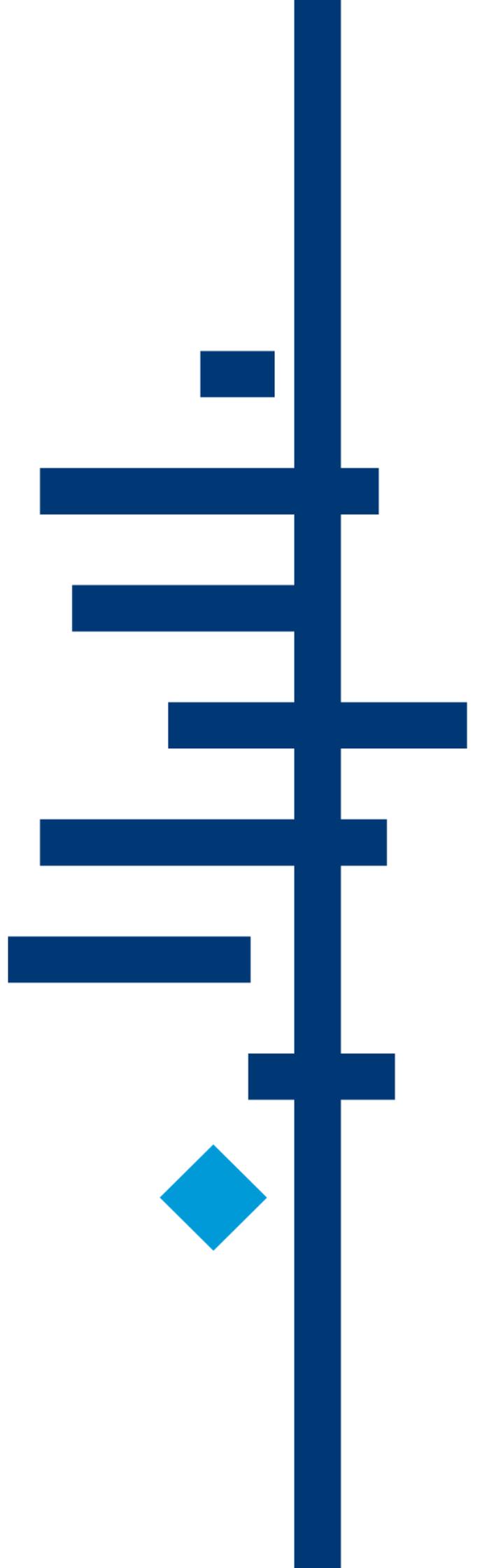


# Antiarrhythmic drugs versus catheter ablation for the treatment of atrial fibrillation: a systematic review

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*Final report*

Johanna Damen  
Demy Idema  
Kevin Jenniskens  
Linde Huis in 't Veld  
Mike Kusters  
Lotty Hoof



**Project team:****Reviewers**

- Dr. J.A.A. Damen, Cochrane Netherlands, Julius Center, UMC Utrecht
- Drs. D.L. Idema, Cochrane Netherlands, Julius Center, UMC Utrecht
- Dr. K. Jenniskens, Cochrane Netherlands, Julius Center, UMC Utrecht
- Drs. L. Huis in 't Veld, Cochrane Netherlands, Julius Center, UMC Utrecht
- Drs. M.P.T. Kusters, Cochrane Netherlands, Julius Center, UMC Utrecht
- Prof. dr. L. Hooft, Cochrane Netherlands, Julius Center, UMC Utrecht

**Information specialist**

- Drs. R. Spijker, Cochrane Netherlands, Julius Center, UMC Utrecht

**Contact details**

Prof. dr. Lotty Hooft  
Cochrane Netherlands / Julius Center  
University Medical Center Utrecht  
Huispostnummer Str. 6.131  
Postbus 85500  
3508 GA Utrecht  
T: 088 755 9301  
E: [cochrane@umcutrecht.nl](mailto:cochrane@umcutrecht.nl)  
W: [www.cochrane.nl](http://www.cochrane.nl)

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## List of abbreviations

AAD	Antiarrhythmic drugs
AF	Atrial fibrillation
AFEQT	Atrial fibrillation effect on quality-of-life
BMI	Body mass index
DCCV	Direct current cardioversion
DOAC	Direct oral anticoagulant
ECG	Electrocardiography
EQ-5D	EuroQol 5 dimensions
GRADE	Grading of recommendations, assessment, development, and evaluations
IQR	Interquartile range
MD	Mean difference
MeSH	Medical subject headings
MID	Minimal important difference
NICE	National Institute for Health and Care Excellence
NR	Not reported
PICOTS	Population, intervention, comparator, outcome, timing, study design
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RCT(s)	Randomized controlled trial(s)
RoB	Risk of bias
SD	Standard deviation
SF-36	36-item short-form health survey
TIA	Transient ischemic attack
UK	United Kingdom
US	United States
VAS	Visual analogue scale

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## Nederlandse samenvatting

**Introductie:** Zorginstituut Nederland is een ziektemodel aan het ontwikkelen voor de behandeling van atriumfibrilleren (AF), om de kosteneffectiviteit van behandeling met antiarritmica te vergelijken met behandeling met katheterablatie. Inputparameters voor effectiviteit en veiligheid van de behandelingen voor dit model worden (deels) gebaseerd op een systematisch literatuuroverzicht. Het doel van dit literatuuroverzicht is dus het samenvatten van de effectiviteit en bijwerkingen van antiarritmica, katheterablatie en de onderlinge vergelijking bij patiënten met AF. Hierin wordt onderscheid gemaakt tussen patiënten met paroxysmaal- of persistent AF, en patiënten die naïef zijn voor behandeling en patiënten die al eerder behandeld zijn met antiarritmica en/of katheterablatie.

**Methoden:** Om deze onderzoeksvraag te beantwoorden, wordt een eerder literatuuroverzicht van de 'National Institute for Health and Care Excellence' (NICE), gepubliceerd in april 2021, geupdate en uitgebreid met studies passend bij onze PICOTS. Referenties uit het NICE rapport die behandeling met antiarritmica vergeleken met ieder type katheterablatie (of een mix van verschillende types) werden geïdentificeerd uit tabellen met geïnccludeerde studies en een lijst van geëxcludeerde studies. Voor de update is in oktober 2024 een nieuwe zoekopdracht uitgevoerd in MEDLINE, Embase en Cochrane CENTRAL. Titel- en abstractscreening, en daarna de beoordeling van het volledige artikel, werd onafhankelijk van elkaar door twee onderzoekers uitgevoerd. Discrepancies werden opgelost middels onderling overleg of door een derde onderzoeker.

Studiekenmerken, populatiekenmerken en informatie over de interventie- en vergelijkingsgroep werden geëxtraheerd uit alle geïnccludeerde studies. Daarnaast werden resultaten voor relevante uitkomsten geëxtraheerd, bij voorkeur als gemiddelde met standaarddeviatie per groep aan het einde van de studie voor continue uitkomsten en aantal deelnemers met de uitkomst voor dichotome variabelen. Kwaliteit van de studies werd beoordeeld met de Cochrane Risk of Bias 2 tool. Dichotome variabelen die gepoold konden worden, werden geanalyseerd met een frequentistische gepaarde meta-analyse voor de proportie patiënten met de uitkomst per groep en het relatief risico tussen de groepen. Voor de continue uitkomsten werd een frequentistische gepaarde meta-analyse gedaan op het gemiddelde verschil tussen de twee groepen.

De GRADE-methodologie werd toegepast om de zekerheid van het bewijs te beoordelen. Elke combinatie van populatie en uitkomst werd beoordeeld op beperkingen in onderzoeksopzet (risico op vertekening ('bias')), inconsistentie, indirectheid en imprecisie van het bewijs.

**Resultaten:** Er werden 19 relevante referenties geïnccludeerd uit het NICE rapport, en de zoekactie leverde nog 12 extra referenties op. In totaal werden dus 31 referenties voor 22 studies geïnccludeerd. Dertien studies hiervan includeerden deelnemers met paroxysmaal AF, twee studies includeerden deelnemers met persistent AF en zeven studies includeerden een mix van beide. Het risico op bias werd bij 20 van de 22 studies beoordeeld als hoog, meestal door het feit dat deelnemers tijdens de studie mochten wisselen van behandeling.

Uitkomsten met een vergelijking tussen de twee groepen waarvoor de zekerheid van het bewijs ‘matig’ of ‘hoog’ was, worden hier uitgelicht. Voor effectiviteit van de behandeling vonden we dat er waarschijnlijk meer terugkeer is van (symptomatisch) AF bij behandeling met antiarritmica dan bij behandeling met katheterablatie in deelnemers met paroxysmaal AF waarvan sommige deelnemers eerder behandeld waren met antiarritmica en alle deelnemers eerder behandeld waren met katheterablatie (relatief risico [RR] 2,12; 95% betrouwbaarheidsinterval [BI] 1,61 tot 2,80; 1 studie, 154 deelnemers; GRADE: matig). Daarnaast zijn er waarschijnlijk meer ziekenhuisopnames voor AF bij behandeling met antiarritmica in deelnemers met paroxysmaal AF (RR 2,61; 95% BI 1,31 tot 5,23; 4 studies, 1073 deelnemers; GRADE: matig). Er is waarschijnlijk geen verschil in kwaliteit van leven gemeten met de EQ-5D index score (gemiddeld verschil [‘mean difference’, MD] -0,03; 95% BI -0,04 tot -0,01; 4 studies, 935 deelnemers; GRADE: matig), de EQ-5D VAS score (MD -3,63; 95% BI -5,97 tot -1,28; 6 studies, 1360 deelnemers; GRADE: matig), de SF-36 ‘mental component summary’ (MD: -1,96; 95% BI -3,80 tot -0,13; 6 studies, 1070 deelnemers; GRADE: matig) en de SF-36 ‘physical component summary’ (MD: -2,09; 95% BI -3,82 tot -0,35; 6 studies, 1070 deelnemers; GRADE: matig) tussen de twee groepen in deelnemers met paroxysmaal AF.

Voor herhaalde ablatie, serieuze bijwerkingen die alleen gerelateerd waren aan katheterablatie en medicijn-gerelateerde bijwerkingen door antiarritmica, werden alleen de proporties deelnemers met de uitkomst beoordeeld, en deze konden vastgesteld worden met een zekerheid van bewijs variërend van ‘laag’ tot ‘hoog’. De voornaamste redenen dat sommige uitkomsten uitkwamen op een ‘lage’ zekerheid van bewijs waren inconsistentie van de resultaten tussen studies en indirectheid van het bewijs.

**Discussie:** In dit systematische literatuuroverzicht hebben we bewijs voor het effect van antiarritmica en katheterablatie voor de behandeling van atriumfibrilleren samengevat. We vonden dat behandeling met katheterablatie vaak beter was dan behandeling met antiarritmica, gekeken naar terugkeer van (symptomatische) AF, hospitalisatie met AF en mortaliteit (met verschillende zekerheden van bewijs). Daarnaast presenteren we gegevens met betrekking tot de frequentie van bijwerkingen van antiarritmica en katheterablatie. Deze informatie zal worden gebruikt als input voor AF ziektemodellen van het Zorginstituut Nederland.

Er zijn tijdens de data-extractie en analyse verschillende keuzes gemaakt die belangrijk zijn bij de interpretatie van het bewijs, zoals de inclusie van studies met specifieke populaties. Daarnaast is er door het toepassen van een continuïteitscorrectie bij studies met nul uitkomsten in een of beide groepen een lichte inflatie van de proportie bij het combineren van twee of meer studies. Ten slotte is er bij de interpretatie van de zekerheid van het bewijs voorzichtigheid geboden omdat het voor de proportie uitkomsten niet mogelijk was om imprecisie te beoordelen en eventueel te downgraden hiervoor.

## 1. Introduction

The National Health Care Institute (Zorginstituut Nederland) is developing a disease model for atrial fibrillation (AF) in the context of the project ‘Doorontwikkeling pakketbeheer: Implementatie gebruik ziektemodellen’. This disease model will be used for assessing cost-effectiveness of catheter ablation versus antiarrhythmic drugs. This model needs input parameters for the efficacy and adverse events of the interventions, which will be (partly) based on a systematic review and meta-analysis of the relevant medical literature.

## 2. Objective

The objective of this systematic review and meta-analysis was to summarize the efficacy and adverse events of antiarrhythmic drugs (AAD), catheter ablation and AAD compared to catheter ablation for the treatment of AF. To answer this question, a distinction was made between paroxysmal- and persistent AF, as well as populations naïve or previously exposed to either or both treatments, resulting in six different PICOTS (Table 1).

