3 (0.15 to 0.43)	0
DVT/PE	33	0.15 (0.09 to 0.21)	0
Pneumothorax	22	0.2 (0.08 to 0.29)	0
Hemothorax	25	0.2 (0.10 to 0.28)	0
Sepsis, abscesses, or endocarditis	20	0.1 (0.06 to 0.24)	0
Valve damage	26	0.2 (0.08 to 0.25)	0

DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

*Only number of studies (not number of participants) was reported by Gupta 2013; however, each study had to have at least 100 participants per their inclusion criteria.

†Pulmonary vein stenosis defined as >50% stenosis and requiring intervention

‡Vascular complications included bleeding, hematoma, arteriovenous fistula, and femoral pseudoaneurysm

Major complications for more contemporary study period (2007 to 2012)

Complication	No. studies*	Complication rate, % (95% CI)	I^2 (%)
Acute complication rate	140	2.6 (2.31 to 2.95)	82.2
Type of complication			
Death	45	0.06 (0.03 to 0.09)	0
Atrioesophageal fistula	53	0.07 (0.04 to 0.11)	0
Pulmonary vein stenosis†	90	0.4 (0.30 to 0.58)	76.8
Vascular complications‡	86	1.2 (0.83 to 1.72)	95.4
Arteriovenous fistula	32	0.4 (0.24 to 0.58)	50.2
Femoral pseudoaneurysm	38	0.4 (0.29 to 0.57)	40.6
Stroke/TIA	119	0.55 (0.46 to 0.65)	48.3

Stroke	85	0.3 (0.26 to 0.43)	37.8
TIA	74	0.3 (0.25 to 0.43)	36.1
Tamponade	99	0.9 (0.75 to 1.10)	67.7
Pericardial effusion	55	0.7 (0.52 to 0.83)	44.9
Phrenic nerve injury	38	0.4 (0.19 to 0.60)	74.7
Diaphragmatic paralysis	15	0.2 (0.10 to 0.40)	0
DVT/PE	23	0.1 (0.08 to 0.21)	0
Pneumothorax	17	0.15 (0.06 to 0.28)	0
Hemothorax	22	0.2(0.10 to 0.29)	0
Sepsis, abscesses, or endocarditis	16	0.1 (0.04 to 0.24)	0
Valve damage	22	0.15 (0.08 to 0.25)	0

DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

*Only number of studies (not number of participants) was reported by Gupta 2013; however, each study had to have at least 100 participants per their inclusion criteria.

†Pulmonary vein stenosis defined as >50% stenosis and requiring intervention

‡Vascular complications included bleeding, hematoma, arteriovenous fistula, and femoral pseudoaneurysm

Major complications in studies that prospectively defined major complications

Complication	**No. studies***	**Complication rate, % (95% CI)**	**I^2 (%)**
Acute complication rate	42	3.5 (2.90 to 4.14)	89.2
Type of complication			
Death	17	0.03 (0.01 to 0.07)	0
Atrioesophageal fistula	18	0.06 (0.02 to 0.11)	0
Pulmonary vein stenosis†	25	0.3 (0.15 to 0.58)	89
Vascular complications‡	34	1.9 (1.05 to 2.93)	97.5
Arteriovenous fistula	14	0.3 (0.19 to 0.51)	45.8
Femoral pseudoaneurysm	15	0.5 (0.30 to 0.75)	68.3
Stroke/TIA	41	0.5 (0.38 to 0.65)	64.1
Stroke	29	0.3 (0.21 to 0.49)	66.2
TIA	22	0.2 (0.13 to 0.34)	34.2
Tamponade	28	1.0 (0.65 to 1.28)	82.3
Pericardial effusion	16	0.6 (0.37 to 0.82)	64.9
Phrenic nerve injury	12	0.5 (0.13 to 1.07)	89
Diaphragmatic paralysis	1	0.1 (0.08 to 0.74)	n/a
DVT/PE	7	0.1 (0.05 to 0.20)	0
Pneumothorax	3	0.1 (0.01 to 0.30)	0
Hemothorax	6	0.2 (0.08 to 0.36)	0
Sepsis, abscesses, or endocarditis	3	0.15 (0.02 to 0.38)	0
Valve damage	6	0.1 (0.04 to 0.30)	0

DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

*Only number of studies (not number of participants) was reported by Gupta 2013; however, each study had to have at least 100 participants per their inclusion criteria.

†Pulmonary vein stenosis defined as >50% stenosis and requiring intervention

‡Vascular complications included bleeding, hematoma, arteriovenous fistula, and femoral pseudoaneurysm

HAKALAHTI 2015

Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Europace. 2015 Mar;17(3):370-8. Epub 2015 Feb 1. PubMed

Relevant for FAQ3

- **Study design:** systematic review and meta-analysis of randomized trials
- **Population:** adults with recurrent, symptomatic atrial fibrillation (AF) without previous treatment with class I or class III antiarrhythmic drugs
    - Inclusion criteria
        - Age
            - 2 trials limited to patients ≤75 years old; 1 trial limited to patients ≤70 years old
        - AF history
            - 2 trials limited to paroxysmal symptomatic AF for ≥6 months
            - 1 trial limited to symptomatic AF for ≥3 months
            - Overall, 98.7% of patients had paroxysmal AF
        - previous antiarrhythmic drug use
            - 2 trials limited to patients with no previous treatment with antiarrhythmic drugs
            - 1 trial limited to patients with no previous or ongoing treatment with class IC or class III antiarrhythmic drugs
    - Most patients (98.7%) had paroxysmal atrial fibrillation
    - Patients in included trials did not have heart failure or other major comorbidity

- **Intervention:** radiofrequency catheter ablation
- **Comparison:** antiarrhythmic drugs

- **Number of studies:** 3 randomized trials
- **Number of participants:** 491
- **Duration of follow-up:** 1 year (1 trial) to 2 years (2 trials)

- **Certainty and Results:**

Outcome	**Radiofrequency catheter ablation group event rate**	**Antiarrhythmic drugs group event rate**	**Relative risk (95% CI)**	**Certainty**
symptomatic AF recurrence*	27.7% (66/238)	42.1% (102/242)	0.57 (0.30 to 1.08)	Very low (downgraded due to risk of bias**, indirectness***, inconsistency, and imprecision)

* Although the 3 trials had a total of 491 patients, the outcome of symptomatic AF recurrence was based on 480 patients
** Risk of bias downgrade because all 3 trials had unclear risk of bias for allocation concealment and high risk of bias for blinding of patients and personnel
*** Indirectness downgrade due to only including trials of patients without previous treatment with antiarrhythmic medication (i.e., testing catheter ablation versus antiarrhythmic medication as first-line therapy for atrial fibrillation). Therefore, results may not be applicable to patients previously treated with antiarrhythmic medication. Additionally, aside from thromboembolic

prophylaxis, medical therapy for atrial fibrillation can include rate-controlling or rhythm-controlling medication, and this systematic review focuses on rhythm-controlling medication (antiarrhythmics), thus furthering the issue of indirectness.

- **Other considerations**: Nielsen 2012/MANTRA-PAF 2012 randomized 146 patients to ablation and 148 patients to drug therapy. Hakalahti 2015's Figure 3 forest plot for MANTRA-PAF 2012 reported 46/140 in the ablation group and 61/146 in the drug therapy group had symptomatic AF events. It is not clear where Hakalahti 2015 extracted these numbers from, though Hakalahti 2015 did report "[r]elevant unreported data were retrieved from all available sources and authors were contacted if necessary". In Nielsen 2012/MANTRA-PAF 2012, the intention to treat analysis including all randomized patients reported that 93% in the ablation group vs. 84% in the drug therapy group were free from symptomatic AF at 24 months (p = 0.01). This would calculate to 136/146 in the ablation group and 124/148 in the drug group being free from symptomatic AF (and consequently 10/146 in the ablation group and 24/148 in the drug group not being free from symptomatic AF) at 24 months. If these 'not free from symptomatic AF at 24 months' data from Nielsen 2012/MANTRA-PAF 2012 were used instead of the data reported in Hakalahti 2015, the pooled RR would likely change from not statistically significant to statistically significant for the outcome of symptomatic AF recurrence, favoring ablation. However, we note (1) being free from symptomatic AF at the 24-month point does not necessarily exclude the possibility that some of these patients might have previously had a symptomatic recurrence of AF that resolved before the 24-month point, and (2) our main concerns as above-noted would remain unchanged, so the findings are of Very low certainty regardless.

KHAN 2014

Khan AR, Khan S, Sheikh MA, Khuder S, Grubb B, Moukarbel GV. Catheter ablation and antiarrhythmic drug therapy as first- or second-line therapy in the management of atrial fibrillation: systematic review and meta-analysis. Circ Arrhythm Electrophysiol. 2014 Oct;7(5):853-60. Epub 2014 Aug 10. PubMed
Relevant to FAQ3, FAQ5, FAQ7

- **Study design:** systematic review of randomized trials
- **Population:** 1,481 adults with atrial fibrillation without heart failure in 11 trials (Study selection did not state that trials were limited to patients without heart failure and this was assumed [see 'Additional Comment' below])
  - 8 trials were conducted in patients with previous use of antiarrhythmics and 3 in patients who were antiarrhythmics -naive
  - mean age
    - in the 50s for 9 trials
    - in the 60s for 2 trials
  - left atrial dimension < 50 mm in all trials
  - in most trials patients had few comorbidities such as hypertension and structural heart disease
  - all but 1 trial included patients with both paroxysmal and persistent atrial fibrillation (1 included patients with only persistent)
- **Intervention:** catheter ablation
- **Comparison:** antiarrhythmic drug therapy
- **Outcome:** recurrence of atrial tachyarrhythmia, quality of life, adverse events
- **Duration of follow-up:** 9 months in 1 trial, 12 months in 9 trials, and 24 months in 1 trial

- **Certainty:**
  - **Risk of bias:** none of the trials were blinded and none described withdrawals/dropouts
  - **Precision:**
  - **Directness:**
  - **Consistency:** For quality of life outcome, systematic review reported only mean differences pooled from 4 out of the 6 trials that measured SF-36 mental and physical domains; no measure of consistency was reported among these 4 trials pooled (or the 2 trials that were not included in pooled analysis because they measured quality of life using different instruments). Therefore, full-text of these 6 trial reports were reviewed to determine whether the effects on physical and mental domains of quality of life were consistent across trials. The table below this summary includes the results from these 6 trials on both domains (where available) and shows that the effects were consistent across trials and comparable to the pooled mean differences of 4 to 5 (out of 100) reported in the systematic review.
  - **Other considerations:**
    - We do not consider the safety data reported by Khan 2014 to be as applicable/appropriate for estimation of complications compared to Gupta 2013, due mainly to concerns about low event rates and sample sizes raising concern for imprecision in estimates. Therefore, Khan 2014 safety data was not used for estimating complications in the subsequent sections of our Evidence Report (ie, Evidence Review [Part 4] and Evidence Synthesis [Part 5]).
- **Results:**
  - comparing catheter ablation vs. medication
    - recurrence of atrial tachyarrhythmia
      - we report the data here, but we do not consider this outcome in further sections of our evidence report (Parts 4 and 5) due to our specified scoping (using recurrence of atrial dysrhythmia as a surrogate only if more meaningful outcomes were not found)
      - catheter ablation associated with decrease in recurrence in overall analysis in 11 trials with 1,481 patients
        - RR 0.4 (95% CI 0.31 to 0.52)
        - recurrent atrial arrhythmia in 64.8% of medication group
        - results limited by significant heterogeneity
        - consistent effects in patients with and without previous use of antiarrhythmics
          - RR 0.37 (95% CI 0.31 to 0.52 in patients with previous use of antiarrhythmics in analysis of 8 trials with 998 patients, results limited by significant heterogeneity
          - RR 0.52 (95% CI 0.3 to 0.91) in patients who were antiarrhythmics-naive in analysis of 3 trials with 483 patients, results limited by significant heterogeneity
      - quality of life reported in 6 trials
        - catheter ablation associated with improved quality of life in pooled analysis of 4 trials that used 36-item Short Form General Health Survey
          - physical dimension slightly improved (pooled mean difference 5.0 points)
            - no standard deviation or other measure of variance reported