**Table 1: PICOTS**

Population	<ol style="list-style-type: none"> <li>1. Patients with paroxysmal AF not previously treated</li> <li>2. Patients with persistent AF not previously treated</li> <li>3. Patients with recurrent paroxysmal AF after treatment with AAD</li> <li>4. Patients with recurrent persistent AF after treatment with AAD</li> <li>5. Patients with recurrent paroxysmal AF after treatment with catheter ablation</li> <li>6. Patients with recurrent paroxysmal AF after treatment with catheter ablation</li> </ol>
Intervention	<ol style="list-style-type: none"> <li>1. and 2. Any type of AAD in the first line of treatment</li> <li>3. and 4. Any type of AAD in the second<sup>1</sup> line of treatment</li> <li>5. and 6. Any type of AAD in the second<sup>1</sup> line of treatment</li> </ol>
Comparator	<ol style="list-style-type: none"> <li>1. and 2. Any type of catheter ablation in the first line of treatment</li> <li>3. and 4. Any type of catheter ablation in the second<sup>1</sup> line of treatment</li> <li>5. and 6. Re-ablation with any type of catheter</li> </ol>
Outcomes	<ul style="list-style-type: none"> <li>- Recurrence of symptomatic atrial fibrillation</li> <li>- Ischemic stroke or systemic embolism</li> <li>- Hemorrhagic stroke</li> <li>- Transient ischemic attack</li> <li>- Heart failure incidence or deterioration</li> <li>- Hospitalization with primary diagnosis atrial fibrillation</li> <li>- Emergency room visits related to atrial fibrillation</li> <li>- Life-threatening/major bleeding</li> <li>- All-cause mortality</li> <li>- Repeat ablation (catheter or surgical)</li> <li>- Serious adverse events<sup>2</sup></li> <li>- Medication side-effects<sup>2</sup></li> <li>- Discontinuations due to side-effects</li> <li>- Quality of life (AFEQT, EQ-5D, SF-36)</li> </ul>

	- Physical functioning (SF-36)
Timing	Not specified
Study design	Randomized controlled trials (RCTs)

<sup>1</sup> Second line of treatment or later.

<sup>2</sup> Serious adverse events and medication side-effects based on the international standard set of outcome measures for patients with atrial fibrillation (1)

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; AFEQT: atrial fibrillation effect on quality-of-life; EQ-5D: EuroQol 5 dimensions; RCTs: randomized controlled trials; SF-36: 36-item short-form health survey.

### 3. Methods

This systematic review was reported following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (2).

#### 3.1 Identification and selection of studies

To answer the review question, an existing review performed by the National Institute for Health and Care Excellence (NICE) on the diagnosis and management of AF was used as a source of relevant primary studies (3). From the tables of included studies, any study that compared medical therapy to any type of catheter ablation in a population that did not consist of only heart failure or diabetes patients, was included. Studies focusing on the previously mentioned populations were deemed too specific to reflect the general population of AF patients and were thus excluded.

Since NICE decided to analyze the different types of catheter ablation separately, they excluded any studies in which participants could have received more than one type of catheter ablation. Considering our analyses were not split on type of catheter ablation, we also reviewed their excluded studies to see if studies that were excluded based on a combined intervention were eligible for our review.

As the search date for the NICE report was September 10<sup>th</sup>, 2020, an update of this review was performed to identify studies published after this date. Since we were only interested in primary studies, the search string made by NICE was adjusted slightly to exclude systematic reviews. Additionally, we did not search for reviews in Epistemonikos, and we only searched in MEDLINE, Embase and Cochrane CENTRAL (from January 1<sup>st</sup>, 2020).

MEDLINE and Embase were searched on October 22<sup>nd</sup>, 2024, and Cochrane CENTRAL on October 23<sup>rd</sup>, 2024, using keywords and Medical Subject Headings (MeSH) or Emtree terms relating to AF, catheter ablation and randomized controlled trials (Appendix 1). Articles were eligible for inclusion if they were randomized controlled trials that compared AAD to any type of catheter ablation (or a combination thereof) in a general population of AF patients and reported on any of the outcomes mentioned in the PICOTS (Table 1). Systematic reviews and meta-analyses were included when screening title- and abstract to later use them to identify potential additional relevant references of primary studies.

Review authors independently screened references in duplicate, first on title and abstract and subsequently on full text. Disagreements were solved through discussion or by consulting a third reviewer.

#### 3.2 Data extraction and quality assessment

Data extraction and risk of bias assessment using the Cochrane Risk of Bias 2 tool (RoB 2) (4) was performed by one reviewer and verified by a second reviewer. Any disagreements between the two reviewers were resolved through discussion between them or through group discussion. Data were extracted on study design, study dates, funding, conflicts of interest, eligibility criteria (including type of AF, line of treatment and previous exposure to catheter ablation and/or AAD), population characteristics (including age, sex, weight, inclusion of heart failure patients, CHA<sub>2</sub>DS<sub>2</sub>-VASc score and use of

anticoagulants), information on the intervention and comparator, any crossover between treatments during the study, and outcome information (including duration of follow-up). For studies that reported outcomes at multiple times throughout follow-up, a follow-up time of one year (i.e. 52 weeks) was preferred for all outcomes.

For continuous outcomes (only quality of life and physical functioning), we extracted the total number of participants analyzed per treatment group, as well as a measure of average score and spread per group (preferably mean with standard deviation [SD]). For quality of life, only the overall score on AFEQT, the visual analogue scale (VAS) or index of the EQ-5D and the physical component summary, mental component summary and physical functioning domain of the SF-36 were extracted. If a follow-up result with measure of spread was available, this was preferred over a change score (5). For discrete outcomes (all other outcomes), we extracted the total number of participants analyzed per treatment group, as well as the number of participants who experienced an event. As some outcomes were only relevant for catheter ablation (repeat ablation and several serious adverse events), we also extracted the number of participants that crossed over from AAD therapy to catheter ablation during the follow-up of the study and analyzed these together with the participants in the catheter ablation treatment group. Medication side-effects and discontinuations due to side-effects were only analyzed for the AAD treatment group.

### 3.3 Analyses

Characteristics of included studies were presented in tables and study quality was presented graphically. For dichotomous outcomes that could be pooled and for which outcome data was available in both treatment groups, a frequentist pairwise meta-analysis was performed on the proportion of events in both treatment groups, as well as the relative risk for the AAD treatment group compared to the catheter ablation treatment group. For outcomes that were only applicable to one treatment group (either AAD treatment or catheter ablation), only event proportions were analyzed. When analyzing proportions, only studies with outcomes reported at 52 weeks were included to ensure comparability and usability in the economic model. Exceptions to this were made for repeat ablation during the blanking period (in which follow-up was always 11-13 weeks) and serious adverse events that applied only to catheter ablation, because these were expected to happen shortly after the procedure. For continuous outcomes that could be pooled, a pairwise meta-analysis was performed for the mean difference (MD) between groups.

A random-effects meta-analysis with restricted maximum likelihood estimator was used except when the number of studies that could be pooled was smaller than five, in which case a fixed-effects meta-analysis was used (5). In the case of random-effects meta-analysis, for outcomes without zero events in either treatment groups, the Knapp-Hartung method was used together with the restricted maximum likelihood estimator (6). For studies with zero events in either or both treatment groups, a continuity correction of 0.5 was applied. The results of the meta-analyses were presented as a mean proportion with 95% confidence interval and 95% prediction interval (for random-effects meta-analysis) or only a 95% confidence interval (for fixed-effects meta-analysis) per treatment group or a relative risk with 95% confidence interval (and 95% prediction interval) for the AAD treatment group compared to the catheter ablation treatment group.

For several outcomes the distinction between the types of AF (paroxysmal and persistent) and/or the previous exposure to the two treatment options (naïve or exposed) was deemed less relevant and hence multiple groups were analyzed together (Table 2). For outcomes for which it was deemed relevant to analyze populations with paroxysmal AF separately from persistent AF, mixed populations were classified to either paroxysmal AF or persistent AF when the respective percentage of included participants with this type of AF exceeded 70%.

**Table 2: Combination of populations the analyses**

Outcome(s)	Type of AF (paroxysmal/persistent)	Previous exposure to AADs	Previous exposure to catheter ablation
<b>Recurrence of symptomatic AF</b>	Split	Split	Split
<b>Any type of stroke</b>	Split	Combine	Combine
<b>TIA</b>	Split	Combine	Combine
<b>Heart failure incidence or deterioration</b>	Split	Combine	Combine
<b>Hospitalization with primary diagnosis AF</b>	Split	Combine	Combine
<b>Emergency room visits related to AF</b>	Split	Combine	Combine
<b>Life-threatening/major bleeding</b>	Split	Combine	Combine
<b>All-cause mortality</b>	Split	Combine	Split
<b>Repeat ablation (catheter or surgical)</b>	Split	Split	Split
<b>Serious adverse events</b>	Combine	Combine	Split
<b>Medication side-effects</b>	Combine	Split	Combine
<b>Discontinuations due to side-effects</b>	Combine	Split	Combine
<b>Quality of life (AFEQT, EQ-5D, SF-36)</b>	Split	Combine	Combine
<b>Physical functioning (SF-36)</b>	Split	Combine	Combine

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; AFEQT: atrial fibrillation effect on quality of life; EQ-5D: EuroQol 5 dimensions; SF-36: 36-item short-form health survey; TIA: transient ischemic attack.

All analyses were performed using Rstudio version 2024.12.0+467 (7) using the ‘rma’ and ‘predict’ functions from the package metafor (8). A p-value <0.05 was considered statistically significant.

### 3.4 Certainty of evidence

The certainty of the evidence was rated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach (9) that considers risk of bias, indirectness, inconsistency, imprecision, and publication bias when determining the level of evidence for a particular outcome. For grading of the evidence, we mainly followed the same assessment criteria as were used in the NICE report (10) (see below). For dichotomous outcomes, when a relative risk was available for a particular outcome, we graded the relative risk. If not, we graded the proportions of events (per treatment group if applicable).

- Risk of bias: if more than half of the included studies for an outcome had a high overall risk of bias we downgraded once. If more than half of the included studies had a high risk of bias for the first domain (risk of bias arising from the randomization process), we downgraded twice.
- Indirectness: indirectness in individual studies could arise from the inclusion of only elderly participants (> 60 years or > 65 years), the classification of mixed populations to either paroxysmal

or persistent AF, or an outcome definition that did not exactly match the outcome from the PICOTS (i.e. AF recurrence instead of *symptomatic* AF recurrence). If more than half of included studies had one source of indirectness, we downgraded once. If more than half of studies had two sources of indirectness, we downgraded twice.

- Inconsistency: if the  $I^2$  of a pooled outcome was 50-74%, we downgraded once, and if it was 75% or more, we downgraded twice.
- Imprecision:
  - Relative risks (except mortality): we downgraded once if the confidence interval of a relative risk crossed either the minimal important difference (MID) of 0.8 or 1.25 and downgraded twice if the CI crossed both.
  - Relative risks (mortality): we downgraded once if the confidence interval of the relative risk crossed the line of no effect (i.e. RR = 1).
  - Continuous outcomes: the MIDs were taken as half the median of the baseline standard deviation (or the follow-up score for the comparator group if not available) of that outcome (on both sides of the line of no effect), and we downgraded once if one of the MIDs was crossed by the CI and downgraded twice if both MIDs were crossed.
  - Proportions: for the outcomes in which the proportions of a single treatment group were graded, we did not downgrade for imprecision, as we did not have any MIDs available. Therefore, it was also not possible to give a target of certainty for these outcomes.

The GRADE certainty of evidence was presented for each outcome and population combination (where applicable), and a target of certainty was added when the final grading was something other than very low. For effect statements, we followed GRADE guidance for informative statements to communicate systematic review findings (11).

## 4. Results

### 4.1 Study selection

We identified 22 records from the NICE review that seemed relevant for our review, of which one could not be retrieved and two were excluded based on full text (one excluded on the comparator (12), the other on outcome (13)). The search strategy yielded 1490 unique records that were screened on title and abstract. Of the 93 reports that were sought for retrieval, 88 were retrieved. Full text screening of these records yielded an additional 12 records, so 31 reports on 22 studies were included in the review (Figure 1). Reports were mainly excluded on publication type and outcome. The latter usually meant a post-hoc analysis that did not provide additional relevant outcomes compared to the main publication. References excluded on publication type were mostly systematic reviews and meta-analyses that were used as source for potential additional relevant records. An overview of excluded studies with reasons for exclusion can be found in Appendix 2.

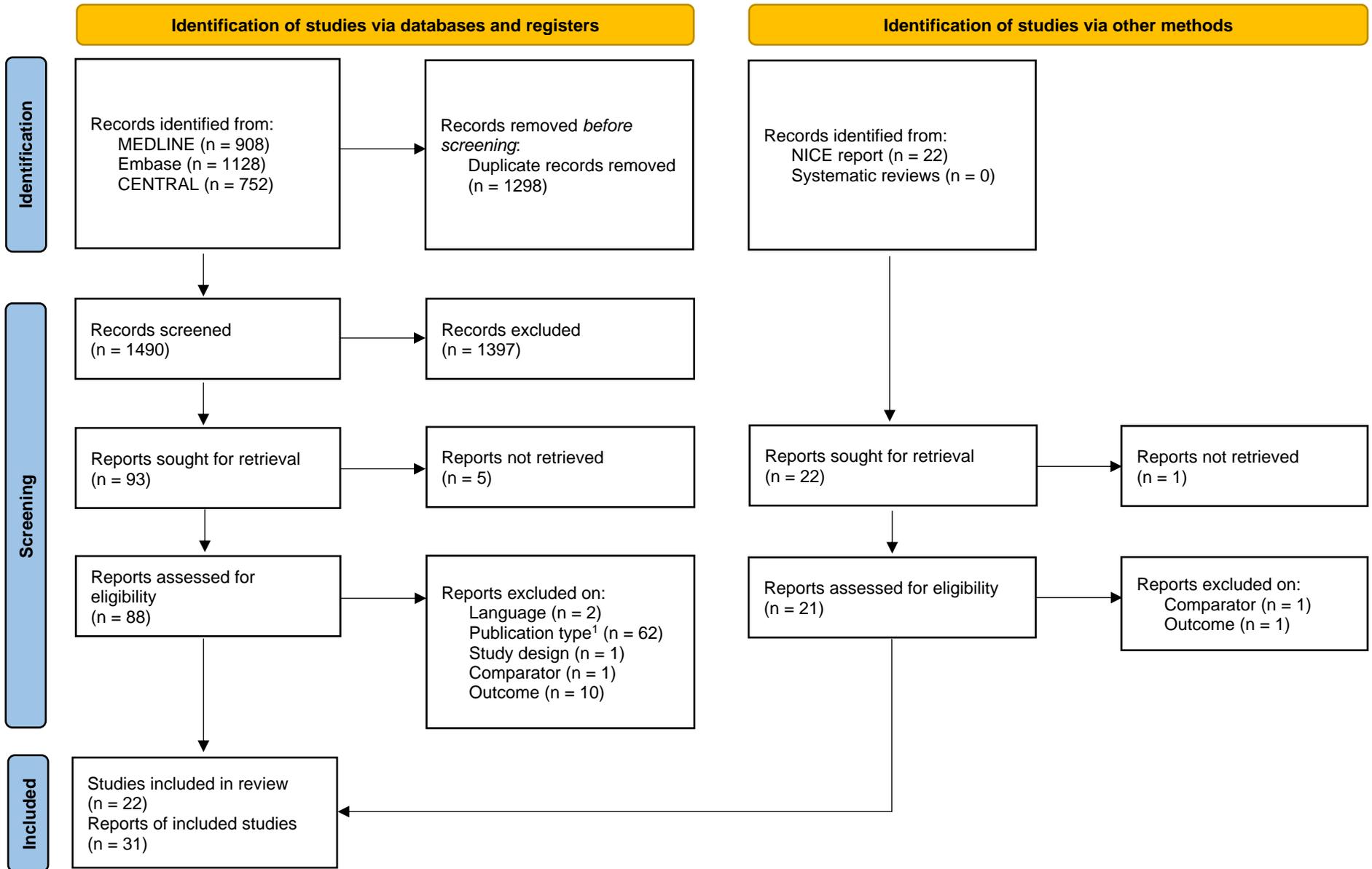


Figure 1: PRISMA flow diagram

<sup>1</sup>Systematic reviews and meta-analyses were used to identify additional relevant records.

## 4.2 Description of included studies

We included 22 studies, of which 13 were performed in participants with paroxysmal AF, two in participants with persistent AF, and seven in a mixed population (Appendix 3). Seven studies investigated AAD or catheter ablation as first-line treatment, while 13 studies included participants with previous exposure to therapy. In one study previous exposure to therapy was mixed, and for another it was not reported. Most studies investigated radiofrequency as the type of catheter ablation (14 studies), while the others used either cryoballoon (6 studies) or a mixture of different types (2 studies).

The total number of randomized participants ranged from 60 to 2204 (median 183). Included participants had a median age of 57.8 years (IQR 55.4-60.8 years). On average 68% of included participants were male (IQR 63-77%), and of the nine studies that reported BMI, the median was 28.1 kg/m<sup>2</sup> (IQR 27.1-30.0 kg/m<sup>2</sup>). Eight studies reported on participants' CHA<sub>2</sub>DS<sub>2</sub>-VASc score and in these studies, an average of 35% of participants had a score equal or greater than 2 (IQR 19-62%). All baseline characteristics per included study can be found in Appendix 4.

## 4.3 Risk of bias in included studies

Twenty studies were assessed to be at overall high risk of bias, one at some concerns and no studies had an overall low risk of bias (Figure 2, Appendix 5). The main reason for the high risk of bias in all studies was bias due to deviations from intended interventions. This was due to participants switching from AAD therapy to catheter ablation during the study, and/or participants who had catheter ablation also receiving AAD during follow-up. This was the case for most outcomes, except for AF recurrence, which was not always at high risk of bias for this domain if the crossover to another treatment was only permitted after recurrence of AF had occurred. Additionally, this applied to outcomes that were only applicable to one treatment group (either catheter ablation or AAD), where we assumed the outcome was always caused by catheter ablation or AAD, respectively.

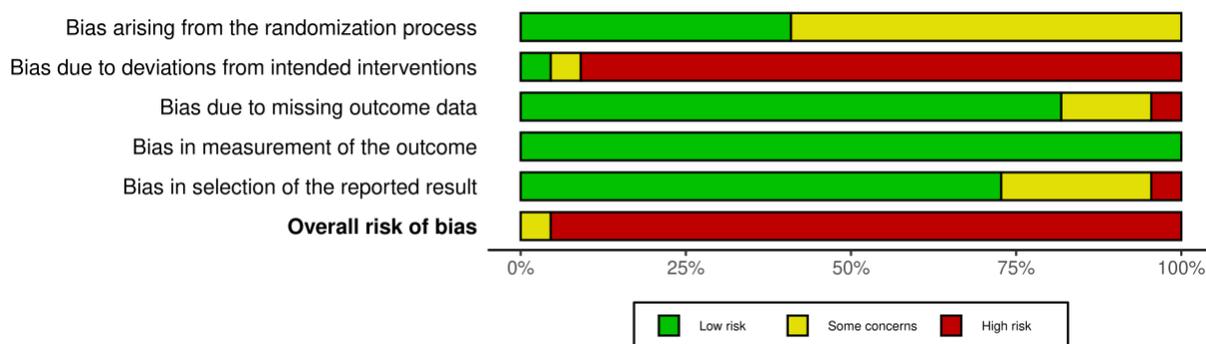


Figure 2: Summary of risk of bias assessment

## 4.4 Outcomes

Of the 22 included studies, all but one reported on one or more efficacy endpoints. Eighteen studies reported on repeat ablation, either during the blanking period, after the blanking period or both and on one or more serious adverse events. Medication side-effects were reported by only five studies, and any measure of quality of life by 15 studies. See Appendix 3 for an overview of outcomes reported by each study. In the following subsections, mainly the results with a GRADE rating other than 'Very low' will be highlighted (unless otherwise stated). All results can be found in Appendices 6-11.

### 4.4.1 Efficacy

- Recurrence of (symptomatic) atrial fibrillation
  - Moderate certainty: There is probably more recurrence of (symptomatic) AF when treated with AAD than with catheter ablation in the group of participants with paroxysmal AF who had mixed previous exposure to AAD and were all previously treated with catheter ablation (RR 2.12, 95% CI 1.61 to 2.80, 1 study, 154 participants).
  - Low certainty: There may be more recurrence of (symptomatic) AF when treated with AAD than with catheter ablation in the group of participants with paroxysmal AF who received these as first line treatment (RR 1.76, 95% CI 1.34 to 2.32, 6 studies, 1122 participants), in participants with persistent AF who were only previously exposed to AAD (RR 1.62, 95% CI 1.40 to 1.87, 2 studies, 853 participants) and in a population with different types of AF with mixed previous exposure to AAD and unclear previous exposure to catheter ablation (RR 2.04 95% CI 1.51 to 2.76, 1 study, 96 participants).
- Hospitalization with primary diagnosis atrial fibrillation
  - Moderate certainty: There is probably more hospitalization when treated with AAD than with catheter ablation in the group of participants with paroxysmal AF (RR 2.61, 95% CI 1.31 to 5.23, 4 studies, 1073 participants).
- Emergency room visits related to atrial fibrillation
  - Low certainty: There may be no difference in emergency room visits when treated with AAD compared to catheter ablation in the group of participants with paroxysmal AF (RR 1.22, 95% CI 0.80 to 1.85, 2 studies, 624 participants).
- All-cause mortality
  - Low certainty: There may be more all-cause mortality when treated with AAD than with catheter ablation in the group of participants with paroxysmal AF (RR 1.79, 95% CI 0.80 to 4.02, 10 studies, 2929 participants) as well as in the group of participants with persistent AF (RR 1.45, 95% CI 0.56 to 3.75, 3 studies, 1613 participants).

For stroke (ischemic or hemorrhagic), transient ischemic attack, heart failure incidence or deterioration, and life-threatening/major bleeding, the certainty of evidence for all populations for which there was evidence, was very low. All results can be found in Appendix 6.

#### 4.4.2 Repeat ablation

Because imprecision could not be judged for outcomes that only applied to one treatment group, all outcomes have a GRADE rating higher than very low, and only the outcomes with rating 'High' will be highlighted here. All results can be found in Appendix 7.

- During the blanking period: The proportion of repeat ablations during the blanking period was 0.024 (95% CI 0.011 to 0.052) (3 studies, 327 participants) for paroxysmal AF participants with first line treatment, and 0.092 (95% CI 0.058 to 0.140, 1 study, 218 participants) for paroxysmal AF participants with mixed previous exposure to AAD and naïve to catheter ablation.
- After the blanking period: The proportion of repeat ablations after the blanking period was 0.110 (95% CI 0.073 to 0.161, 1 study, 218 participants) for participants with mixed type of AF with mixed previous exposure to AAD and naïve to catheter ablation.
- During total follow-up (or unclear): The proportion of repeat ablations during total follow-up duration (or an unclear period) was 0.007 (95% CI 0.001 to 0.050, 2 studies, 170 participants) for participants with paroxysmal AF who received first-line treatment, and 0.082 (95% CI 0.038 to 0.159, 1 study, 98 participants) for participants with persistent AF who were previously only exposed to AAD.

#### 4.4.3 Serious adverse events (both treatment groups)

For the serious adverse events that applied to both treatment groups, i.e. deep vein thrombosis, intracardiac thrombus, pulmonary embolism, thromboembolism, ventricular tachyarrhythmia, ventricular tachycardia and life-threatening/major bleeding, the certainty of evidence was very low. All results can be found in Appendix 8.

#### 4.4.4 Serious adverse events (only for catheter ablation)

Because imprecision could not be judged for outcomes that only applied to one treatment group, all outcomes have a GRADE rating higher than very low, and only the outcomes with rating 'High' will be highlighted here. All results can be found in Appendix 9.

- Atrio-oesophageal fistula: The proportion of participants with atrio-oesophageal fistula was 0.003 (95% CI 0.001 to 0.008, 7 studies, 1882 participants) in participants who were naïve to previous exposure with catheter ablation.
- Pericardial tamponade: The proportion of participants with pericardial tamponade was 0.013 (95% CI 0.008 to 0.021, 10 studies, 2405 participants) in participants who were naïve to previous exposure with catheter ablation, and 0.025 (95% 0.006 to 0.077, 1 study, 120 participants) in participants previously exposed to treatment with catheter ablation.
- Pericardial tamponade or pericardial effusion: The proportion of participants with pericardial tamponade or pericardial effusion was 0.023 (95% CI 0.004 to 0.088, 1 study, 87 participants) in participants who were naïve to previous exposure with catheter ablation.
- Pericardial tamponade or pericardial effusion (drainage warranted): The proportion of participants with pericardial tamponade or pericardial effusion for which drainage was needed was 0.005 (95% CI 0.000 to 0.033, 1 study, 190 participants) in participants who were naïve to previous exposure with catheter ablation.

- Pericarditis: The proportion of participants with pericarditis was 0.011 (95% CI 0.005 to 0.025, 5 studies, 724 participants) in participants who were naïve to previous exposure with catheter ablation.
- Perimyocarditis: The proportion of participants with perimyocarditis was 0.005 (95% CI 0.000 to 0.032, 1 study, 200 participants) in participants who were naïve to previous exposure with catheter ablation.
- Phrenic nerve palsy (persistent): The proportion of participants with persistent phrenic nerve palsy was 0.018 (95% CI 0.006 to 0.047, 1 study, 228 participants) in participants who were naïve to previous exposure with catheter ablation.
- Phrenic nerve paralysis: The proportion of participants with phrenic nerve paralysis was 0.021 (95% CI 0.011 to 0.041, 4 studies, 579 participants) in participants who were naïve to previous exposure with catheter ablation.

#### 4.4.5 Medication side-effects

All medication side-effects outcomes have a GRADE rating of ‘High’ and are described below. Further details on the results can be found in Appendix 10.

- Discontinuations due to side-effects: The proportion of participants that discontinued the study/studies due to side-effects was 0.121 (95% CI 0.067 to 0.206, 1 study, 99 participants) in participants who were naïve to treatment with AAD, and 0.225 (95% CI 0.161 to 0.305, 2 studies, 129 participants) in participants previously treated with AAD.
- Diarrhea: The proportion of participants that experienced diarrhea during the study was 0.020 (95% CI 0.004 to 0.078, 1 study, 99 participants) in participants not previously treated with AAD.
- Eructation: The proportion of participants that experienced eructation during the study was 0.010 (95% CI 0.001 to 0.063, 1 study, 99 participants) in participants not previously treated with AAD.
- Presyncope: The proportion of participants that experienced presyncope during the studies was 0.027 (95% CI 0.012 to 0.060, 2 studies, 248 participants) in participants not previously treated with AAD.
- Syncope: The proportion of participants that experienced syncope during the studies was 0.013 (95% CI 0.005 to 0.033, 3 studies, 359 participants) in participants not previously treated with AAD.
- Anxiety: The proportion of participants that experienced anxiety during the study was 0.010 (95% CI 0.001 to 0.063, 1 study, 99 participants) in participants not previously treated with AAD.
- Dizziness: The proportion of participants that experienced dizziness during the study was 0.030 (95% CI 0.008 to 0.092, 1 study, 99 participants) in participants not previously treated with AAD.
- Dyspnea: The proportion of participants that experienced dyspnea during the study was 0.030 (95% CI 0.008 to 0.092, 1 study, 99 participants) in participants not previously treated with AAD.
- Erectile dysfunction: The proportion of participants that experienced erectile dysfunction during the studies was 0.008 (95% CI 0.002 to 0.032, 2 studies, 248 participants) in participants not previously treated with AAD.
- Fatigue: The proportion of participants that experienced fatigue during the study was 0.020 (95% CI 0.004 to 0.078, 1 study, 99 participants) in participants not previously treated with AAD.
- Joint pain: The proportion of participants that experienced joint pain during the study was 0.013 (95% CI 0.002 to 0.053, 1 study, 149 participants) in participants not previously treated with AAD.