                - range not reported in publication but is typically 0-100 for SF-36 and its domains
            - mental dimension slightly improved (pooled mean difference 4.2)
                - no standard deviation reported
                - range not reported in publication but is typically 0-100 for SF-36 and its domains
        - no significant difference in 2 other trials that used different quality of life instruments

    - safety outcomes
        - catheter ablation associated with increase in major adverse events in analysis of 11 trials with 1,468 patients
            - 5% (38 events) vs. 2% (13 events)
            - RR 2.04 (95% CI 1.10 to 3.77)
            - commonly reported major adverse events included cardiovascular accident/transient ischemic attack; pericardial complications; hemorrhage, and pulmonary vein stenosis
        - no significant difference in all adverse events (9% vs. 11%)
        - We do not consider the safety data reported by Khan 2014 to be as applicable/appropriate for estimation of complications compared to Gupta 2013, due mainly to concerns about low event rates and sample sizes raising concern for imprecision in estimates. Therefore, Khan 2014 safety data was not used for estimating complications in the subsequent sections of our Evidence Report (ie, Evidence Review [Part 4] and Evidence Synthesis [Part 5]).

- **Additional Comment**:
    - Inclusion criteria did not specify restriction to patients without heart failure, and this was assumed based on the following: 1) the included 11 trials are identical to the 11 trials in patients without heart failure included in the 2018 Khan review (summarized above); 2) 3 of the 6 trials in patients with heart failure included in the Khan 2018 review were published before the close of the search window of Khan 2014 (ie, March 2014) but were not included in Khan 2018 review; and 3) mean ejection fraction was > 50% in all included trials, as indicated in Supplemental Table 2.
    - Quality-of-life physical and mental domain outcome data from 6 trials that reported quality of life outcomes:

Study	**No. of participants**	Results for physical and mental quality of life components
Trials from KHAN 2014 systematic review reported to include SF-36 physical and mental quality of life domains		
Jaïs 2008 Circulation 19029470	112	"At the 1-year follow-up, the physical and mental component summary scores of the ablation group were significantly higher than those of the AAD group (52.0 +/- 7.6 versus 48.9 +/- 7.2

		and 56.6 +/- 7.8 versus 51.9 +/- 9.7, respectively; P = 0.01)." (consistent effects at day 91 and day 180)
Forleo 2009 J Cardiovasc Electrophysiol 18775050	70	"Comparing the differences between the two groups, patients in PVI group reported significantly greater improvement in QoL scores as compared with patients in the ADT group for 5 of 8 SF-36 subscales. The significant differences in mean change of QoL scores between groups (P < 0.05, PVI vs ADT group) were: ... 8.4 for physical functioning, ... There were trends toward additional improvement for the other 3 SF-36 subscales (mental health, vitality, and role physical)." (follow-up at 1 year)
Wilber 2010 JAMA 20103757	167	SF-36 mental domain: mean difference at 3 months favoring ablation (mean difference [MD] 6.9, 95% CI 2.6 to 11.2, p < 0.001) SF-36 physical domain: MD at 3 months favoring ablation (MD 6.6, 95% CI 3.6-9.4, p < 0.001) Results text reported that improvements at 3 months persisted without significant change at 6 months and 9 months
Nielsen 2012 N Engl J Med 23094720	294	Results text reported that "The physical-component summary score improved more over time in the ablation group than in the drug-therapy group (Table 2)." (with no significant difference over time for mental-component summary score). Table 2 reports that at 12 months and 24 months scores for physical and mental components were similar between groups but slightly favored ablation group (mean difference between groups ranged from high of 2.7 points [range 0-100] for physical component at 12 months to low of 0.2 points [range 0-100] for mental component at 24 months)
Trials from KHAN 2014 systematic review reported to include quality of life measure other than SF-36		
Morillo 2014 JAMA 24549549	127	only overall quality of life reported (using EQ5D tariff score and visual analog score, both at 12 months), with no separate reporting of physical and mental domains. No significant difference in overall quality of life, although both tariff score and visual analog score slightly favored ablation group.
Mont 2014 Eur Heart J 24135832	146	Physical and psychological domains of Atrial Fibrillation (AF)-QoL questionnaire were reported at 6 months and 12 months and showed no significant differences between groups at either time point (Table 3). The outcomes for both domains nonsignificantly favored ablation at both time points (with mean difference between groups ranging from low of 0.6 points at 12 months for physical domain [range 0-100, with higher scores better*] to 7.6 points [range 0-100, with higher scores better*] for psychological domain at 6 months.

*Range of AF-QoL domains not reported in Mont 2014 Eur Heart J and was assumed to be 0-100 as that is the range to which scores for AF-QoL domains have typically been standardized to improve interpretation and comprehension (Arribas 2010 EP Europace).

KHAN 2018

Khan SU, Rahman H, Talluri S, Kaluski E. The Clinical Benefits and Mortality Reduction Associated With Catheter Ablation in Subjects With Atrial Fibrillation: A Systematic Review and Meta-Analysis. JACC Clin Electrophysiol. 2018 May;4(5):626-635. Epub 2018 May 2. PubMed
Relevant to FAQ2, FAQ4, FAQ5, FAQ7

- **Study design:** systematic review of randomized trials
- **Population:** 2,272 adults with atrial fibrillation with or without heart failure with reduced ejection fraction in 17 randomized trials
    - 775 patients with atrial fibrillation with heart failure (left ventricular ejection fraction <50% and New York Heart Association functional class ≥ II) in 6 trials
        - left ventricular ejection fraction
            - mean 28% at baseline
            - differed across included trials per inclusion criteria
                - ≤ 35% in 3 trials (including the largest trial)
                - ≤ 45% in 1 trial
                - ≤ 40% in 1 trial
                - ≤50% in 1 trial
        - about 44% had coronary artery disease
        - 95% had persistent AF and 5% had paroxysmal AF
        - patients were relatively young with mean age 61.2 years old
        - about 85% were male
    - 1,497 adults with atrial fibrillation without heart failure in 11 trials
        - about 8% had coronary artery disease69% had paroxysmal AF and 31% had AF
        - mean age was 56 years old
        - about 70% were male

- **Intervention:** catheter ablation using various procedural techniques
- **Comparison:** rhythm- or rate-control medications, which varied across trials
- **Outcomes:**
    - efficacy: all-cause mortality, cardiac hospitalizations, recurrent atrial arrhythmia, stroke, need for cardioversion, 6-min walk test, left ventricular ejection fraction, maximal oxygen consumption
    - safety: major bleeding, pericardial complications, pulmonary vein stenosis
- **Duration of follow-up:**
    - in patients with atrial fibrillation with heart failure
        - mean 19 months
        - range 6 months to 60 months
        - 60 months in largest trial
    - in patients with atrial fibrillation without heart failure
        - mean 14 months
        - range 9 to 24 months
- **Certainty and Results:**
    - **Risk of bias:** patients and physicians not blinded to treatment assignment
    - **Precision:**

- **Directness:**
- **Consistency:**
- **Other considerations:** We do not consider the safety data reported by Khan 2018 to be as applicable/appropriate for estimation of complications compared to Gupta 2013, due mainly to concerns about low event rates and sample sizes raising concern for imprecision in estimates. Therefore, Khan 2018 safety data was not used for estimating complications in the subsequent sections of our Evidence Report (ie, Evidence Review [Part 4] and Evidence Synthesis [Part 5]).

Summary of findings of **efficacy outcomes** comparing catheter ablation vs. medication in patients with atrial fibrillation **with heart failure**

Outcome	**No. of Participants (studies)**	**Effect estimates**	**Control group event rate**	**Certainty**
all-cause mortality	670 (4)	risk ratio (RR) **0.52 (95% CI 0.36 to 0.76)**	19.3%	Moderate (downgraded due to no blinding of patients and physicians)
cardiac hospitalizations	632 (3)	RR **0.63 (95% CI 0.46 to 0.87)**	47.5%	Moderate (downgraded due to no blinding of patients and physicians)
recurrent atrial arrhythmia	780 (6)	RR **0.44 (95% CI 0.31 to 0.61)**	71.9%	Moderate (downgraded due to no blinding of patients and physicians)
6-minute walk test	(4)	mean difference (MD) **12.18 m, 95% CI 1.10 to 23.26 m**	NA	Moderate (downgraded due to no blinding of patients and physicians)
left ventricular ejection fraction	(6)	MD **5.29% (95% CI 1.51% to 9.08%)**	NA	Moderate (downgraded due to no blinding of patients and physicians)
maximal oxygen	(2)	MD **3.07 mL/kg per minute (95% CI 1.35 to 4.79 mL/kg**	NA	Moderate (downgraded due

consumption at peak exercise		**per minute)**		to no blinding of patients and physicians)
stroke	709 (3)	RR 0.72 (95% CI 0.24 to 2.21)	3.1%	Low (downgraded due to no blinding of patients and physicians and serious imprecision)
need for cardioversion	244 (2)	RR 0.29 (95% CI 0.01 to 11.65)	4.3%	Very low (downgraded due to no blinding of patients and physicians and very serious imprecision) (This CI was so wide, we did not further consider this outcome.)

Statistically significant effect estimates are bolded.

Summary of findings of **efficacy outcomes** comparing catheter ablation vs. medication in patients with atrial fibrillation **without heart failure**

Outcome	**No of Participants (studies)**	**Effect estimates**	**Control group event rate**	**Certainty**
all-cause mortality	710 (4)	RR 0.88 (95% CI 0.29 to 2.61)	2.1%	Low (downgraded due to imprecision and no blinding of patients and physicians)
cardiac hospitalizations	629 (4)	RR **0.32 (95% CI 0.23 to 0.45)**	31.5%	Moderate (downgraded due to no blinding of patients and physicians)
recurrent atrial arrhythmia	1,481 (11)	RR **0.4 (95% CI 0.31 to 0.52)**	63.8%	Moderate (downgraded due to no blinding of

				patients and physicians)
need for cardioversion	216 (2)	RR 0.69 (95% CI 0.47 to 1.01)	31.3%	Low (downgraded due to imprecision and no blinding of patients and physicians)
need for pacemaker	637 (4)	RR 0.97 (95% CI 0.23 to 4.17)	0.96%	Very low (downgraded due to serious imprecision and no blinding of patients and physicians) (This CI was so wide, we did not further consider this outcome.)

Statistically significant effect estimates are bolded.

Summary of findings **of safety outcomes** comparing catheter ablation vs. medication in patients with atrial fibrillation **with or without heart failure** (combined analysis)

Outcome	**No of Participants (studies)**	**Effect estimates**	**Control group event rate**	**Certainty**
major bleeding	811 (7)	RR **3.98 (95% CI 1.31 to 12.16)**	0.2%	Moderate (downgraded due to no blinding of patients and physicians)
pericardial complications	1,890 (12)	RR **3.71 (95% CI 1.58 to 8.73)**	0.1%	Moderate (downgraded due to no blinding of patients and physicians)
pulmonary vein stenosis	1,109 (6)	RR 3.02 (95% CI 0.83 to 10.93)	0%	Low (downgraded due to no blinding of patients and physicians and imprecision)

Statistically significant effect estimates are bolded.

PHAN 2016

Phan K, Phan S, Thiagalingam A, Medi C, Yan TD. Thoracoscopic surgical ablation versus catheter ablation for atrial fibrillation. Eur J Cardiothorac Surg. 2016 Apr;49(4):1044-51. Epub 2015 May 23. PubMed

Relevant for FAQ7

- **Study design:** systematic review and meta-analysis of randomized, controlled trials and observational studies
- **Population:** patients with atrial fibrillation receiving either catheter ablation or minimally-invasive thoracoscopic surgical ablation
    - *Note*: only the catheter ablation arm is considered here (surgical arm irrelevant for purposes of this evidence report)
        - mean age 55.2 years, 74.6% male, 43.6% persistent atrial fibrillation (56.4% paroxysmal), mean left ventricular ejection fraction 59.7%, mean duration of atrial fibrillation of 5.7 years
    - 8 studies totaling 699 patients met inclusion criteria (3 randomized, controlled trials; 5 retrospective observational studies)
        - 2 studies studied patients with paroxysmal atrial fibrillation, 2 studied patients with persistent atrial fibrillation, and 4 studied mixed populations
- **Intervention:** minimally-invasive thoracoscopic surgical ablation
- **Comparison:** catheter ablation
- **Outcome:**
    - primary outcome was freedom from atrial fibrillation off antidysrhythmic drugs (note this does not necessarily mean patients were not taking rate-controlling medication)
    - secondary outcomes included repeat ablation rate and complications (stroke, transient ischaemic attack (TIA), pneumonia, pleural effusions, pneumothorax, pericardial effusion/tamponade, groin haematoma and pacemaker implantations)
- **Duration of follow-up:** of studies reporting mean follow-up duration, mean follow-up duration ranged from 6 months to 30.6 ± 18.9 months (one study only reported range of 6 to 40 months)
- **Certainty: Low for freedom off antidysrhythmic drugs and repeat ablation rates; Very Low for complications (if using for complications data; see "Other considerations" for discussion about why these data are not as applicable compared to other evidence sources)**; may also consider up to a full additional downgrade (where possible) for patients with comorbid heart failure with reduced ejection fraction/reduced systolic function depending on concern about directness
    - **Risk of bias:** unclear risk of bias due to loss to follow-up; specified as "low risk of bias" for 5 of 8 included trials, but quality of this assessment is unclear (see other considerations), and is not reported in any fashion (even "unclear") for 3 of 8 studies
    - **Precision:** repeat ablation and freedom from atrial fibrillation off antidysrhythmic drugs suffer from imprecision of potential clinical relevance (whether to downgrade for repeat ablations may depend on threshold); low sample size and number of events for complications data (15 complications among 193 patients) raises serious concern for precision
    - **Directness:** results may not apply as directly to patients undergoing ablation for atrial fibrillation with comorbid heart failure with reduced ejection fraction/reduced systolic function, so one might consider a downgrade for indirectness in that population
    - **Consistency:** high heterogeneity in many of the results (see below)
    - **Other considerations:**
        - We do not consider the complications data by Phan 2016 to be as applicable/appropriate for estimation of complications compared to Gupta 2013, due mainly to concerns about low event rates and sample sizes (15 complications among 193 patients in 4 studies) raising concern for imprecision

in estimates. Therefore, the Phan 2016 complications data were not used for estimating complications in the subsequent sections (Parts 4 and 5) of our evidence report.

- The authors report completing a quality assessment using a checklist developed by the Dutch Cochrane Working Group according to the MOOSE recommendations for systematic reviews of observational studies; however, the reliability of this assessment is questionable, as certain domains were not clearly assessed (i.e., blank space, not even specified as unclear risk of bias), and all 8 studies were deemed to have "high risk of bias" for "sufficient duration of follow-up", which they defined as a minimum of 12 months (and 6 studies provided 12-month data for freedom from atrial fibrillation off antidysrhythmic drugs)

- **Results:**

Freedom from atrial fibrillation off antidysrhythmic drugs and repeat ablations

Outcome*	No. of participants (studies)	n/N (pooled rate)	Meta-analyzed proportion†	Range of individual proportions
freedom from atrial fibrillation off antidysrhythmic drugs				
6 months	157 (4)	101/157 (64.3%)	66.8% (95% CI 43.5% to 86.7%; I^2 = 84.5%) 67.0% (95% CI 45.1% to 88.8%; I^2 = 88.2%)	44.4% to 90%
12 months	326 (6)	173/326 (53.1%)	51.4% (95% CI 39.1% to 63.7%; I^2 = 78.1%) 51.3% (95% CI 39.3% to 63.3%; I^2 = 79.4%)	36.5% to 75%
overall	368 (8)	204/368 (55.4%)	57.0% (95% CI 43.6% to 69.9%; I^2 = 82.7%) 57.7% (95% CI 44.6% to 70.9%; I^2 = 85.7%)	36.5% to 90%
repeat ablations	127 (3)	31/127 (24.4%)	22.1% (95% CI 12.2% to 33.8%; I^2 = 38.5%) 20.5% (95% CI 9.1% to 31.9%; I^2 = 56.5%)	8.3% to 27.7%

*Freedom from atrial fibrillation off antidysrhythmic medication at 3 months not captured by this evidence review, as this is a less relevant outcome during the "blanking"/stabilization period. Note being off antidysrhythmic medication is not necessarily the same as being off medication, because the two primary options for managing the dysrhythmia *per se* are rhythm control (antidysrhythmic medication; e.g., amiodarone) and rate control (rate-controlling medication; e.g., metoprolol). Need for anticoagulation is also a separate consideration, determined on a person-by-person basis.

† Top: Freeman-Turkey double arcsine proportion; bottom: untransformed proportion; all estimates are via random-effects, Sidik-Jonkman/Hartung-Knapp-Sidik-Jonkman model (OpenMeta[Analyst])

Complication rate

Complication	Rate (%)	No. of participants (studies)*
Any	7.8	193 (4)
Mortality	0.5	193 (4)
Stroke	0.7	193 (4)
TIA	1	193 (4)
Pneumonia	1.3	193 (4)
Pleural effusion	0	193 (4)
Pneumothorax	0	193 (4)
Pericardial effusion/tamponade	1.7	193 (4)
Groin hematoma	2.8	193 (4)
Pacemaker implantation	1.1	193 (4)

* Note: We include the overall complication rate (pooled rate for catheter ablation group for the meta-analysis of complications), but we note this is based on 4 studies totaling 193 patients with a total of 15 complications. It is unclear whether all 4 studies also contributed to the estimates for individual complications, but we have assumed that here.

TURAGAM 2018

Turagam MK, Garg J, Whang W, Sartori S, Koruth JS, Miller MA, Langan N, Sofi A, Gomes A, Choudry S, Dukkipati SR, Reddy VY. Catheter Ablation of Atrial Fibrillation in Patients With Heart Failure: A Meta-analysis of Randomized Controlled Trials. Ann Intern Med. 2018 Dec 25 [Epub ahead of print] PubMed

Relevant to FAQ2, FAQ3, FAQ4, FAQ5, FAQ7

- **Study design:** systematic review of randomized trials
- **Population:** 775 adults with atrial fibrillation with heart failure in 6 randomized trials
  - left ventricular ejection fraction mean 28% at baseline
  - 5 trials included only patients with persistent AF, and in 1 trial (the largest) 52% of patients had paroxysmal AF
  - mean age ranged from 55 to 64 years old
  - mean duration of persistent AF > 12 months in 5 trials and 8.2 months in 1 trial
  - predominant cause of heart failure was ischemic cardiomyopathy
- **Intervention:**
  - radiofrequency catheter ablation
    - pulmonary vein isolation was key ablation strategy in all trials
    - further ablation done outside pulmonary veins for most patients
- **Comparison:**
  - rhythm control or rate control
    - rate control used in 4 trials
    - rhythm control used in 1 trial
    - rate control in two-thirds of patients and rhythm control in one-third of patients in 1 trial
- **Outcome:**

    - efficacy: all-cause mortality, cardiac hospitalizations, recurrent atrial arrhythmia, quality of life, 6-min walk test, left ventricular ejection fraction, maximal oxygen consumption
    - safety: vascular puncture site complications, pericardial effusion, heart failure, pulmonary venous stenosis, thromboembolic events
- **Duration of follow-up:** range from 6 to 60 months
- **Certainty and Results:**
    - **Risk of bias:** patients and physicians not blinded to treatment assignment
    - **Precision:**
    - **Directness:**
    - **Consistency:**
    - **Other considerations:** We do not consider the safety data reported by Turagam 2018 to be as applicable/appropriate for estimation of complications compared to Gupta 2013, due mainly to concerns about low event rates and sample sizes raising concern for imprecision in estimates. Therefore, Turagam 2018 safety data was not used for estimating complications in the subsequent sections of our Evidence Report (ie, Evidence Review [Part 4] and Evidence Synthesis [Part 5]).

Summary of findings of efficacy outcomes comparing catheter ablation vs. medication in patients with atrial fibrillation with heart failure

Outcome	**No. of Participants (studies)**	**Effect estimates**	**Control group event rate**	**Certainty**
all-cause mortality	732 (5)	RR **0.52 (95% CI 0.33 to 0.81)**	17.7%	Moderate (downgraded due to no blinding of patients and physicians)
cardiac hospitalizations	517 (4)	RR **0.60 (95% CI 0.39 to 0.93)**	27.6%	Moderate (downgraded due to no blinding of patients and physicians)
recurrent atrial arrhythmia*	346 (4)	ablation associated with decrease in proportion with recurrent arrhythmia in comparison of pooled event rates between groups **(66% decrease, 95% CI 27% to 96% decrease)†**		Moderate (downgraded due to no blinding of patients and physicians)
6-minute walk test	438 (5)	MD **20.93 m (95% CI 5.91 to 35.95 m)**	NA	Moderate (downgraded due to no blinding of

				patients and physicians)
left ventricular ejection fraction	495 (6)	MD **6.95% (95% CI 3.00 to 10.9%)**	NA	Moderate (downgraded due to no blinding of patients and physicians)
maximal oxygen consumption at peak exercise	100 (2)	MD **3.17 mL/kg per minute (95% CI 1.26 to 5.07 mL/kg per minute)**	NA	Moderate (downgraded due to no blinding of patients and physicians)
quality of life	341 (4)	MD -9.02 points favoring ablation [range: 0 to 105], 95% CI -19.75 to 1.71 points)‡	NA	Low (downgraded due to imprecision and no blinding of patients and physicians)

Statistically significant effect estimates are bolded.
* We report the data for this outcome here, but we do not consider this outcome in further sections of our evidence report (Parts 4 and 5) due to our specified scoping (using recurrence of atrial dysrhythmia as a surrogate only if more meaningful outcomes were not found)
† Pooled proportion with recurrence in drug therapy group was 96% (95% CI 0.62% to 1.00%) with significant heterogeneity among drug arms and pooled proportion with recurrence in catheter ablation group was 27% (95% CI 7% to 54%) with significant heterogeneity among ablation arms. The difference in proportion with recurrence was reported to be 66% (95% CI 27% to 96%) and the footnote to the Figure that reports this forest plot (Figure 5) notes that this comparison between groups was done with a Freeman–Tukey arcsine transformation.
‡ Turagam 2018 used a random-effects model with the restricted maximum likelihood (REML) τ^2 estimator for continuous outcomes, and they also employed the Hartung-Knapp (HK) small sample adjustment for all outcomes since they analyzed fewer than 10 studies. We do not take issue with this conservative approach, but we do note that an estimate with a narrower confidence interval would very likely result if one used the REML method without the HK small-sample adjustment or used other random-effects models that are more commonly used (e.g., DerSimonian-Laird).