#### 4.4.6 Quality of life

- AFEQT Total score
  - Low certainty: There may be no difference in AFEQT Total score when comparing treatment with AADs to treatment with catheter ablation in the group of participants with paroxysmal AF (MD -7.10, 95% CI -10.58 to -3.63, 5 studies, 1770 participants) and the group of participants with persistent AF (MD -4.30, 95% -6.28 to -2.32, 1 study, 1038 participants).
- EQ-5D Index score
  - Moderate certainty: There is probably no difference in EQ-5D Index score when comparing treatment with AADs to treatment with catheter ablation in the group of participants with paroxysmal AF (MD -0.03, 95% CI -0.04 to -0.01, 4 studies, 935 participants).
  - Low certainty: There may be no difference in EQ-5D Index score when comparing treatment with AADs to treatment with catheter ablation in a group of participants with mixed types of AF (MD -0.02, 95% CI -0.03 to -0.01, 1 study, 2204 participants).
- EQ-5D VAS score
  - Moderate certainty: There is probably no difference in EQ-5D VAS score when comparing treatment with AADs to treatment with catheter ablation in the group of participants with paroxysmal AF (MD -3.63, 95% CI -5.97 to -1.28, 6 studies, 1360 participants).
  - Low certainty: There may be no difference in EQ-5D VAS score when comparing treatment with AADs to treatment with catheter ablation in a group of participants with mixed types of AF (MD -4.40, 95% CI -5.81 to -2.99, 1 study, 2204 participants).
- SF-36 Mental component summary
  - Moderate certainty: There is probably no difference in SF-36 mental component summary when comparing treatment with AADs to treatment with catheter ablation in the group of participants with paroxysmal AF (MD -1.96, 95% CI -3.80 to -0.13, 6 studies, 1070 participants).
- SF-36 Physical component summary
  - Moderate certainty: There is probably no difference in SF-36 physical component summary when comparing treatment with AADs to treatment with catheter ablation in the group of participants with paroxysmal AF (MD -2.09, 95% CI -3.82 to -0.35, 6 studies, 1070 participants).
- SF-36 Physical functioning
  - Low certainty: There is probably no difference in SF-36 physical functioning when comparing treatment with AADs to treatment with catheter ablation in the group of participants with mixed type of AF (MD -4.70, 95% CI -17.81 to 8.41, 2 studies, 2300 participants).

All results can be found in Appendix 11.

## 5. Discussion

In this systematic review and meta-analysis, we summarized and synthesized evidence for the effect of treatment with AAD compared to catheter ablation in patients with AF to serve as input parameters of a disease model developed by the National Health Care Institute. In this review we looked at efficacy outcomes and quality of life. We found that treatment with catheter ablation was usually superior to treatment with AAD when considering recurrence of symptomatic AF, hospitalization with primary diagnosis AF and all-cause mortality (with varying degrees of certainty of evidence), and that there was no difference in quality of life between the two treatment options. Furthermore, we summarized the proportions of participants treated with catheter ablation that experienced serious adverse events that could be related to that treatment and participants treated with anti-arrhythmic drugs that experienced medication side-effects.

There are several limitations inherent to the included studies or to our review, as well as choices in the data-extraction and -analysis processes, that we would like to highlight and further clarify.

For inclusion into the review, we preferred studies that assessed the two treatments in the ‘general population’ of AF patients and would therefore not pose too restrictive eligibility criteria when selecting participants. This is why we excluded trials that only included participants with heart failure or type 2 diabetes, for example. However, we did include three studies that included only elderly participants (at least 60 years old (14) or at least 65 years (15) or included participants that were at least 65 years old, or participants <65 years old that had a risk factor for stroke (16)). We took this into account when rating the certainty of the evidence and downgraded for indirectness when more than half of the included studies for an outcome included such a specific population.

One of our outcomes of interest was recurrence of *symptomatic AF*, but during data-extraction we noticed that only a small number of studies reported this outcome specifically (only three studies out of 18). We have therefore also included outcomes related to recurrence of symptomatic atrial fibrillation such as any AF, any AF/atrial tachycardia/flutter, or symptomatic atrial arrhythmia. As a result, in our GRADE assessments for the outcome ‘recurrence of symptomatic atrial fibrillation’, we downgraded for indirectness when more than half of the included studies reported only one of these other outcomes.

During data-extraction it also became apparent that reporting of serious adverse events varied greatly between studies. This made it impossible to determine which events would be deemed serious adverse events. Therefore, it was not possible to extract the total number of participants who experienced a serious adverse event from each study. In consultation with the National Health Care Institute and experts in the field, we decided to extract all serious adverse events that were reported in the international standard set of outcome measures for patients with AF (1) separately.

Additionally, we initially planned stratified analyses for ischemic stroke and hemorrhagic stroke, as the first is a consequence of the disease and the latter is a complication of treatment. Unfortunately, this

distinction was not made in the included articles, and we had to analyze the composite outcome of ‘stroke’ that we now considered in the efficacy outcomes.

In consultation with the National Health Care Institute, we decided to combine populations with different types of AF (paroxysmal or persistent) or populations with previous exposure to AAD or catheter ablation for specific outcomes. For outcomes in which the type of AF or previous exposure were expected to impact the results, we kept these as separate groups. For studies with a mixed population (e.g. including both paroxysmal and persistent AF), we tried to classify them to either paroxysmal or persistent AF based on the percentages of paroxysmal and persistent AF participants included in the study: if either percentage was above 70%, the whole study was classified as that type of AF. For studies that were classified based on a percentage of 70-90%, we took indirectness of the population into account when rating the certainty of evidence. For populations with mixed previous exposures to AAD or catheter ablation, percentages were never reported so these could never be classified as either naïve or exposed to treatment.

As it is important for the disease model to have proportions of outcomes that could be compared between studies, we aimed to analyze linearized occurrence rates of outcomes rather than incidence over an entire follow-up period. Unfortunately, this turned out not to be possible because none of the included studies reported patient-years of follow-up. To ensure some comparability of proportions, we excluded studies with a follow-up other than 52 weeks when analyzing proportions per treatment group (but not when analyzing relative risks or mean differences). We did this for all outcomes, except for repeat ablation during the blanking period (which was always 11-13 weeks) and serious adverse events for catheter ablation, which were expected to occur shortly after the procedure.

When analyzing the data there were many studies that reported zero events in one (or both) treatment groups, which was expected as many of the outcomes of interest are rare. For random-effects meta-analysis we usually prefer using the Knapp-Hartung method together with the restricted maximum likelihood estimator as it designed to provide more accurate error rates when number of studies is small or when combining studies of different sizes (17). However, it is not recommended when heterogeneity between studies is small (i.e.  $\tau^2$  close to zero) (6) which occurs when there are a lot of studies with zero events included in the meta-analysis, which was the case for many of our outcomes. Hence, for random-effects analyses other than for recurrence of symptomatic AF or quality of life, we performed the meta-analysis using the restricted maximum likelihood estimator without the Knapp-Hartung adjustment.

Another issue that arises when analyzing studies with zero events, is that a 0.5 continuity correction is required for all treatment arms with 0 events. A disadvantage of this is that it slightly inflates the pooled proportions that are calculated when combining two or more studies. This is highlighted best when looking at the example of atrio-oesophageal fistula, for which all individual studies reported zero patients with the event, but the pooled proportion is still 0.003 (95% CI 0.001 to 0.008).

Finally, we would like to give some additional information regarding the GRADE ratings for the certainty of evidence. There is a large discrepancy between GRADE ratings for efficacy outcomes, that are often rated ‘Very low’, compared to the serious adverse events and medication side-effects outcomes, for which

the rating is nearly always 'High'. One reason for this is that the certainty of evidence for the efficacy outcomes is often downgraded for risk of bias in the domain 'bias due to deviations from the intended interventions' as participants were usually allowed to switch to the other treatment group during the follow-up period, resulting in high risk of bias for the outcomes in which the two groups are compared. On the other hand, for the serious adverse events that were deemed only to be caused by catheter ablation, and the medication side-effects that were only caused by AAD, switching between groups during follow-up did not result in a high risk of bias and it was therefore not necessary to downgrade the certainty of evidence. Additionally, GRADE does not give guidance for rating imprecision in single-arm outcomes, and therefore imprecision could not be graded (and hence downgraded) for the aforementioned outcomes.

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## Appendices

- Appendix 1. Search strategy
- Appendix 2. Excluded studies
- Appendix 3. Characteristics of included studies
- Appendix 4. Baseline description of included studies
- Appendix 5. Risk of bias assessments
- Appendix 6. Efficacy results
- Appendix 7. Repeat ablation results
- Appendix 8. Serious adverse events (both groups) results
- Appendix 9. Serious adverse events (only ablation) results
- Appendix 10. Medication side-effects results
- Appendix 11. Quality of life results

## Appendix 1. Search strategy

### MEDLINE

Search date: October 22<sup>nd</sup>, 2024

#	Searches	Results
1	exp atrial fibrillation/	76307
2	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.	99856
3	AF.ti,ab.	58238
4	1 or 2 or 3	131952
5	letter/	1277410
6	editorial/	710003
7	news/	227906
8	exp historical article/	414047
9	Anecdotes as Topic/	4747
10	comment/	1043979
11	case reports/	2441549
12	(letter or comment*).ti.	205591
13	or/5-12	5167284
14	randomized controlled trial/ or random*.ti,ab.	1695371
15	13 not 14	5132345
16	animals/ not humans/	5235320
17	exp Animals, Laboratory/	976176
18	exp Animal Experimentation/	10603
19	exp Models, Animal/	663919
20	exp Rodentia/	3652442
21	(rat or rats or mouse or mice).ti.	1482826
22	or/15-21	11323917
23	4 not 22	99222
24	limit 23 to english language	90289
25	exp Ablation Techniques/	135642
26	ablat*.ti,ab.	148804
27	(cryoablat* or cryoballoon* or cryo balloon*).ti,ab.	6632
28	phased array.ti,ab.	3214
29	*Pulmonary Veins/	13061
30	((pulmonary vein adj2 isolation) or PVI or PVAI).ti,ab.	7096
31	radiofrequency therapy/	1288

32	((radiofrequenc* or radio frequenc* or RF or hybrid) adj2 (therap* or surg* or procedure*)).ti,ab.	6205
33	"point by point".ti,ab.	1336
34	Lasers/	42031
35	laser*.ti,ab.	338930
36	(maze adj2 (procedure* or surg*)).ti,ab.	1506
37	cox-maze.ti,ab.	550
38	or/25-37	534502
39	24 and 38	17202
40	randomized controlled trial.pt.	623924
41	controlled clinical trial.pt.	95624
42	randomi#ed.ab.	793963
43	placebo.ab.	252955
44	randomly.ab.	444848
45	clinical trials as topic.sh.	203634
46	trial.ti.	320786
47	or/40-46	1686094
48	39 and 47	2467
49	limit 48 to yr="2020 -Current"	908

## Embase

Search date: October 22<sup>nd</sup>, 2024

#	Searches	Results
1	exp atrial fibrillation/	147657
2	((atrial or atria or atrium or auricular) adj3 fibrillat*).ti,ab.	182334
3	AF.ti,ab.	110125
4	1 or 2 or 3	258182
5	letter.pt. or letter/	1355976
6	note.pt.	1005457
7	editorial.pt.	826693
8	case report/ or case study/	3244222
9	(letter or comment*).ti.	260921
10	or/5-9	6164321
11	randomized controlled trial/ or random*.ti,ab.	2270867
12	10 not 11	6100873

13	animal/ not human/	1651841
14	nonhuman/	7904221
15	exp Animal Experiment/	3263850
16	exp Experimental Animal/	905771
17	animal model/	1844379
18	exp Rodent/	4674239
19	(rat or rats or mouse or mice).ti.	1866079
20	or/12-19	16550269
21	4 not 20	192087
22	limit 21 to english language	180045
23	exp ablation therapy/	74269
24	ablat*.ti,ab.	229342
25	(cryoablat* or cryoballoon* or cryo balloon*).ti,ab.	12100
26	phased array.ti,ab.	3909
27	pulmonary vein isolation/ or pulmonary vein/	33612
28	((pulmonary vein adj2 isolation) or PVI or PVAI).ti,ab.	15290
29	catheter ablation/	44455
30	((radiofrequenc* or radio frequenc* or RF or hybrid) adj2 (therap* or surg* or procedure*)).ti,ab.	10029
31	"point by point".ti,ab.	1950
32	laser/ or low level laser therapy/ or laser surgery/	166175
33	laser*.ti,ab.	355683
34	(maze adj2 (procedure* or surg*)).ti,ab.	2187
35	cox-maze.ti,ab.	712
36	or/23-35	644759
37	22 and 36	35330
38	random*.ti,ab.	2146855
39	factorial*.ti,ab.	51208
40	(crossover* or cross over*).ti,ab.	134503
41	((doubl* or singl*) adj blind*).ti,ab.	294705
42	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1362313
43	crossover procedure/	80427
44	single blind procedure/	56805
45	randomized controlled trial/	852136
46	double blind procedure/	227635
47	or/38-46	3168106
48	37 and 47	5039

49	limit 48 to yr="2020 -Current"	1877
50	limit 49 to conference abstract	649
51	49 not 50	1228