- safety outcomes
    - vascular puncture site complications in 1.3% (5 events) vs. 0% (0 events) (no p-value reported)
    - pericardial effusion in 2% (8 events) vs. 0% (0 events) (no p-value reported)
    - heart failure in 1% (4 events) vs. 0.5% (2 events) (no p-value reported)
    - pulmonary venous stenosis in 0.7% (3 events) vs. 0% (0 events) (no p-value reported)
    - thromboembolic events in 2.3% (9 events) vs. 3.1% (12 events) (no p-value reported)

Part 4 - Evidence Review

Methods

For each FAQ, the key concepts (results and factors affecting certainty of the results) from the included studies that are most relevant to evidence synthesis will be summarized in Evidence Review Tables. Where evidence is very limited, or the FAQ is for descriptive summary, summary text will be provided.

Results

FAQ 1: What does the treatment involve?

Descriptive Overview

Any patient being considered for a catheter ablation/pulmonary vein isolation (PVI) procedure should have first undergone a thorough investigation for possible underlying illnesses or modifiable risk factors that can cause or contribute to atrial fibrillation. Examples include, but are not limited to, hyperthyroidism, sleep apnea, obesity and sedentary lifestyles, and inappropriate/excessive alcohol consumption. Before moving forward with PVI, patients should ideally receive optimized treatment for any underlying illnesses or modifiable risk factors that may contribute to or cause atrial fibrillation. We also note this is part of good practice for the management of atrial fibrillation in general, not just when one is considering PVI.

(Calkins 2017)

Pulmonary vein isolation (FAQ1a)

Descriptive Overview

The pulmonary veins are responsible for taking blood from the lungs back to the top left chamber of the heart, which is called the left atrium. The pulmonary veins and the left atrium are made of different tissue types. In people with atrial fibrillation, the abnormal electrical signals that cause the atrial fibrillation originate where these two types of tissue meet.

Pulmonary vein isolation (PVI) uses small tube-like devices called catheters to isolate this area where the two tissue types meet, and then uses either heat energy (“radiofrequency”) or cold energy (“cryo”) to destroy (“ablate”) this small area of tissue. Scar tissue will then form at this area, and this scar tissue helps prevent the abnormal electrical signals that cause atrial fibrillation.

PVI can be performed using local numbing medication and sedation to help you relax, but in some case, you will be put to sleep for the procedure using general anesthesia. Your healthcare team will discuss this with you prior to the procedure. If you get local numbing medication and sedation, then it will be important for you to remain very quiet and still and avoid taking deep breaths.

The catheters are typically inserted into veins in the leg/groin area (but possibly also the neck) and then advanced to the heart. Once at the heart, the catheters will either pass through an existing hole in your heart (if you have one) or a small hole will be made to allow the catheters to get to where they need to be. In addition to the mapping mechanisms that help identify the area of abnormal electrical activity, a type of x-ray and ultrasound will be used to help guide the procedure.

Once the catheter is in the right place, energy will be applied to destroy the small area of tissue and promote scarring. This will be repeated for each of the pulmonary veins. You may feel some discomfort during this part of the procedure, such as a slight burning sensation or heaviness in your chest. If this occurs, you can inform the nurse, physician, or other caregiver in the room, and they can give you more medication if needed.

The procedure itself may generally last 4 to 6 hours, but each patient is different. After the procedure, you will stay in bed for several hours and will need to keep your legs still to help prevent bleeding at the catheter insertion area. You will stay in the hospital overnight, but can normally go home the next day. You may have general soreness, some chest discomfort, and/or fatigue in the first 48 hours or so after the procedure. Additionally, because it takes time for the scar tissue to form, it is common for people to have extra or irregular heartbeats in the first 8 to 10 weeks after the procedure. You can usually return to normal, general activities 48 hours after the procedure, but you will probably be given restrictions on the weight you are allowed to lift for at least the first week and will probably need to refrain from vigorous exercise for at least 3 weeks.

Your healthcare team will also tell you about medications you will need to take after the procedure. You should expect to take a blood thinning medication for about 2 to 3 months after the procedure, and you may have to take this for even longer depending on your specific risk factors for stroke. You may also need to take a medication to help prevent abnormal heart rhythms for about 1 to 3 months.

The long-term goal of PVI is to reduce or eliminate the medications used to treat atrial fibrillation. Ideally, the procedure allows the patient to eliminate medications that help manage or treat the abnormal electrical signals that cause atrial fibrillation. Many patients are also ultimately able to stop their blood thinner (if they take one), but again, this will be assessed on a case-by-case basis. However, atrial fibrillation comes back and requires additional treatment in some patients.

(Calkins 2012; Calkins 2017; Cleveland Clinic 2017; Dudley 2014; University Hospital Southampton NHS Foundation Trust 2015)

Medical therapy (FAQ1b)

Descriptive Overview

Your healthcare professional will discuss two areas with you where medication is used for atrial fibrillation. The first area has to do with the abnormal electrical signals of atrial fibrillation. The second area has to do with how atrial fibrillation increases your risk for blood clots, which can cause stroke or block the flow of blood to other areas of your body (such as your arms or legs).
For the first area, you will either take a “rhythm control” or “rate control” medication. “Rhythm control” medications try to keep atrial fibrillation from occurring. “Rate control” medications try to keep the heart rate controlled even if atrial fibrillation occurs. Either is an acceptable choice, so you and your healthcare professional will decide which is best for you based on things like your other health conditions, cost, side effects, and other factors. For the second area, you and your healthcare professional will determine your risk of blood clots due to your atrial fibrillation. The risk is different for each person. If your risk of blood clots is high, you and your healthcare professional will discuss going on a medication to thin your blood.
(DynaMed Plus 2018; January 2014; Kirchhof 2016)

FAQ2: Will I live longer?

Evidence Review Table

Comparing catheter ablation vs. medication on all-cause mortality

Study (author year)	No. of participants (studies)	Effect estimates for all-cause mortality	Medical therapy group all-cause mortality rate	Catheter ablation group all-cause mortality rate	Certainty (reason for downgrade)
in trials of patients with atrial fibrillation **with heart failure**					
Khan 2018	670 (4*)	risk ratio (RR) **0.52 (95% CI 0.36 to 0.76)** at 6 to 60 months follow-up	19.3%	10.0% (95% CI 6.9% to 14.7%)	Moderate (downgraded due to no blinding of patients and physicians)
Turagam 2018	732 (5*)	RR **0.52 (95% CI 0.33 to 0.81)** at 6 to 37.8 months follow-up	17.7%	9.2% (95% CI 5.8% to 14.3%)	Moderate (downgraded due to no blinding of patients and physicians)
in trials of patients with atrial fibrillation **without heart failure†**					
Khan 2018	710 (4)	RR 0.88 (95% CI 0.29 to 2.61) at 9 to 24 months follow-up	2.1%	1.8% (95% CI 0.6% to 5.5%)	Low (downgraded due to imprecision and no blinding of patients and physicians)

Statistically significant effect estimates are bolded.

* Khan 2018 excluded CAMERA-MRI 2017 trial from their meta-analysis on the all-cause mortality outcome and Turagam 2018 included it. CAMERA-MRI 2017 had no deaths in either group and therefore it is more appropriate to exclude it from the meta-analysis because trials with no events do not provide any indication of either the direction or magnitude of the relative effect of treatment [Cochrane Handbook, Section 16.9.3 'Studies with no events')]. For our evidence synthesis in Part 5, we use the all-cause mortality data from Khan 2018.

† Khan 2014 limited to patients without heart failure but did not report all-cause mortality outcome.

FAQ3: Will my symptoms improve?

Evidence Review Tables

Comparing catheter ablation vs. medication on quality of life

Study (author year)	Quality of life outcome	No. of participants (studies)	Effect estimates for quality of life	Certainty (reasons for downgrade)
in trials of patients with atrial fibrillation **with heart failure***				
Turagam 2018	heart failure-related quality of life (as assessed by Minnesota Living with Heart Failure Questionnaire)	341 (4)	MD -9.02 points favoring ablation [range: 0 to 105] (95% CI -19.75 to 1.71 points) at 6 to 24 months follow-up	Low (downgraded due to imprecision and no blinding of patients and physicians)
in trials of patients with atrial fibrillation **without heart failure***				
Khan 2014	6 trials reported quality of life (QoL), but data from only 4 trials that used the same QoL instrument (SF-36) were pooled, for physical and mental domains; the other 2 trials that measured QoL using instruments other than SF-36 were each reported only as showing no difference in quality of life (with no quantitative estimates provided)	916 (6)		

Study (author year)	Quality of life outcome	No. of participants (studies)	Effect estimates for quality of life	Certainty (reasons for downgrade)
	SF-36 physical domain	643 (4)	only reported as "(pooled mean difference, 5.0)" • no SDs or other measure of variance reported • range not reported in systematic review but is typically 0-100 points for SF-36 domains • full-text publications of the 4 trials contributing to pooled MD for SF-36 physical domain, as well as the other 2 trials that used different QoL instruments and did not contribute to pooled MD, were reviewed and all 6 were determined to have consistent effect sizes and therefore we did not downgrade for lack of consistency (see Khan 2014 summary in Part 3, Critical Appraisal)	Low (downgraded due to no blinding of patients and physicians and imprecision)
	SF-36 mental domain	643 (4)	only reported as "(pooled mean difference, 4.2)" • no SDs or other measure of variance reported • range not reported in systematic review but is typically 0-100 points for SF-36 domains • full-text publications for the 4 trials contributing to pooled MD for SF-36 mental domain, as well as the 2 other trials that used different QoL instruments and did not contribute to the pooled MD, were reviewed and all 6 were determined to have consistent effect sizes and therefore we did not downgrade for lack of consistency (see Khan 2014 summary in Part 3, Critical Appraisal)	Low (downgraded due to no blinding of patients and physicians and imprecision)

*Khan 2018 did not report quality of life outcome in patients with heart failure or in patients without heart failure.

Comparing catheter ablation vs. medication on symptomatic recurrence of atrial fibrillation

Study (author year)	No. of participants (studies)	Rate in antidysrhythmic therapy group	Relative risk (95% CI)	Certainty (reasons for downgrade)
Hakalahti 2015	491* (3)	42.1% (102/242)	0.57 (0.30 to 1.08)	Very low (downgraded due to unclear risk of bias for allocation concealment and high risk of bias for blinding of patients and personnel, indirectness†, inconsistency, and imprecision)

* There were 491 total participants in the trials, but estimates are from 480 participants

† Indirectness downgrade due to only including trials of patients without previous treatment with antidysrhythmic medication (i.e., testing catheter ablation versus antidysrhythmic medication as first-line therapy for atrial fibrillation). Therefore, results may not be applicable to patients previously treated with antidysrhythmic medication. Additionally, aside from thromboembolic prophylaxis, medical therapy for atrial fibrillation can include rate-controlling or rhythm-controlling medication, and this systematic review focuses on rhythm-controlling medication (antidysrhythmics), thus furthering the issue of indirectness.