## Cochrane CENTRAL

Search date: October 23<sup>rd</sup>, 2024

ID	Search	Hits
#1	MeSH descriptor: [Atrial Fibrillation] explode all trees	7390
#2	((atrial or atria or atrium or auricular) near/3 fibrillat*):ti,ab	15372
#3	AF:ti,ab	9750
#4	#1 or #2 or #3	18096
#5	MeSH descriptor: [Ablation Techniques] explode all trees	8455
#6	ablat*:ti,ab	12523
#7	(cryoablat* or cryoballoon* or cryo balloon*):ti,ab	855
#8	phased array:ti,ab	89
#9	MeSH descriptor: [Pulmonary Veins] explode all trees	709
#10	pulmonary vein near/2 isolation:ti,ab	1568
#11	(PVI or PVAI):ti,ab	1347
#12	MeSH descriptor: [Radiofrequency Therapy] explode all trees	2869
#13	((radiofrequenc* or radio frequenc* or RF or hybrid) near/2 (therap* or surg* or procedure*)):ti,ab	2296
#14	point by point:ti,ab	86637
#15	MeSH descriptor: [Lasers] explode all trees	3861
#16	laser*:ti,ab	24032
#17	(maze near/2 (procedure* or surg*)):ti,ab	113
#18	cox-maze:ti,ab	36
#19	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	123878
#20	#4 and #19 with Publication Year from 2020 to 2024, in Trials	1584
#21	(conference OR 'Trial registry record'):pt	785034
#22	#20 NOT #21	752

## Appendix 2. Excluded studies

Reference (1-78)	Excluded on
Al-Kaisey (2023)	Outcome
Allan (2020)	Publication type
Andrade (2022)	Publication type
Andrade (2023)	Outcome
Andrade (2024)	Publication type
Bahnson (2022)	Outcome
Berman (2023)	Publication type
Briceno (2020)	Publication type
Cappato (2024)	Outcome
Cardoso (2022)	Language
Chander (2024)	Publication type
Chen (2021)	Publication type
Chen (2022)	Publication type
Chew (2022)	Outcome
Crawford (2024)	Publication type
Deering (2023) - "Chapter 3: Evidence..."	Publication type
Deering (2023) - "Chapter 4: Evidence..."	Publication type
Deshpande (2022)	Publication type
Elsayed (2022)	Publication type
Ezzeddine (2023)	Publication type
Fong (2023)	Publication type
Guo (2024)	Publication type
Hansen (2024)	Publication type
Imberti (2021)	Publication type
Jaiswal (2024)	Publication type
Jansson (2021)	Outcome
Kanorskii (2023)	Publication type
Karim (2024)	Publication type
Kewcharoen (2021)	Publication type
Khan (2020)	Publication type
Kheiri (2021)	Publication type
Kheshti (2024)	Publication type
Kumar (2021)	Publication type
Leung (2022)	Publication type
Liu (2020)	Publication type
Liu (2023)	Publication type
Mao (2020)	Publication type
Mao (2021)	Publication type
Mao (2023)	Publication type

Reference (1-78)	Excluded on
Mazetto (2024)	Publication type
Messori (2021)	Publication type
NICE (2021) - "J2: Ablation"	Publication type
NICE (2021) - "J3: Ablation"	Publication type
Nielsen (2017)	Outcome
Osmancik (2022)	Publication type
Paisey (2024)	Publication type
Parlavecchio (2023)	Publication type
Patel (2021)	Publication type
Providencia (2024)	Publication type
Rasti (2024)	Publication type
Ravi (2022)	Publication type
Razzack (2022)	Publication type
Rettmann (2021)	Outcome
Russo (2021)	Outcome
Saad-Omer (2020)	Publication type
Saglietto (2020)	Publication type
Saglietto (2021)	Publication type
Schleberger (2021)	Language
Shaik (2022)	Publication type
Song (2022)	Publication type
Song (2024)	Publication type
Stabile (2006)	Comparator
Sun (2021)	Publication type
Syeed (2024)	Publication type
Thomas (2021)	Outcome
Trippoli (2022)	Publication type
Turagam (2021)	Publication type
Ullah (2024)	Publication type
Wang (2021)	Publication type
Wang (2022)	Publication type
Wazni (2023)	Publication type
Wu (2021)	Comparator
Yamane (2024)	Study type
Zafeiropoulos (2024)	Publication type
Zahoor (2023)	Publication type
Zeitler (2023)	Outcome
Zhao (2024)	Publication type
Zheng (2021)	Publication type

Note: Articles excluded on publication type were systematic reviews and meta-analyses that were reviewed to identify additional records.

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### Appendix 3. Characteristics of included studies

Reference	Countries	Population	Type of atrial fibrillation	Sample size	Intervention(s)	Comparator	Outcomes	Follow-up duration
Acronym	Study dates		Line of treatment					
Trial registration number			Previous treatments					
Al-Kaisey et al. 2023 (1)	Australia	Patients (18 to 80 years) with paroxysmal or persistent atrial fibrillation	Mixed types of AF					
REMEDIAL	Enrollment: June 2018 to March 2020		Second line treatment	100	Radiofrequency ablation (multi-electrode)	AAD	(Symptomatic) AF recurrence Quality of life	52 weeks
ACTRN126180000622 24			Previous ablation not reported; mixed previous treatment with AADs					
Andrade et al. 2021 (2)	Canada	Patients (at least 18 years) with symptomatic atrial fibrillation and at least one episode detected on ECG within 24 months before randomization	Mixed types of AF				(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Mortality Heart failure deterioration Hospitalization Emergency room visits Repeat ablation Serious adverse events Medication side effects Quality of life	
EARLY-AF	Enrollment: January 2017 to December 2018		First line treatment	303	Cryoballoon ablation	Physician's choice AAD		52 weeks
NCT02825979			Ablation and AAD naïve					
Blomström-Lundqvist et al. 2019 (3)	Finland, Sweden	Patients (30 to 70 years) with more than 6 months of atrial fibrillation and treatment failure with 1 AAD or beta-blocker	Mixed types of AF				(Symptomatic) AF recurrence TIA Repeat ablation Serious adverse events Quality of life	
CAPTAF	July 2008 to September 2017		Second line treatment	155	Mixed types of ablation	Physician's choice AAD, according to current guidelines		208 weeks
EUCTR: 2008-001384-11			Ablation naïve; AAD exposed					
<i>Extension study:</i> Wettervik et al. 2024 (4)								
Ding et al. 2022 (5)	China	Patients (18 to 80 years) with paroxysmal atrial fibrillation, who experienced 1 or more episodes in the	Paroxysmal AF				(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Life-threatening/major bleeding	
NR	Enrollment: January 2018 to November 2018		First line treatment	204	Cryoballoon ablation	Physician's choice class I/III AAD		156 weeks
NR			Ablation and AAD naïve					

Reference		Type of atrial fibrillation						
Acronym	Countries	Population	Line of treatment	Sample size	Intervention(s)	Comparator	Outcomes	Follow-up duration
Trial registration number	Study dates		Previous treatments					
		6 months prior to randomization					Mortality Hospitalization Serious adverse events	
Hummel et al. 2014 (6)	Netherlands, US	Patients (18 to 70 years) with persistent atrial fibrillation lasting 7 days to 4 years who failed DCCV and had failed at least 1 class I or III AAD	Persistent AF (mixed duration)	210	Radiofrequency ablation (multi-electrode)	Physician's choice AAD, according to current guidelines	Stroke (ischemic or hemorrhagic) Mortality Life-threatening/major bleeding Heart failure incidence Repeat ablation Serious adverse events	26 weeks
TTOP-AF	November 2007 to May 2010		Second line treatment					
NR			Ablation naïve; AAD exposed					
Jaïs et al. 2008 (7)	France, Switzerland, US	Patients (at least 18 years) with symptomatic paroxysmal AF for at least 6 months resistant to at least 1 AAD	Paroxysmal AF	112	Radiofrequency ablation (point by point)	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence Mortality Repeat ablation Serious adverse events Quality of life	52 weeks
A4 STUDY			Second line treatment					
NCT00540787	NR		Ablation naïve; AAD exposed					
Kanagaratnam et al. 2023 (8)	UK	Patients (18 to 80 years) with paroxysmal atrial fibrillation considered to be failing their current treatment strategy	Paroxysmal AF	321	Cryoballoon ablation (two protocols)	Physician's choice AAD, according to current guidelines	Stroke (ischemic or hemorrhagic) TIA Mortality Hospitalization Emergency room visits Repeat ablation Serious adverse events Quality of life	52 weeks
AVATAR-AF	Enrollment: April 2015 to August 2017		Mixed line of treatment					
NCT02459574			Ablation naïve; mixed previous treatment with AADs					
Kuck et al. 2021 (9)	Austria, Belgium, Germany, Hungary, Ireland, Italy, Korea, Latvia, Norway, Russia, Spain, Sweden, UK	Patients (at least 60 years) with paroxysmal atrial fibrillation for at least 2 years and at least 2 episodes over the last 6 months	Paroxysmal AF	255	Radiofrequency ablation (multi-electrode)	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) Heart failure incidence Repeat ablation Serious adverse events	156 weeks
ATTEST			Second line treatment					
NCT01570361	February 2012 to May 2018		Ablation naïve; AAD exposed					
Kuniss et al. 2021 (10)	Argentina, Australia,	Patients (18 to 75 years) with recurrent	Paroxysmal AF	218	Cryoballoon ablation	Class I/III medication	(Symptomatic) AF recurrence Stroke (ischemic or	52 weeks

Reference	Acronym	Countries	Population	Type of atrial fibrillation	Sample size	Intervention(s)	Comparator	Outcomes	Follow-up duration
Trial registration number	Study dates		Line of treatment	Previous treatments					
Cryo-FIRST NCT01803438 <i>Post-hoc study:</i> Pavlovic et al. 2021 (11)	Belgium, Croatia, France, Germany, Italy, Netherlands, Norway  Enrollment: April 2014 to October 2018	paroxysmal atrial fibrillation who were AAD naïve	First line treatment  Ablation and AAD naïve					hemorrhagic TIA Mortality Repeat ablation Serious adverse events Medication side effects Quality of life	
Martins et al. 2024 (12)  NR NCT04023461	Brazil  Randomization: September 2017 to March 2020	Patients (at least 65 years) with paroxysmal atrial fibrillation and recurrence after the use of at least one AAD	Paroxysmal AF  Second line treatment  Ablation naïve; AAD exposed		60	Radiofrequency ablation (multi-electrode)	Physician's choice AAD	(Symptomatic) AF recurrence Repeat ablation Serious adverse events Discontinuation due to side effects	Median 103 weeks
Mont et al. 2014 (13)  SARA NCT00863213	Spain  May 2009 to November 2011	Patients (18 to 70 years) with symptomatic persistent atrial fibrillation refractory to at least one class I or class III AAD	Persistent AF (< 1 year)  Second line treatment  Ablation naïve; AAD exposed		146	Radiofrequency ablation (point by point)	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Mortality Hospitalization Repeat ablation Serious adverse events	52 weeks
Morillo et al. 2014 (14)  RAAFT-2 NCT00392054	Canada, Czechia, Germany, Italy, US  July 2006 to February 2012	Patients (18 to 75 years) with paroxysmal atrial fibrillation without previous antiarrhythmic drug treatment or ablation	Paroxysmal AF  First line treatment  Ablation and AAD naïve		127	Radiofrequency ablation (point by point)	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Mortality Repeat ablation Serious adverse events Medication side effects Quality of life	104 weeks
Nielsen et al. 2012 (15)  MANTRA-PAF NCT00133211	Denmark  Enrollment: June 2005 to March 2009	Patients (younger than 70 years) with paroxysmal atrial fibrillation without previous treatment with AADs or ablation	Paroxysmal AF  First line treatment  Ablation and AAD naïve		294	Radiofrequency ablation (point by point)	Class IC/III medication	Stroke (ischemic or hemorrhagic) TIA Mortality Heart failure incidence or deterioration	104 weeks

Reference	Type of atrial fibrillation							
Acronym	Countries	Population	Line of treatment	Sample size	Intervention(s)	Comparator	Outcomes	Follow-up duration
Trial registration number	Study dates		Previous treatments					
<i>Post-hoc study:</i> Walfridsson et al. 2015 (16)							Repeat ablation Serious adverse events Quality of life	
Packer et al. 2013 (17) STOP AF NCT00523978	Canada, US  NR	Patients with more than 2 episodes of paroxysmal atrial fibrillation in the last 2 months who failed at least one membrane-active drug	Mixed types of AF  Second line treatment  Ablation naïve; AAD exposed	258	Cryoballoon ablation	Flecainide or Propafenone or Sotalol	(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Mortality Life-threatening/major bleeding Heart failure incidence or deterioration Hospitalization Repeat ablation Serious adverse events	52 weeks
Packer et al. 2019 (18) CABANA NCT00911508 <i>Post-hoc studies:</i> Mark et al. 2019 (19) Monahan et al. 2022 (20) Poole et al. 2020 (21)	Australia, Canada, China, Czechia, Germany, Italy, Republic of Korea, Russia, UK, US  November 2009 to December 2017	Patients with symptomatic atrial fibrillation, aged 65 years and older, or younger than 65 years with 1 or more risk factors for stroke	Mixed types of AF  Second line treatment  Ablation naïve; AAD exposed	2204	Mixed types of ablation	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Mortality Life-threatening/major bleeding Heart failure incidence Hospitalization Repeat ablation Serious adverse events Medication side effects Quality of life	Median 211 weeks
Pappone et al. 2006 (22) APAF NCT00340314 <i>Post-hoc/extension study:</i>	Italy  Enrollment: January 2005 to May 2005	Patients (18 to 70 years) with paroxysmal atrial fibrillation for at least 6 months and at least 2 episodes per month in the last 6 months who already failed AADs	Paroxysmal AF  Second line treatment  Ablation naïve; AAD exposed	198	Radiofrequency ablation (point by point)	Flecainide 200-300 mg per day or Sotalol 240-320 mg per day or Amiodarone 200 mg per day (after	(Symptomatic) AF recurrence TIA Repeat ablation Discontinuation due to side effects Quality of life	52 weeks