FAQ 4: What is my risk for being hospitalized later?

Evidence Review Table

Comparing catheter ablation vs. medication on cardiac hospitalization

Study (author year)	**No. of participants (studies)**	**Effect estimates for cardiac hospitalizations**	**Medical therapy group cardiac hospitalization rate**	**Catheter ablation group cardiac hospitalization rate**	**Certainty (reason for downgrade)**
in trials of patients with atrial fibrillation **with heart failure***					
Khan 2018	632 (3)	RR **0.63 (95% CI 0.46 to 0.87)** at 6 to 60 months follow-up	47.5%	29.9% (95% CI 21.9% to 41.3%)	Moderate (downgraded due to no blinding of patients and physicians)
in trials of patients with atrial fibrillation **without heart failure†**					
Khan 2018	629 (4)	RR **0.32 (95% CI 0.23 to 0.45)** at 12 to 24 months follow-up	31.5%	10.1% (95% CI 7.2% to 14.2%)	Moderate (downgraded due to no blinding of patients and physicians)

Statistically significant effect estimates are bolded.

* Turagam 2018 reported on "heart-failure hospitalization"; however, we included only the cardiac hospitalization outcome reported in Khan 2018 (which would include heart-failure hospitalization events as well as atrial fibrillation-related hospitalization events).

† Khan 2014 did not report cardiac hospitalization outcome.

FAQ 5: What are the risks?

Pulmonary vein isolation (FAQ5a)

Evidence Review Description

Evidence comes primarily from Gupta 2013, a systematic review dedicated to complications of catheter ablation in atrial fibrillation, totaling 83,236 patients from 192 studies (34 randomized, controlled trials and 158 observational studies). We did not find any more current systematic review dedicated to complications (see Part 2).

Gupta 2013 provides estimates for the overall study period of 2000 to 2012, for the more contemporary period of 2007 to 2012, and for the subset of studies that prospectively defined major complications. Most studies (140/192) were published between 2007 and 2012. Complication rates are largely comparable across the three approaches to estimation, with some possible differences in certain areas (e.g., the overall complication rate is somewhat higher among studies that prospectively defined major complication rates). (Low certainty)

For completeness, we also considered complication rates reported by other bodies of evidence, but we assessed these as having Very low certainty or not being as applicable or appropriate for estimation of complications compared to Gupta 2013, due to key reasons noted below:

- Khan 2014, Khan 2018, Phan 2016, and Turagam 2018 are all systematic reviews and meta-analyses. Khan 2014, Khan 2018, and Turagam 2018 included only randomized, controlled trials of catheter ablation versus medical therapy in atrial fibrillation. Phan 2016 included randomized, controlled trials and observational studies investigating catheter ablation versus minimally-invasive thoracoscopic surgical ablation in atrial fibrillation (we considered only the catheter ablation arm for complications and need for additional treatment). In Part 3, we have provided the complications data they captured as part of their work, but we are less confident in these estimates and consider them less applicable/appropriate compared to Gupta 2013, mainly due to low event rates and sample sizes and the consequent concerns about precision in any estimates provided (e.g., Phan 2016 had a total of 15 complications among 193 patients in the catheter ablation group). We therefore did not carry these estimates forward to Part 4.
- Calkins 2017 is a multiorganizational consensus statement on catheter ablation in atrial fibrillation, and they included a table with incidence rates for “selected” complications. However, it is not clear whether their report on “selected” complication rates was informed by a systematic review of the literature. We are thus less certain about these estimates compared to Gupta 2013.
    - We have included below tabulated rates of complications from Calkins 2017 that were not specifically reported by Gupta 2013, but again, we consider these Very low certainty estimates.

Evidence Review Tables

Summary table for complications data from Gupta 2013

	Entire study period: 2000 to 2012		Studies published between 2007 to 2012		Studies that prospectively defined major complication	
Complication	**Rate (%), 95% CI**	**No. of studies***	**Rate (%), 95% CI**	**No. of studies***	**Rate (%), 95% CI**	**No. of studies***
Acute complication rate	2.9 (2.60 to 3.22)	183	2.6 (2.31 to 2.95)	140	3.5 (2.90 to 4.14)	42
Type of complication						
Death	0.06 (0.03 to 0.09)	58	0.06 (0.03 to 0.09)	45	0.03 (0.01 to 0.07)	17
Atrioesophageal fistula	0.08 (0.05 to 0.11)	67	0.07 (0.04 to 0.11)	53	0.06 (0.02 to 0.11)	18
Pulmonary vein stenosis†	0.5 (0.34 to 0.60)	118	0.4 (0.30 to 0.58)	90	0.3 (0.15 to 0.58)	25
Vascular complications‡	1.4 (1.02 to 1.79)	117	1.2 (0.83 to 1.72)	86	1.9 (1.05 to 2.93)	34
Arteriovenous fistula	0.40 (0.28 to 0.55)	45	0.4 (0.24 to 0.58)	32	0.3 (0.19 to 0.51)	14
Femoral pseudoaneurysm	0.5 (0.34 to 0.60)	49	0.4 (0.29 to 0.57)	38	0.5 (0.30 to 0.75)	15
Stroke/TIA	0.6 (0.50 to 0.67)	155	0.55 (0.46 to 0.65)	119	0.5 (0.38 to 0.65)	41
Stroke	0.4 (0.30 to 0.44)	111	0.3 (0.26 to 0.43)	85	0.3 (0.21 to 0.49)	29
TIA	0.4 (0.28 to 0.47)	94	0.3 (0.25 to 0.43)	74	0.2 (0.13 to 0.34)	22
Tamponade	1.0 (0.83 to 1.14)	131	0.9 (0.75 to 1.10)	99	1.0 (0.65 to 1.28)	28
Pericardial effusion	0.7 (0.56 to 0.88)	67	0.7 (0.52 to 0.83)	55	0.6 (0.37 to 0.82)	16
Phrenic nerve injury	0.4 (0.22 to 0.54)	48	0.4 (0.19 to 0.60)	38	0.5 (0.13 to 1.07)	12
Diaphragmatic paralysis	0.3 (0.15 to 0.43)	21	0.2 (0.10 to 0.40)	15	0.1 (0.08 to 0.74)	1
DVT/PE	0.15 (0.09 to 0.21)	33	0.1 (0.08 to 0.21)	23	0.1 (0.05 to 0.20)	7
Pneumothorax	0.2 (0.08 to 0.29)	22	0.15 (0.06 to 0.28)	17	0.1 (0.01 to 0.30)	3
Hemothorax	0.2 (0.10 to 0.28)	25	0.2(0.10 to 0.29)	22	0.2 (0.08 to 0.36)	6
Sepsis, abscesses, or endocarditis	0.1 (0.06 to 0.24)	20	0.1 (0.04 to 0.24)	16	0.15 (0.02 to 0.38)	3
Valve damage	0.2 (0.08 to 0.25)	26	0.15 (0.08 to 0.25)	22	0.1 (0.04 to 0.30)	6

DVT, deep vein thrombosis; PE, pulmonary embolism; TIA, transient ischemic attack.

*Only number of studies (not number of participants) was reported by Gupta 2013; however, each study had to have at least 100 participants per their inclusion criteria.

†Pulmonary vein stenosis defined as >50% stenosis and requiring intervention

‡Vascular complications included bleeding, hematoma, arteriovenous fistula, and femoral pseudoaneurysm

Complication rates (Calkins 2017)

Complication	No. of studies*	Rate (%)
Air embolism	6	<1
Asymptomatic cerebral emboli (ACE)	18	2 to 15
Coronary artery stenosis/occlusion	9	<0.1
Gastric hypomotility	13	0 to 17
Mitral valve entrapment	8	<0.1
Pericarditis†	8	0 to 50
Radiation injury	20	<0.1
Stiff left atrial syndrome	8	<1.5

* This is number of studies *referenced*. Calkins 2017 did not clearly specify either the number of participants from the studies cited, nor did they clearly indicate a systematic review for the generation of their complication estimates.
†This is listed in their table as a complication, so we include it here as well. However, as they note, "when transmural lesions are generated during catheter ablation for AF [atrial fibrillation], some epicardial inflammation, and therefore some pericarditis, is inevitable." Consequently, it is very common for patients to experience "some pleuritic chest pain in the first several days following their procedure" or for there to be "'trace' pericardial effusion following AF ablation". However, "[t]hese largely self-limited manifestations of AF ablation-induced pericarditis are so common and of so little consequence that they are considered as part of the standard clinical course for patients who undergo AF ablation rather than as a complication of the procedure. A small subset of these patients will go on to develop more severe and clinically significant manifestations of pericarditis [such as Dressler syndrome, pericarditis leading to cardiac tamponade, and constrictive pericarditis]."

Medical therapy (FAQ5b)

Descriptive Overview

Risks will depend on the therapy in question. Below, we briefly address some of the major classes of medications within each of the strategies of "rate control" and "rhythm control" and some key risks noted for the class of medication or for medications commonly used within that class. This is not intended to be an exhaustive compilation of risks and does not necessarily address possible differences for specific medications within a class, as this is beyond the scope of this evidence report.

Rate control

Beta-blockers (e.g., metoprolol, carvedilol): bradycardia, atrioventricular block, hypotension; bronchospasm is rare (can minimize further by using cardioselective/β_1-selective beta-blocker)

Nondihydropyridine calcium channel blockers (verapamil, diltiazem): bradycardia, atrioventricular block, hypotension (possibly prolonged with verapamil)

Rhythm control

Class III antidysrhythmics (e.g., amiodarone, dronedarone): pulmonary toxicity (amiodarone), hepatotoxic effects (amiodarone, dronedarone), thyroid dysfunction (amiodarone), eye complications (amiodarone), bradycardia (amiodarone, dronedarone), rhythm disturbances (e.g., prolonged QT interval; amiodarone, dronedarone)

Class I antidysrhythmics (e.g., flecainide, propafenone): rhythm disturbances (brady- and tachydysrhythmias; prodysrhythmic effects)

(DynaMed Plus 2018; Kirchhof 2016)

FAQ 6: What are the side effects?

Consideration of thromboembolic prophylaxis is a part of both approaches. As this is not a differentiating factor, we do not address that here.

Pulmonary vein isolation (FAQ6a)

Descriptive Overview

You may have general soreness, some chest discomfort, and/or fatigue in the first 48 hours or so after the procedure. Additionally, because it takes time for the scar tissue to form, it is common for people to have extra or irregular heartbeats in the first 8 to 12 weeks after the procedure. This period of time is often called the "blanking" period or stabilization period.

(Calkins 2017; Cleveland Clinic 2017; University Hospital Southampton NHS Foundation Trust 2015)

Medical therapy (FAQ6b)

Descriptive Overview

Side effects from medical therapy will depend on the therapy in question. Below, we briefly address some of the major classes of medications within each of the strategies of "rate control" and "rhythm control" and some common side effects noted for the class of medication or for medications commonly used within that class. This is not intended to be an exhaustive compilation of adverse effect data and is not intended to address possible differences in rates for specific medications within a class, as this is beyond the scope of this evidence report.

<u>Rate control</u>

Beta-blockers (e.g., metoprolol, carvedilol): lethargy, upper respiratory tract symptoms, gastrointestinal upset, and dizziness

Nondihydropyridine calcium channel blockers (verapamil, diltiazem): dizziness, malaise/lethargy, edema, headache, hot flushes, constipation

<u>Rhythm control</u>

Class III antidysrhythmics (e.g., amiodarone, dronedarone): photosensitivity, neuropathy, tremor, malaise/fatigue, gastrointestinal upset, constipation

Class I antidysrhythmics (e.g., flecainide, propafenone): dizziness, headache, nausea, fatigue, blurred vision, photopsia, palpitations, dyspnea, xerostomia, dysgeusia

(DynaMed Plus 2018; Kirchhof 2016)

FAQ 7: Will I need additional treatment?

Among the elements addressed by FAQ 1 are: (1) the requirement for at least a period of anticoagulation after pulmonary vein isolation (possibly also including antidysrhythmic medication for a similar period), and (2) the fact that a long-term goal of pulmonary vein isolation is to be able to reduce or eliminate medication for atrial fibrillation. As such, we do not readdress these concepts here even though this FAQ is titled "Will I need additional treatment?".

Pulmonary vein isolation (FAQ7a)

Recurrences of atrial dysrhythmias are common during the first 2 to 3 months after catheter ablation (the "blanking" or stabilization period), and many of these resolve spontaneously. Therefore, repeat ablation should be deferred for at least 3 months following an initial ablation if possible.

(Calkins 2017)

Evidence Review Description – Pulmonary vein isolation vs. medical therapy

In systematic reviews of randomized trials, the only informative clinical outcome related to need for additional treatment is "Need for electrical cardioversion", which was reported in 2 trials of 216 patients with atrial fibrillation with comorbid heart failure in Khan 2018 (RR 0.69, 95% CI 0.47 to 1.01; rate in medical therapy group 31.3%). (Low certainty)

Evidence Review Tables – Pulmonary vein isolation

The other outcomes reported below include repeat ablation rates, freedom from atrial dysrhythmia off antidysrhythmic medication, and number of ablations received, all coming from observational data (Al-Hijji 2016) or systematic reviews and meta-analyses of data from observational studies and randomized trials (Clarnette 2018, Ganesan 2013, and Phan 2016).

Repeat ablation rates

Reference	No. of participants (studies)	Key findings	Follow-up	Certainty
Al-Hijji 2016	8,468 (1)	Any repeat ablation: 1,263/8,648 (14.6%; 95% CI 13.9% to 15.4%) • median time to repeat ablation: 0.7 (IQR 0.4 to 1.4) years • among those receiving any repeat ablation, timing was: ○ within 1 month: 49/1,263 (3.9%) ○ between 1 and 3 months: 119/1,263 (9.4%) ○ within 3 months: 168/1,263 (13.3%) ○ between 3 and 12 months: 647/1,263 (51.2%) ○ within 12 months: 815/1,263 (64.5%) ○ >12 months: 448/1,263 (35.5%) Repeat ablation beyond the 3-month period: 1,095/8,648 (12.7%; 95% CI 12.0% to 13.4%) • 647/1,095 (59.1%) were between the 3- and 12-month period • 448/1,095 (40.9%) were beyond the 12-month period Presence/absence of heart failure: No clear difference in rates of repeat ablation between those with and those without congestive heart failure (HR 0.94, 95% CI 0.82 to 1.09)	Median follow-up was 1.1 (IQR 0.5 to 2.3) years; total of 14,280.6 person-years of follow-up for repeat ablation outcome	Moderate (see Part 3)
Phan 2016	127 (3)	Any repeat ablation Pooled rate: 31/127 (24.4%) Meta-analyzed rate:* • 22.1% (95% CI 12.2% to 33.8%) • 20.5% (95% CI 9.1% to 31.9%) Range from individual studies: 8.3% to 27.7%	Range for mean follow-up: 6 months to 30.6 ± 18.9 months (one study only reported range of follow-up from 6 to 40 months)	Low (see Part 3)

* First rate is the Freeman-Turkey double arcsine proportion; the second rate is the untransformed proportion; all estimates are via random-effects, Sidik-Jonkman/Hartung-Knapp-Sidik-Jonkman model (OpenMeta[Analyst])

Number of procedures

Reference	No. of participants (studies)	Key findings	Follow-up	Certainty
Clarnette 2018	79 cohorts (each had to include at least 60 people, but total number of participants not reported)	Mean number of procedures in the "multiple-procedure" cohorts*: 1.37 ± 0.3 (range 1 to 2.3)	All studies had to have a defined follow-up of at least 12 months Mean follow-up was 25 ± 12 months (range 12 to 59 months)	Moderate (see Part 3)
Ganesan 2013	6,167 (19)	Average number of procedures for overall cohort: 1.51 (95% CI 1.36 to 1.67) • with paroxysmal atrial fibrillation (PAF): 1.45 (95% CI 1.31 to 1.59) • with non-paroxysmal atrial fibrillation (NPAF): 1.67 (95% CI 1.31 to 2.06)	All studies had to have an evaluation of outcomes at 3 years or more and a mean/median follow-up duration of at least 2 years Mean or median duration of follow-up varied from 28 to 71 months (6 studies had mean or median follow-up durations of 30 months or less; 13 had durations of at least 39 months)	Moderate (see Part 3)

* Defined as those either having multiple ablation procedures and/or using antidysrhythmic drugs for greater than 3 months after the index procedure

Freedom from atrial dysrhythmia off antidysrhythmic medication

Note being off antidysrhythmic medication is not necessarily the same as being off medication, because the two primary options for managing the dysrhythmia of atrial fibrillation *per se* are rhythm control (antidysrhythmic medication; e.g., amiodarone) and rate control (rate-controlling medication; e.g., metoprolol). Need for anticoagulation is also a separate consideration, determined on a person-by-person basis.

Reference	No. of participants (studies)	Key findings	Follow-up	Certainty
Clarnette 2018	74 cohorts (each had to include at least 60 people, but total number of participants not reported)	Single-procedure, ADM-free freedom from atrial dysrhythmia: 43% (95% CI 39% to 47%)	All had follow-up of ≥12 months Mean follow-up was 25 ± 12 months (range 12 to 59 months)	Moderate (see Part 3)
Ganesan 2013	14 studies (total number of participants not reported; overall sample was 6,167 patients from 19 studies, and only 3 studies had total number <100 who were receiving/had received PVI)	Late, single-procedure, ADM-free rate of not having atrial dysrhythmia or needing a repeat procedure within 12 months: 57.4% (95% CI 50.9% to 63.8%)*	All had evaluation of outcomes at ≥3 years and a mean/median follow-up duration of ≥2 years Mean or median duration of follow-up varied from 28 to 71 months (6 studies had mean or median follow-up durations ≤30 months; 13 had durations ≥39 months)	Moderate (see Part 3)
Phan 2016	157 (4)	6-month freedom from AF off ADM: Pooled rate: 101/157 (64.3%) Meta-analyzed rate:† • 66.8% (95% CI 43.5% to 86.7%) • 67.0% (95% CI 45.1% to 88.8%) Range of rates from individual studies: 44.4% to 90%	Range for mean follow-up: 6 months to 30.6 ± 18.9 months (one study only reported range of follow-up from 6 to 40 months)	Low (see Part 3)
	326 (6)	12-month freedom from AF off ADM: Pooled rate: 173/326 (53.1%)	Range for mean follow-up: 6 months to 30.6 ± 18.9 months (one study only reported range of follow-up from 6 to 40 months)	Low (see Part 3)

		Meta-analyzed rate:† • 51.4% (95% CI 39.1% to 63.7%) • 51.3% (95% CI 39.3% to 63.3%) Range of rates from individual studies: 36.5% to 75%		
	368 (8)	<u>Overall freedom from AF off ADM</u>: Pooled rate: 204/368 (55.4%) Meta-analyzed rate:† • 57.0% (95% CI 43.6% to 69.9%) • 57.7% (95% CI 44.6% to 70.9%) Range of rates from individual studies: 36.5% to 90%	Range for mean follow-up: 6 months to 30.6 ± 18.9 months (one study only reported range of follow-up from 6 to 40 months)	Low (see Part 3)

ADM, antidysrhythmic medication; AF, atrial fibrillation; PVI, pulmonary vein isolation

*They call this "drug-free success", but they specify conducting this analysis to assess "the impact of antidysrhythmic drugs" and do not make mention of rate-controlling medication elsewhere, so we assume this is actually antidysrhythmic drug-free success, consistent with what other studies report. The time point of latest follow-up in a study was defined as the last time point reporting a minimum of 30 subjects at risk.

† First rate is the Freeman-Turkey double arcsine proportion; the second rate is the untransformed proportion; all estimates are via random-effects, Sidik-Jonkman/Hartung-Knapp-Sidik-Jonkman model (OpenMeta[Analyst])

Medical therapy (FAQ7b)

Descriptive Overview

You may need to have your rate or rhythm control medication adjusted over time to maintain control of your atrial fibrillation.

Part 5 - Evidence Synthesis

Methods

Evidence synthesis process

Synthesis methods will be based on the most appropriate methods matching the available evidence. We will systematically consider synthesis methods with the following questions:

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

State "Yes" or "No". Provide justification if "No".

If "Yes", what method is the best approach?

Pick one of the following and justify:

(1) meta-analysis already done

(2) meta-analysis created from the evidence results

(3) median of sufficiently-valid results, stating cutoff for validity

(4) median of all results

If "No", what method is best to represent the evidence synthesis?

Pick one of the following and justify:

(1) range of all results

(2) range of sufficiently valid results

(3) descriptive summary without quantitative representation (e.g., consistency in direction, but inconsistency in magnitude)

(4) statement of inconsistency too limiting for single synthesized conclusion

Where evidence is very limited or the FAQ is for descriptive summary, such that summary text was provided instead of Evidence Review Tables, the Descriptive Evidence Summary will be noted.

Results

FAQ 1: What does the treatment involve?

Any patient being considered for pulmonary vein isolation should have first undergone a thorough investigation for possible underlying illnesses or modifiable risk factors that can cause or contribute to atrial fibrillation. Examples include, but are not limited to, hyperthyroidism, sleep apnea, obesity and sedentary lifestyles, and inappropriate/excessive alcohol consumption. Before receiving pulmonary vein isolation, patients should ideally receive optimized treatment for underlying illnesses or modifiable risk factors that may contribute to or cause atrial fibrillation. We note this is part of good practice for the management of atrial fibrillation in general, not just when one is considering pulmonary vein isolation.

(Calkins 2017)

Pulmonary vein isolation (FAQ1a)

Pre-Synthesis Efforts: Not applicable

Descriptive Overview

Atrial fibrillation is caused by extra electrical activity in your heart. Pulmonary vein isolation is a procedure to help prevent this extra activity. Scar tissue is created where the extra activity occurs. The scar tissue can help block the extra activity so your heart's electrical activity can return to normal.