Reference	Countries		Type of atrial fibrillation					
Acronym	Study dates	Population	Line of treatment	Sample size	Intervention(s)	Comparator	Outcomes	Follow-up duration
Trial registration number			Previous treatments					
Pappone et al. 2011 (23)						loading dosages)		
Pokushalov et al. 2013 (24) NR NCT01709682	Russia  Initial procedure: November 2007 to January 2009	Patients with a history of symptomatic paroxysmal atrial fibrillation eligible for AAD therapy or reablation after a previous failed initial RFA procedure	Paroxysmal AF  Second line treatment  Ablation exposed; mixed previous treatment with AADs	154	Radiofrequency ablation (point by point)	Propafenone 450-900 mg per day or Flecainide 200-400 mg per day or Sotalolol 160-320 mg per day	(Symptomatic) AF recurrence TIA Repeat ablation Serious adverse events	156 weeks
Sohara et al. 2016 (25) NR NR	Japan  NR	Patients (20 to 75 years) with symptomatic paroxysmal atrial fibrillation refractory to 1 or more class I/IV AADs and with at least 2 episodes during the 6 months before treatment	Paroxysmal AF  Second line treatment  Ablation naïve; AAD exposed	153	Radiofrequency ablation (HotBalloon)	Physician's choice AAD	(Symptomatic) AF recurrence Serious adverse events Quality of life	52 weeks
Wazni et al. 2005 (26) RAAFT NR	Germany, Italy  Enrollment: December 2001 to July 2002	Patients (80 to 75 years) who experienced monthly symptomatic atrial fibrillation episodes for at least 3 months and had not been treated with AADs	Mixed types of AF  First line treatment  Ablation and AAD naïve	70	Radiofrequency ablation (point by point)	Physician's choice AAD	(Symptomatic) AF recurrence Stroke (ischemic or hemorrhagic) TIA Repeat ablation Serious adverse events Quality of life	52 weeks
Wazni et al. 2021 (27) STOP AF First NCT03118518 <i>Post-hoc study:</i> Wazni et al. 2022 (28)	US  Enrollment: June 2017 to May 2019	Patients (18 to 80 years) with recurrent symptomatic paroxysmal atrial fibrillation who had not previously received rhythm-control therapy	Paroxysmal AF  First line treatment  Ablation and AAD naïve	210	Cryoballoon ablation	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence TIA Heart failure incidence Repeat ablation Serious adverse events Medication side effects Discontinuations due to side effects Quality of life	52 weeks

Reference	Acronym	Countries	Population	Type of atrial fibrillation	Sample size	Intervention(s)	Comparator	Outcomes	Follow-up duration
Trial registration number	Study dates		Line of treatment	Previous treatments					
Wilber et al. 2010 (29)	ThermoCool AF	Brazil, Canada, Czechia, Italy, US	Patients (at least 18 years) with at least 3 symptomatic paroxysmal atrial fibrillation episodes within 6 months before randomization and not responding to at least 1 AAD	Paroxysmal AF Second line treatment	167	Radiofrequency ablation (point by point)	Physician's choice AAD, according to current guidelines	(Symptomatic) AF recurrence Mortality Heart failure incidence Repeat ablation Quality of life	52 weeks
NCT00116428	October 2004 to January 2009			Ablation naïve; AAD exposed					
<i>Post-hoc study:</i> Reynolds et al. 2010 (30)									
Xu et al. 2012 (31)	NR	China	Patients with atrial fibrillation	Mixed types of AF Line of treatment not reported	123	Radiofrequency ablation (point by point)	AAD	Quality of life	26 weeks
NR	NR			Previous treatments not reported					

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; DCCV: direct current cardioversion; ECG: electrocardiography; NR: not reported; TIA: transient ischemic attack; UK: United Kingdom; US: United States.

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## Appendix 4. Baseline description of included studies

Reference Acronym	Age (years), mean (SD)	Sex: male (%)	BMI, mean (SD)	Type of AF (%)	Heart failure (%)	Previous treatment (%)	Current treatment with anticoagulants (%)	CHA2DS2-VASc score (%)
Al-Kaisey et al. 2023 REMEDIAL	59 (12)	67.7%	30 (6.3)	Paroxysmal: 54.2% Persistent: 45.8%	8.3%	Ablation: NR AAD: NR	87.5%	NR
Andrade et al. 2021 EARLY-AF	58.6 (11.5)	70.6%	30.3 (12.0)	Paroxysmal: 94.7% Persistent: 5.3%	9.2%	Ablation: 0% AAD: 0%	Warfarin: 4.6% DOAC: 61.1%	NR
Blomström-Lundqvist et al. 2019 CAPTAF	56.0 (9.8)	77.4%	27.1 (3.7)	Paroxysmal: 72.9% Persistent: 27.1%	3.2%	Ablation: 0% AAD: 100%	61.9%	<2: NR ≥2: 29.0
<i>Extension study:</i> Wettervik et al. 2024								
Ding et al. 2022 NR	60.8 (9.1)	59.3%	25.7 (3.3)	Paroxysmal: 100%	8.3%	Ablation: 0% AAD: 0%	NR	NR
Hummel et al. 2014 TTOP-AF	60.0 (8.5)	83.3%	NR	Persistent: 100%	7.6%	Ablation: 0% AAD: 100%	NR	NR
Jaïs et al. 2008 A4 STUDY	51.1 (11.1)	83.9%	NR	Paroxysmal: 100%	NR	Ablation: 0% AAD: 100%	NR	NR
Kanagaratnam et al. 2023 AVATAR-AF	60.1 (10.6)	58.3%	28.7 (4.9)	Paroxysmal: 100%	NR	Ablation: 0% AAD: NR	69.2%	<2: 59.2% ≥2: 40.5%
Kuck et al. 2021 ATTEST	67.7 (4.7)	42.0%	NR	Paroxysmal: 100%	20.0%	Ablation: 0% AAD: 100%	NR	NR
Kuniss et al. 2021 Cryo-FIRST	52.3 (13.3)	67.9%	NR	Paroxysmal: 100%	0.0%	Ablation: 0% AAD: 0%	39.9%	<2: 73.4% ≥2: 21.6%
<i>Post-hoc study:</i> Pavlovic et al. 2021								
Martins et al. 2024 NR	71.6 (4.6)	46.7%	28.1 (4.9)	Paroxysmal: 100%	NR	Ablation: 0% AAD: 100%	41.7%	<2: 1.7% ≥2: 98.3%

Reference	Age (years), mean (SD)	Sex: male (%)	BMI, mean (SD)	Type of AF (%)	Heart failure (%)	Previous treatment (%)	Current treatment with anticoagulants (%)	CHA2DS2-VASc score (%)
Acronym								
Mont et al. 2014	55 (9)	77.4%	NR	Persistent: 100%	23.3%	Ablation: 0% AAD: 100%	NR	NR
SARA								
Morillo et al. 2014	55.3 (10.5)	75.6%	NR	Paroxysmal: 100%	2.4%	Ablation: 0% AAD: 0%	42.5%	<2: 91.3% ≥2: 8.7%
RAAFT-2								
Nielsen et al. 2012								
MANTRA-PAF	55 (10)	70.1%	27 (4)	Paroxysmal: 100%	11.9%	Ablation: 0% AAD: 0%	Warfarin: 45.6% Aspirin: 35.7%	<2: 87.8% ≥2: 12.2%
<i>Post-hoc study:</i> Walfridsson et al. 2015								
Packer et al. 2013	57 (9)	77.1%	NR	Paroxysmal: 78.0% Persistent: 22.0%	6.5%	Ablation: 0% AAD: 100%	NR	NR
STOP AF								
Packer et al. 2019								
CABANA	Median (IQR): Ablation: 68 (62-72) AAD: 67 (62-72)	62.8%	Median (IQR): Ablation: 30 (27-34) AAD: 30 (26-35)	Paroxysmal: 42.9% Persistent: 57.0%	35.2%	Ablation: 0% AAD: 100%	85.0%	<2: 17.9% ≥2: 82.1%
<i>Post-hoc studies:</i> Mark et al. 2019 Monahan et al. 2022 Poole et al. 2020								
Pappone et al. 2006								
APAF	56 (10)	67.2%	NR	Paroxysmal: 100%	NR	Ablation: 0% AAD: 100%	NR	NR
<i>Post-hoc/extension study:</i> Pappone et al. 2011								
Pokushalov et al. 2013	56.5 (7.0)	74.7%	28 (5.5)	Paroxysmal: 100%	0.0%	Ablation: 100% AAD: NR	NR	NR
NR								
Sohara et al. 2016	59.5 (10.3)	80.4%	NR	Paroxysmal: 100%	NR	Ablation: 0% AAD: 100%	NR	NR
NR								
Wazni et al. 2005	53.5 (8.0)	NR	NR	Paroxysmal: 95.7% Persistent: 4.3%	NR	Ablation: 0% AAD: 0%	NR	NR
RAAFT								
Wazni et al. 2021								
STOP AF First	61.0 (11.2)	59.1%	NR	Paroxysmal: 100%	2.0%	Ablation: 0% AAD: 0%	69.0%	<2: 45.3% ≥2: 54.7%

Reference	Age (years), mean (SD)	Sex: male (%)	BMI, mean (SD)	Type of AF (%)	Heart failure (%)	Previous treatment (%)	Current treatment with anticoagulants (%)	CHA2DS2-VASc score (%)
<i>Post-hoc study:</i> Wazni et al. 2022								
Wilber et al. 2010								
ThermoCool AF	55.7 (10.8)	66.5%	NR	Paroxysmal: 100%	12.0%	Ablation: 0% AAD: 100%	NR	NR
<i>Post-hoc study:</i> Reynolds et al. 2010								
Xu et al. 2012	61.2 (11.9)	65.0%	NR	Paroxysmal: 89.4% Persistent: 10.6%	NR	Ablation: NR AAD: NR	NR	NR
NR								

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; BMI: body mass index; DOAC: direct oral anticoagulant; IQR: interquartile range; NR: not reported; SD: standard deviation.

## Appendix 5. Risk of bias assessments by study

Study	Risk of bias domains					Overall
	D1	D2	D3	D4	D5	
Al-Kaisey et al. 2023 (REMEDIAL)						
Andrade et al. 2021 (EARLY-AF)						
Blomström-Lundqvist et al. 2019 (CAPTAF)						
Ding et al. 2022						
Hummel et al. 2014 (TTOP-AF)						
Jaïs et al. 2008 (A4 STUDY)						
Kanagaratnam et al. 2023 (AVATAR-AF)						
Kuck et al. 2021 (ATTEST)						
Kuniss et al. 2021 (Cryo-FIRST)						
Martins et al. 2024						
Mont et al. 2014 (SARA)						
Morillo et al. 2014 (RAAFT-2)						
Nielsen et al. 2012 (MANTRA-PAF)						
Packer et al. 2013 (STOP AF)						
Packer et al. 2019 (CABANA)						
Pappone et al. 2006 (APAF)						
Pokushalov et al. 2013						
Sohara et al. 2016						
Wazni et al. 2005 (RAAFT)						
Wazni et al. 2021 (STOP AF First)						
Wilber et al. 2010 (ThermoCool AF)						
Xu et al. 2012						

Domains:

D1: Bias arising from the randomization process.

D2: Bias due to deviations from intended interventions.

D3: Bias due to missing outcome data.

D4: Bias in measurement of the outcome.

D5: Bias in selection of the reported result.