To have this procedure, you will be given medicine to make you relaxed and sleepy or you will be put completely to sleep. You can discuss which option is better for you with your healthcare team. The part of your body where the extra activity occurs is reached using small tubes called "catheters". The catheters will be put in blood vessels in your leg and moved up to your heart. Sometimes, a vein in the neck is also used. When the catheters are in the right place, heat or cold will be used to damage the areas where the extra electrical activity is occurring. This is what encourages the body to make scar tissue. If you are awake during the procedure, you may feel some pain when the heat or cold is used. You will be given medicine for pain if this happens.

The procedure often lasts about 4 to 6 hours, but every person is different. After the procedure, you will need to stay in bed for several hours and keep your legs still. You will stay in the hospital overnight, but most people can go home the next day.

You can usually return to normal, general activities about 2 days after the procedure. You will probably be given restrictions on the weight you can lift for at least the first week and be told to avoid vigorous exercise for at least 3 weeks.

Your healthcare team will tell you about medications you will need to take after the procedure. You should expect to take a blood thinning medication for at least 2 to 3 months. You may have to take this medication for even longer depending on your specific risk factors. You may also be told to take a medication to prevent extra or irregular heartbeats for the first 1 to 3 months after the procedure. One of the hopes with this procedure is that you will be able to reduce or stop the medication you currently take for atrial fibrillation. However, not everyone is able to do this.

(Calkins 2012; Calkins 2017; Cleveland Clinic 2017; Dudley 2014; University Hospital Southampton NHS Foundation Trust 2015)

Medical therapy (FAQ1b)

Pre-Synthesis Efforts: Not applicable

Descriptive Evidence Summary

There are two areas where medication is used for atrial fibrillation. The first has to do with the extra electrical activity in your heart. You may take medication to block the extra electrical activity or to control your heart rate. The second has to do with how atrial fibrillation increases your risk for blood clots. These blood clots can lead to stroke or block the flow of blood to other areas of your body, like your arms or legs. Which medications you take will depend on several things specific to you, such as your risk for blood clots, other health conditions you might have, and cost and side effects of the medications. You and your healthcare team will decide which medications are best for you.

(DynaMed Plus 2018; January 2014; Kirchhof 2016)

FAQ 2: Will I live longer?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	21	1 (Turagam 2018)
Second-round (Systematic review searches)	173	4 (AlTurki 2019, Briceño 2018, Chen 2018, Khan 2018)
Third-round (Original study tracing)	Not applicable	
Fourth-round (Original article searches)	18	0

Part 3 Critical Appraisal (evidence evaluated for all-cause mortality for FAQ2):

Certainty rating	Systematic reviews	Randomized trials	Other article types
High			
Moderate	Khan 2018 (4 trials of patients ***with*** comorbid HFrEF, 670 patients) Turagam 2018 (5 trials of patients ***with*** comorbid HFrEF, 732 patients)		
Low	Khan 2018 (4 trials of patients ***without*** comorbid heart failure, 710 patients)		
Very low			
Unusable	AlTurki 2019*, Briceño 2018*, Chen 2018†		
Not applicable			

HFrEF, heart failure with reduced ejection fraction

* Mismatch in trials pooled for analysis (meta-analysis includes the PABA-CHF trial, which studied catheter ablation versus atrioventricular nodal ablation with biventricular pacing)

† Restricted to persistent atrial fibrillation (but not by presence/absence of comorbid HFrEF)

Part 4 Results for FAQ2:

- comparing catheter ablation vs. medication on all-cause mortality
    - catheter ablation **may decrease** all-cause mortality in patients with atrial fibrillation with comorbid heart failure with reduced ejection fraction (HFrEF) based on analysis of 4 trials with 670 patients (Khan 2018, Moderate certainty)
        - risk ratio (RR) 0.52, 95% CI 0.36 to 0.76
        - absolute decrease 9.3% (95% CI 4.6% to 12.4%) with 19.3% mortality in medication group
    - **no significant difference** in patients with atrial fibrillation without comorbid heart failure in analysis of 4 trials with 710 patients (Khan 2018, Low certainty)
        - RR 0.88, 95% CI 0.29 to 2.61
        - absolute decrease 0.25% (95% CI 1.5% decrease to 3.4% increase) with 2.1% mortality in medication group
    - Note: Turagam 2018 included the CAMERA-MRI trial in its all-cause mortality estimate, but this trial had no deaths in either arm. As such, it is appropriate to exclude this trial per the Cochrane Handbook, which is what Khan 2018 did. We therefore use Khan 2018's estimate here.
- None of the systematic reviews reported cause-specific mortality.

Evidence Synthesis Process for FAQ2

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

Results from a 2018 meta-analysis of randomized, controlled trials (for catheter ablation vs. medication) provide relative risk estimates representing the best estimates of effect from the body of evidence.

Comparing catheter ablation vs. medication on *all-cause mortality*, catheter ablation

- **may decrease** all-cause mortality in patients with atrial fibrillation with comorbid HFrEF (RR 0.52, 95% CI 0.36 to 0.76; Moderate certainty, Khan 2018)
- **has an unclear effect** on a relatively low all-cause mortality in patients with atrial fibrillation without comorbid heart failure (RR 0.88, 95% CI 0.29 to 2.61; Low certainty, Khan 2018).

Out of 100 people with atrial fibrillation and heart failure with low pump function:

19 (19%) may die with medication management

10 (10%) may die with catheter ablation

Out of 100 people with atrial fibrillation without heart failure

2 (2%) may die with medication management

2 (2%) may die with catheter ablation

FAQ 3: Will my symptoms get better?

Pre-Synthesis Efforts:

Part 2 Search:*

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	21	2 (Khan 2014, Turagam 2018)
Second-round (Systematic review searches)	173	3 (AlTurki 2019, Briceño 2018, Chen 2018)
Third-round (Original study tracing)	Not applicable	
Fourth-round (Original article searches)	18	0

*In a fifth-round, Universitätsklinikum Schleswig-Holstein (UKSH) reviewed the original Evidence Report and requested summarization of Hakalahti 2015 based on an interest in the outcome of symptomatic recurrence of atrial fibrillation reported in this systematic review. We summarized Hakalahti 2015, and as an additional response, we also checked a 2012 Cochrane review on catheter ablation for paroxysmal and persistent AF (CD007101) and a 2016 Cochrane review on ablation for non-paroxysmal AF (CD012088) to see if either included symptomatic recurrence of atrial fibrillation as an outcome, and neither did.

Part 3 Critical Appraisal (evidence evaluated for quality of life for FAQ3):

Certainty rating	Systematic reviews	Randomized trials	Other article types
High			
Moderate			
Low	Turagam 2018 (4 trials, 341 patients with comorbid HFrEF) Khan 2014 (6 trials, 916 patients without comorbid heart failure)‡		
Very low	Hakalahti 2015		
Unusable	AlTurki 2019*, Briceño 2018*, Chen 2018†		
Not applicable			

HFrEF, heart failure with reduced ejection fraction

* Inappropriate inclusion/exclusion criteria (includes the PABA-CHF trial, which studied catheter ablation versus atrioventricular nodal ablation with biventricular pacing)

† Restricted to persistent atrial fibrillation (but not by presence/absence of HFrEF)

‡ Confirmed to be the most current trial collection based on cross-referencing with Khan 2018

Part 4 Results for FAQ3:

- Catheter ablation **might improve** *quality of life* compared to medication management, but the effect size appears small and uncertain.
    - for heart failure-related quality of life in patients with atrial fibrillation with comorbid HFrEF in analysis of 4 trials with 341 patients (Turagam 2018, Low certainty)
        - mean difference (MD) -9.02 points (95% CI -19.75 to 1.71 points)
        - range 0 to 105 points; lower scores indicate improvement
    - for physical and mental domains of quality of life in patients with atrial fibrillation without comorbid heart failure (Kahn 2014, Low certainty)
        - for physical domain, in analysis of 4 trials with 643 patients
            - MD 5.0 points (confidence interval not reported)
            - range 0-100 points; higher scores indicate improvement
        - for mental domain, in analysis of 4 trials with 643 patients
            - MD 4.2 points (confidence interval not reported)
            - range 0-100 points; higher scores indicate improvement
- None of the systematic reviews reported *resolution rates for symptoms.* Hakalahti 2015 provides estimates for recurrence of symptomatic atrial fibrillation, but these results are of Very low certainty, so we do not recap these results here.

Evidence Synthesis Process for FAQ3

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

Results from a 2018 meta-analysis of randomized trials provides the best estimates of effect for patients with atrial fibrillation with comorbid heart failure with reduced ejection fraction and a 2014 meta-analysis provides the best estimates for patients with atrial fibrillation without comorbid heart failure.

The quantitative results are provided above. In all cases the point estimates of effect size are relatively small but in favor of catheter ablation, and the precision (statistical significance) is limited or uncertain.

A 2015 meta-analysis of randomized trials limited to patients receiving either catheter ablation or antidysrhythmic therapy as a first-line treatment for atrial fibrillation reported on the outcome of recurrence of symptomatic atrial fibrillation, but this outcome is of Very low certainty.

Catheter ablation might improve quality of life to a small degree compared to medication treatment, but the comparison is uncertain. This applies to patients with and without heart failure.

We do not have adequate research to know whether catheter ablation results in a higher, lower, or similar rate of recurrence of symptomatic atrial fibrillation compared to medical therapy.

FAQ 4: What is my risk for being hospitalized later?

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	21	1 (Turagam 2018)
Second-round (Systematic review searches)	173	4 (AlTurki 2019, Briceño 2018, Chen 2018, Khan 2018)
Third-round (Original study tracing)	Not applicable	
Fourth-round (Original article searches)	18	0

Part 3 Critical Appraisal (evidence evaluated for cardiac hospitalization for FAQ4):

Certainty rating	**Systematic reviews**	**Randomized trials**	**Other article types**
High			
Moderate	Khan 2018 (3 trials of patients ***with*** comorbid HFrEF, 632 patients; 4 trials of patients ***without*** comorbid heart failure, 629 patients)		
Low			
Very low			
Unusable	AlTurki 2019*, Briceño 2018*, Chen 2018†		
Not applicable	Turagam 2018‡		

HFrEF, heart failure with reduced ejection fraction

* Mismatch in trials pooled for analysis (meta-analysis includes the PABA-CHF trial, which studied catheter ablation versus atrioventricular nodal ablation with biventricular pacing)

† Restricted to persistent atrial fibrillation (but not by presence/absence of HFrEF)

‡ Turagam 2018 reported on heart-failure hospitalization, but we used Khan 2018's more inclusive cardiac hospitalization (which would include atrial fibrillation-related or heart failure-related hospitalizations)

Part 4 Results for FAQ4:

- catheter ablation **may decrease** *cardiac hospitalization* compared to medication management
    - in patients with atrial fibrillation with comorbid HFrEF based on analysis of 3 trials with 632 patients (Khan 2018, Moderate certainty)
        - risk ratio (RR) 0.63, 95% CI 0.46 to 0.87
        - absolute decrease 17.6% (95% CI 6.2% to 25.7%) with 47.5% cardiac hospitalization in medication group
    - in patients with atrial fibrillation without comorbid HFrEF in analysis of 4 trials with 629 patients (Khan 2018, Moderate certainty)
        - RR 0.32, 95% CI 0.23 to 0.45
        - absolute decrease 21.4% (95% CI 17.3% to 24.3%) with 31.5% cardiac hospitalization in medication group

Evidence Synthesis Process for FAQ4

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

Results from a 2018 meta-analysis of randomized trials comparing catheter ablation vs. medication provides the most reliable relative risk estimates for cardiac hospitalization in patients with atrial fibrillation with HFrEF and in patients with atrial fibrillation without comorbid heart failure.