Judgement

High

Some concerns

Low

## Appendix 6. Efficacy results

### A6.1 Summary of findings

Outcome	Type of AF	Population		Proportions at 52 weeks		Relative risk at any follow-up duration		GRADE rating (Target of certainty)
		Previous exposure to AADs	Previous exposure to catheter ablation	Proportion event in AAD treatment group (95% CI) [95% PI]	Proportion event in catheter ablation treatment group (95% CI) [95% PI]	Number of studies (number of participants)	Relative risk (95% CI) [95% PI]	
<b>Recurrence of (symptomatic) AF</b>	Paroxysmal	Naïve	Naïve	154/455 (5 studies) 0.39 (0.19 to 0.63) [0.06 to 0.87]	81/463 (5 studies) 0.18 (0.08 to 0.35) [0.02 to 0.65]	6 (1122)	1.76 (1.34 to 2.32) [1.34 to 2.32]	Low <sup>1,2</sup> (Clinically significant harm)
	Paroxysmal	Exposed	Naïve	491/809 (8 studies) 0.67 (0.39 to 0.87) [0.06 to 0.98]	282/979 (8 studies) 0.26 (0.18 to 0.36) [0.09 to 0.55]	9 (1848)	2.32 (1.78 to 3.01) [1.27 to 4.24]	Very low <sup>1,2,3,4</sup>
	Paroxysmal	Mixed	Exposed	-	-	1 (154)	2.12 (1.61 to 2.80)	Moderate <sup>2</sup> (Clinically significant harm)
	Persistent	Exposed	Naïve	242/404 (2 studies) 0.60 (0.55 to 0.64)	169/449 (2 studies) 0.38 (0.33 to 0.42)	2 (853)	1.62 (1.40 to 1.87)	Low <sup>1,2</sup> (Clinically significant harm)
	Mixed	Mixed	Unclear	45/47 (1 study) 0.96 (0.84 to 0.99)	23/49 (1 study) 0.47 (0.33 to 0.62)	1 (96)	2.04 (1.51 to 2.76)	Low <sup>1,2</sup> (Clinically significant harm)
<b>Stroke</b>	Paroxysmal	All	All	1/480 (5 studies) 0.007 (0.002 to 0.022) [0.002 to 0.022]	4/674 (5 studies) 0.010 (0.003 to 0.031) [0.002 to 0.059]	9 (2004)	0.86 (0.28 to 2.63) [0.28 to 2.63]	Very low <sup>1,6</sup>
	Persistent	All	All	0/48 (1 study) 0.000 (0.000 to 0.092)	0/98 (1 study) 0.000 (0.000 to 0.047)	2 (356)	0.47 (0.05 to 4.87)	Very low <sup>1,6</sup>
	Mixed	All	All	-	-	1 (2204)	2.36 (0.61 to 9.10)	Very low <sup>1,3,6</sup>
<b>TIA</b>	Paroxysmal	All	All	3/754 (8 studies) 0.008 (0.003 to 0.018) [0.003 to 0.018]	8/956 (8 studies) 0.011 (0.006 to 0.021) [0.006 to 0.021]	13 (3394)	0.85 (0.40 to 1.80) [0.40 to 1.80]	Very low <sup>1,6</sup>
	Persistent	All	All	0/48 (1 study) 0.000 (0.000 to 0.092)	0/98 (1 study) 0.000 (0.000 to 0.047)	2 (1339)	0.46 (0.04 to 5.02)	Very low <sup>1,6</sup>
<b>HF incidence</b>	Paroxysmal	All	All	0/155 (2 studies) 0.007 (0.001 to 0.045)	2/207 (2 studies) 0.010 (0.002 to 0.038)	3 (587)	0.39 (0.06 to 2.45)	Very low <sup>1,6</sup>
<b>HF deterioration</b>	Paroxysmal	All	All	0/149 (1 study) 0.000 (0.000 to 0.031)	1/54 (1 study) 0.006 (0.000 to 0.041)	1 (303)	0.34 (0.01 to 8.39)	Very low <sup>1,6</sup>

Outcome	Type of AF	Population		Proportions at 52 weeks		Relative risk at any follow-up duration		
		Previous exposure to AADs	Previous exposure to catheter ablation	Proportion event in AAD treatment group (95% CI) [95% PI]	Proportion event in catheter ablation treatment group (95% CI) [95% PI]	Number of studies (number of participants)	Relative risk (95% CI) [95% PI]	GRADE rating (Target of certainty)
<b>HF incidence or deterioration</b>	Paroxysmal	All	All	0/82 (1 study) 0.000 (0.000 to 0.056)	1/163 (1 study) 0.006 (0.000 to 0.039)	2 (539)	1.90 (0.21 to 17.07)	Very low <sup>1,6</sup>
<b>Hospitalization</b>	Paroxysmal	All	All	21/334 (3 studies) 0.068 (0.045 to 0.102)	12/535 (3 studies) 0.024 (0.014 to 0.042)	4 (1073)	2.61 (1.31 to 5.23)	Moderate <sup>1</sup> (Clinically significant harm)
	Persistent	All	All	3/48 (1 study) 0.062 (0.016 to 0.182)	2/98 (1 study) 0.020 (0.004 to 0.079)	1 (146)	3.06 (0.53 to 17.72)	Very low <sup>1,6</sup>
	Mixed	All	All	-	-	1 (2204)	1.35 (1.12 to 1.61)	Very low <sup>1,3,5</sup>
<b>Emergency room visits</b>	Paroxysmal	All	All	37/252 (2 studies) 0.162 (0.119 to 0.216)	36/372 (2 studies) 0.125 (0.091 to 0.169)	2 (624)	1.22 (0.80 to 1.85)	Low <sup>1,5</sup> (No clinically important effect)
<b>All-cause mortality</b>	Paroxysmal	All	All	10/1036 (7 studies) 0.014 (0.008 to 0.024) [0.008 to 0.024]	4/1268 (7 studies) 0.005 (0.002 to 0.011) [0.002 to 0.011]	10 (2929)	1.79 (0.80 to 4.02) [0.80 to 4.02]	Low <sup>1,5</sup> (Clinically significant harm)
	Persistent	All	All	9/667 (2 studies) 0.014 (0.008 to 0.027)	6/736 (2 studies) 0.009 (0.004 to 0.019)	3 (1613)	1.45 (0.56 to 3.75)	Low <sup>1,5</sup> (Clinically significant harm)

Note: The (pooled) proportions only include studies with outcome assessment at 52 weeks, the relative risk only contains studies with mean and measure of spread.

<sup>1</sup> Rated down for risk of bias

<sup>2</sup> Rated down for indirectness in the outcome (not all exactly symptomatic AF recurrence)

<sup>3</sup> Rated down for indirectness in the population (including studies that only included elderly participants and/or studies that were classified into paroxysmal/persistent AF but did not have >90% of that type)

<sup>4</sup> Rated down for inconsistency

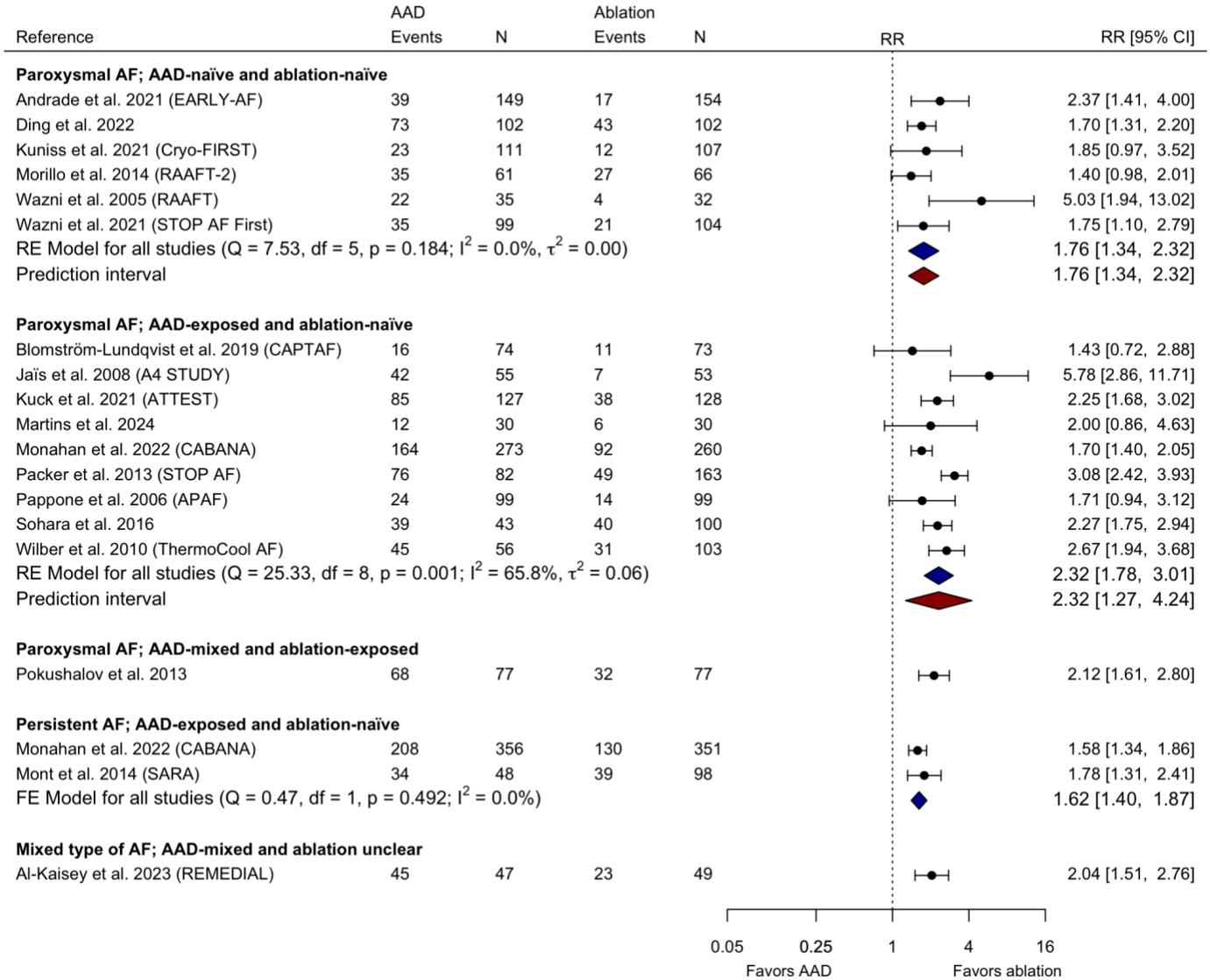
<sup>5</sup> Rated down for imprecision

<sup>6</sup> Rated down twice for imprecision

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; HF: heart failure; PI: prediction interval; TIA: transient ischemic attack.

A6.2A Forest plot recurrence of (symptomatic) AF/AT/AA – relative risk

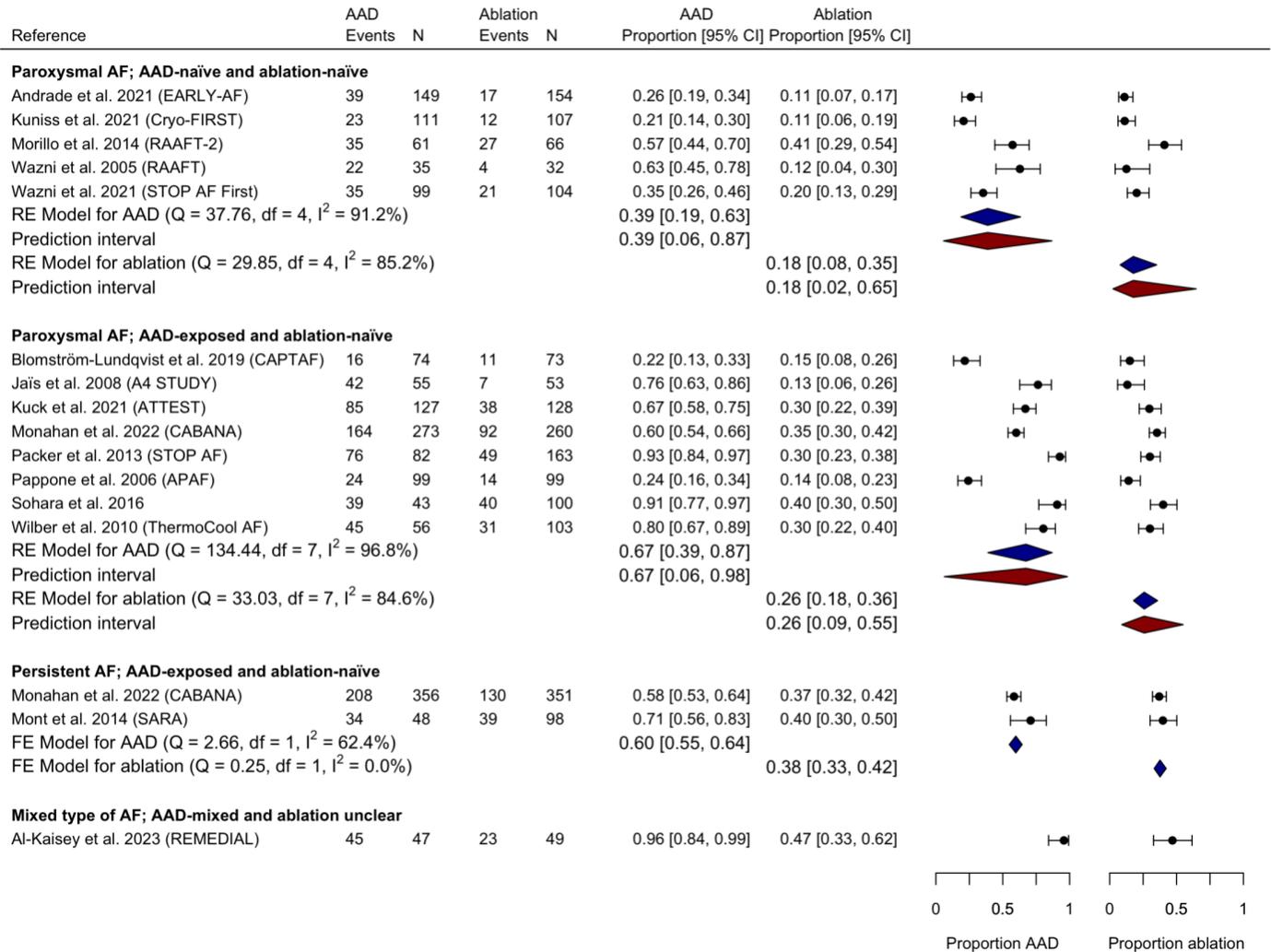
Recurrence of (symptomatic) AF/AT/AA



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects; RR: relative risk.