Compared to medication management alone, catheter ablation may decrease *cardiac hospitalization*

- in patients with atrial fibrillation with comorbid HFrEF (RR 0.63, 95% CI 0.46 to 0.87; Moderate certainty, Khan 2018)
- in patients with atrial fibrillation without comorbid heart failure (RR 0.32, 95% CI 0.23 to 0.45; Moderate certainty, Khan 2018).

Out of 100 people with atrial fibrillation and heart failure with low pump function:

48 (48%) treated with medication management may need to go to the hospital for heart problems

30 (30%) treated with catheter ablation may need to go to the hospital for heart problems

Out of 100 people with atrial fibrillation without heart failure

32 (32%) treated with medication management may need to go to the hospital for heart problems

10 (10%) treated with catheter ablation may need to go to the hospital for heart problems

FAQ 5: What are the risks?

Pulmonary vein isolation (FAQ5a)

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	31	4 (Calkins 2017, Gupta 2013, Khan 2014, Turagam 2018)
Second-round (Systematic review searches)	173	2 (Khan 2018, Phan 2016)*
Third-round (Original study tracing)	Not applicable	
Fourth-round (Original article searches)	18	0

*AlTurki 2019, Briceño 2018, and Chen 2018 were not considered beyond the efficacy FAQs due to the reasons stated in the efficacy FAQs.

Part 3 Critical Appraisal (evidence evaluated for risks/complications for FAQ5):

Certainty rating	Systematic reviews	Randomized trials	Other article types
High			
Moderate			
Low	Gupta 2013 (192 studies [34 trials, 158 observational studies], 83,236 patients)*		
Very low			Calkins 2017 (unclear)†
Unusable			
Not applicable	Khan 2014‡, Khan 2018‡, Phan 2016‡, Turagam 2018‡		

* Provides estimates for different outcomes and in different ways, so the overall number of studies and participants is listed here

† This multiorganizational expert consensus statement provides a table with rates for "selected" complications and references for each reported complication, but it gives no indication of sample size and also did not clearly execute a systematic search of the literature for the complication rates reported, so we do not consider these data as applicable or valid as those offered by Gupta 2013.

‡ These systematic reviews all reported on various complications, but overall event rates and sample sizes were substantially lower than that of Gupta 2013, leading us to have serious concerns about precision. We therefore consider these sources not applicable and deem Gupta 2013 a more reliable source for complications data.

Part 4 Results for FAQ5a:

Pulmonary vein isolation (FAQ5a)

- has a relatively low rate of overall complications, with pooled estimates of
    - 2.9% (95% CI 2.6% to 3.22%) (overall study period from 2000 to 2012)
    - 2.6% (95% CI 2.31% to 2.95%) (studies published between 2007 and 2012)
    - 3.5% (95% CI 2.9% to 4.14%) (studies that prospectively defined major complications)
- considering specific complications, complications with rates ≥ 0.5% include*:
    - pulmonary vein stenosis: range 0.15% to 0.60%
    - vascular complications (bleeding, hematoma, arteriovenous fistula, femoral pseudoaneurysm): range 0.83% to 2.93%
        - arteriovenous fistula: range 0.19% to 0.58%
        - femoral pseudoaneurysm: 0.29% to 0.75%
    - stroke or transient ischemic attack: range 0.38% to 0.67%
        - stroke: 0.21% to 0.49%
        - transient ischemic attack: 0.13% to 0.47%
    - cardiac tamponade: 0.65% to 1.28%
    - pericardial effusion: 0.37% to 0.88%
    - phrenic nerve injury: 0.13% to 1.07%

    (Gupta 2013, Low certainty)

* The range provided is defined by the lowest and highest values from among the point estimates and confidence interval bounds across the three pooled estimates (for the studies covering the entire study period, the studies published between 2007 and 2012, and the studies that prospectively defined major complications). For composite measures, components of the composite are reported where possible.

Evidence Synthesis Process for FAQ5a

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

Yes

If "Yes", what method is the best approach?

(1) meta-analysis already done

Out of 1000 people having catheter ablation, up to 35 (3.5%) may have a complication of some kind, including:

- **up to 6 (0.6%) may have narrowing of one or more lung veins**
- **up to 29 (2.9%) may have other blood vessel problems**

- **up to 7 (0.7%) may have a stroke**
- **up to 13 (1.3%) may get fluid squeezing the heart**

Medical therapy (FAQ5b)

Pre-Synthesis Efforts: Not applicable

Descriptive Summary

The risks of medical therapy depend on the medicines you and your healthcare professional decide are best for you. Some medicines may cause passing out, having a heart rate that is too slow or too fast, or lung damage.

FAQ 6: What are the side effects?

Pulmonary vein isolation (FAQ6a)

Pre-Synthesis Efforts: Not applicable

Descriptive Summary

You may have general soreness, some discomfort in your chest, and/or fatigue in the first 48 hours or so after the procedure. It also takes time for your body to make the scar tissue, so people often feel extra or irregular heartbeats in the first 8 to 10 weeks after the procedure.

(Calkins 2017; Cleveland Clinic 2017; University Hospital Southampton NHS Foundation Trust 2015)

Medical therapy (FAQ6b)

Pre-Synthesis Efforts: Not applicable

Descriptive Summary

The side effects of medical therapy depend on the medicines you and your healthcare professional decide are best for you. Some medicines may cause dizziness, constipation, swollen ankles, or fatigue.

FAQ 7: Will I need additional treatment?

Pulmonary vein isolation (FAQ7a)

Pre-Synthesis Efforts:

Part 2 Search:

	Number of articles evaluated	Number of unique articles selected for evaluation
First-round (DynaMed Plus)	23	3 (Calkins 2012, Calkins 2017, Ganesan 2013)
Second-round (Systematic review searches)	173	3 (Clarnette 2018, Khan 2018, Phan 2016)*
Third-round (Original study tracing)	2	1 (Al-Hijji 2016)
Fourth-round (Original article searches)	18	0

*AlTurki 2019, Briceño 2018, and Chen 2018 were not considered beyond the efficacy FAQs (FAQs 2 through 4) due to the reasons stated in the efficacy FAQs.

Part 3 Critical Appraisal (evidence evaluated for needing additional treatment for FAQ7):

Certainty rating	Systematic reviews	Randomized trials	Other article types
High			
Moderate	Clarnette 2018 (113 studies [4 trials contributing 9 cohorts, 109 observational studies contributing 114 cohorts], 18,657 patients)* Ganesan 2013 (19 studies [2 trials, 17 observational studies], 6,167 patients)*		Al-Hijji 2016 (1 observational study, 8,648 patients)
Low	Khan 2018 (2 trials of patients ***without*** comorbid heart failure, 216 patients)		
Very low	Phan 2016 (8 studies, 699 patients)*		
Unusable			
Not applicable			Calkins 2012‡, Calkins 2017‡

* Provides estimates for different outcomes, so the overall number of studies and participants is listed here
‡ Only used for study tracing (see Parts 2 and 3)

Part 4 Results for FAQ7a:

Pulmonary vein isolation (FAQ7a)*

- Need for electrical cardioversion
    - Pulmonary vein isolation may result in a lower need for electrical cardioversion compared to medical therapy in patients without comorbid heart failure (RR 0.69, 95% CI 0.47 to 1.01) (Low certainty, Khan 2018) – absolute rates not considered reliable because this is reported in only 2 out of 11 trials, one with control event rate 6% and one with control event rate 50%

- Repeat ablation rate may be
    - 14.6% (95% CI 13.9% to 15.4%) at any point after initial ablation, with a median follow-up of 1.1 (IQR 0.5 to 2.3) years (Moderate certainty, Al-Hijji 2016)
        - median time to repeat ablation 0.7 (IQR 0.4 to 1.4) years
        - about 51% of these ablations occurred between 3 months and 12 months, and about 36% of these ablations occurred after 12 months
    - 12.7% (95% CI 12.0% to 13.4%) beyond the 3-month period following the initial ablation, with a median follow-up of 1.1 (IQR 0.5 to 2.3) years (Moderate certainty, Al-Hijji 2016)
        - about 59% occurred between 3 months and 12 months, and about 41% occurred after 12 months
    - no different based on presence/absence of heart failure (HR 0.94, 95% CI 0.82 to 1.09) (Moderate certainty, Al-Hijji 2016)

- Mean number of procedures may be
    - 1.37 ± 0.3 (range 1 to 2.3) over a mean follow-up of 25 ± 12 months (range 12 to 59 months) (Clarnette 2018, Moderate certainty)
    - 1.51 (95% CI 1.36 to 1.67) over a mean/median follow-up of at least 2 years (range 28 to 71 months) (Ganesan 2013, Moderate certainty)
    - no different between those with paroxysmal (1.45; 95% CI 1.31 to 1.59) and non-paroxysmal (1.67; 95% CI 1.31 to 2.06) atrial fibrillation (Ganesan 2013, Moderate certainty)

- Rate of freedom from atrial dysrhythmia off antidysrhythmic medication (does not necessarily mean being off rate-controlling medication and/or antithromboembolic medication) may be
    - 43% (95% CI 39% to 47%) over a mean follow-up of 25 ± 12 months (range 12 to 59 months) (Clarnette 2018, Moderate certainty)
    - 57.4% (95% CI 50.9% to 63.8%) over a mean/median follow-up of at least 2 years (range 28 to 71 months) (Ganesan 2013, Moderate certainty)

*Results for Phan 2016 not recapped here, as they are all Low certainty

Is it useful and appropriate to present the synthesis of evidence results as a combined, single result as the best representation of the body of evidence?

No. For the outcome of repeat ablation rate, the largest evidence source is a single cohort study (Al-Hijji 2016). For the outcomes of number of repeat procedures and rate of freedom from antidysrhythmic medication, the best evidence available comes from two systematic reviews with consistent but not the same quantitative estimates (Clarnette 2018, Ganesan 2013), and these systematic reviews have overlapping but not the same inclusion/exclusion criteria so the most recent systematic review does not account for all the evidence in the earlier systematic review.

If "No", what method is best to represent the evidence synthesis?

Pick one of the following and justify:

(2) range of sufficiently valid results

Catheter ablation may reduce the need for electrical cardioversion compared to medical therapy in patients with heart failure (RR 0.69, 95% CI 0.47 to 1.01) but absolute rates are uncertain (Low certainty, Khan 2018).

Repeat ablations are reported in 12.7% to 14.6% of patients who have catheter ablation, with similar rates for patients with and without heart failure (Moderate certainty, Al-Hijji 2016). Most people who have a repeat ablation may only have one repeat procedure, based on mean number of ablation procedures 1.37 and 1.5 in populations reported in systematic reviews (Moderate certainty, Clarnette 2018 and Ganesan 2013).

About 43% to 57% of patients are able to avoid antidysrhythmic drugs for years after catheter ablation (Moderate certainty, Clarnette 2018 and Ganesan 2013).

Out of 100 people who have catheter ablation:

- **Up to 15 (15%) may get a repeat ablation**
- **About 50 (50%) may avoid drugs to treat the heart rate**

Medical therapy (FAQ7b)

Pre-Synthesis Efforts: Not applicable

Descriptive Summary

You may need to have your medications adjusted over time to keep your atrial fibrillation controlled.

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