A6.2B Forest plot recurrence of (symptomatic) AF/AT/AA – proportions

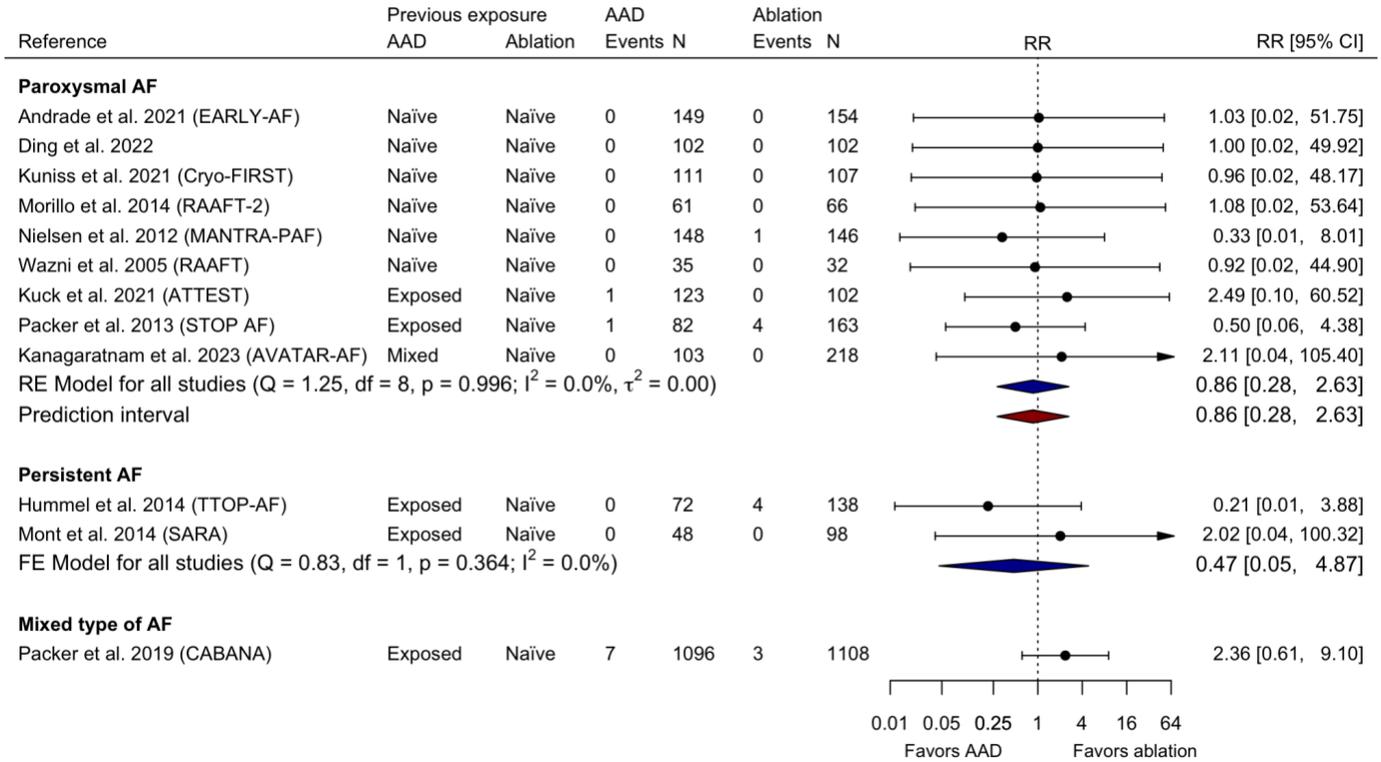
Recurrence of (symptomatic) AF/AT/AA



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects.

A6.3A Forest plot stroke (ischemic or hemorrhagic) – relative risk

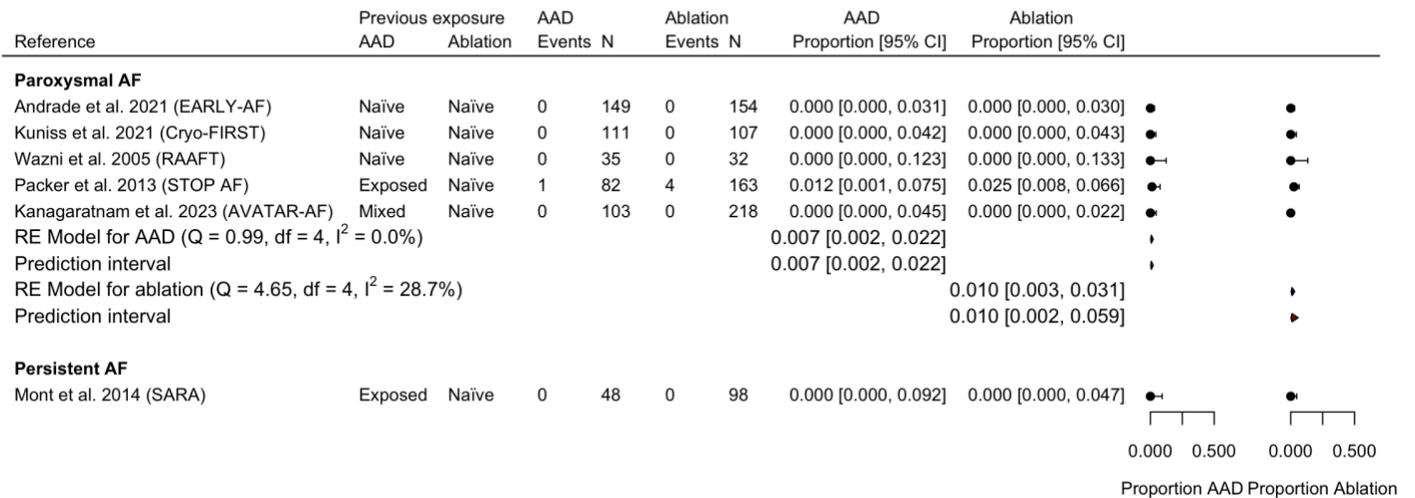
Stroke (ischemic or hemorrhagic)



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects; RR: relative risk.

A6.3B Forest plot stroke (ischemic or hemorrhagic) – proportions

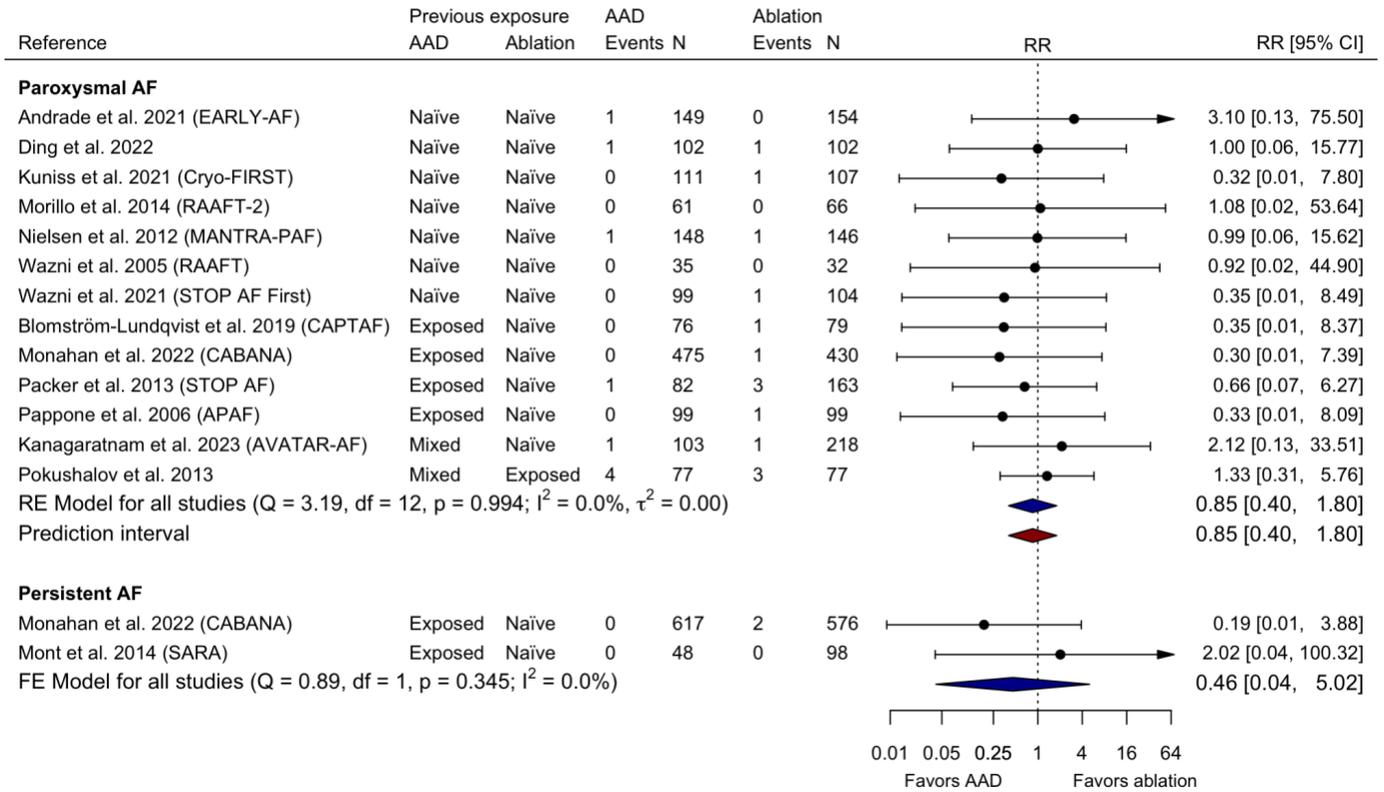
Stroke (ischemic or hemorrhagic)



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects.

A6.4A Forest plot transient ischemic attack (TIA) – relative risk

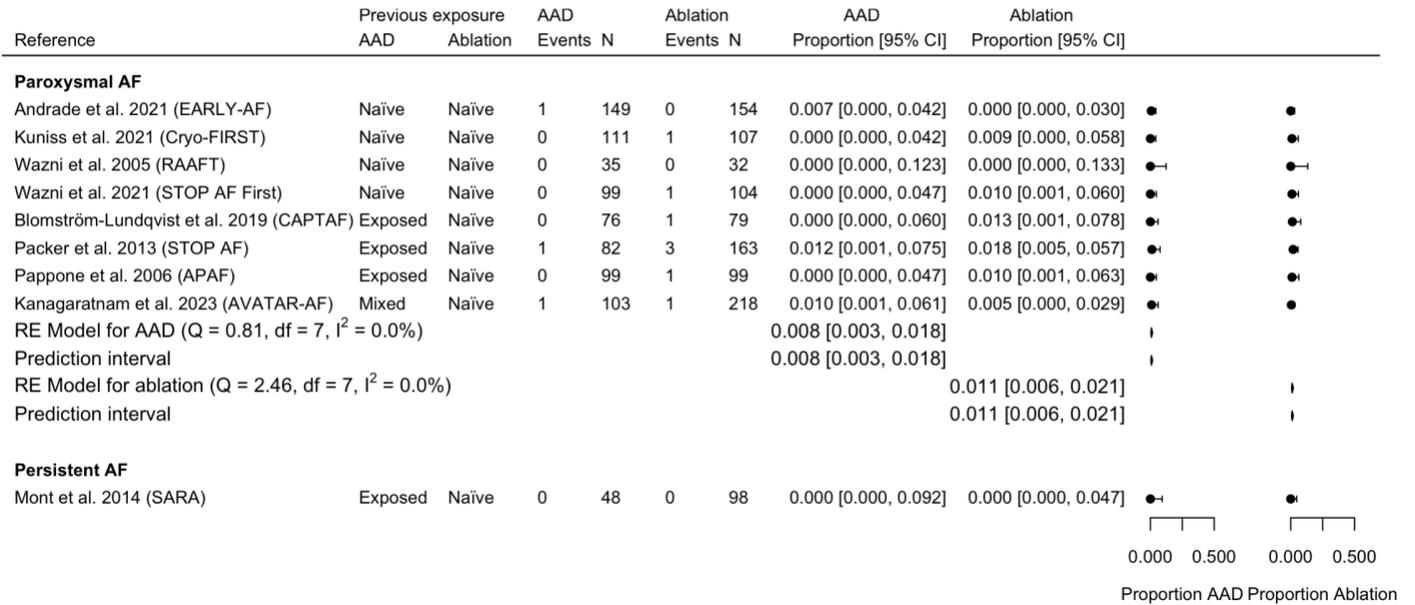
Transient ischemic attack (TIA)



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects; RR: relative risk.

A6.4B Forest plot transient ischemic attack (TIA) – proportions

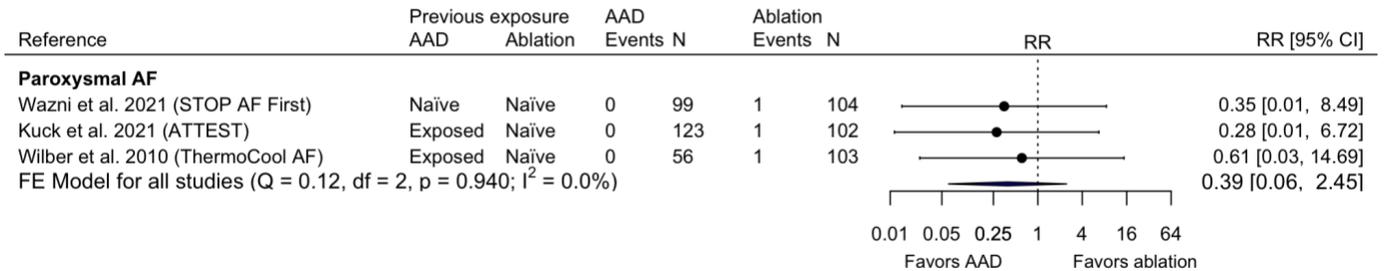
Transient ischemic attack (TIA)



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RE: random-effects.

A6.5A Forest plot heart failure incidence – relative risk

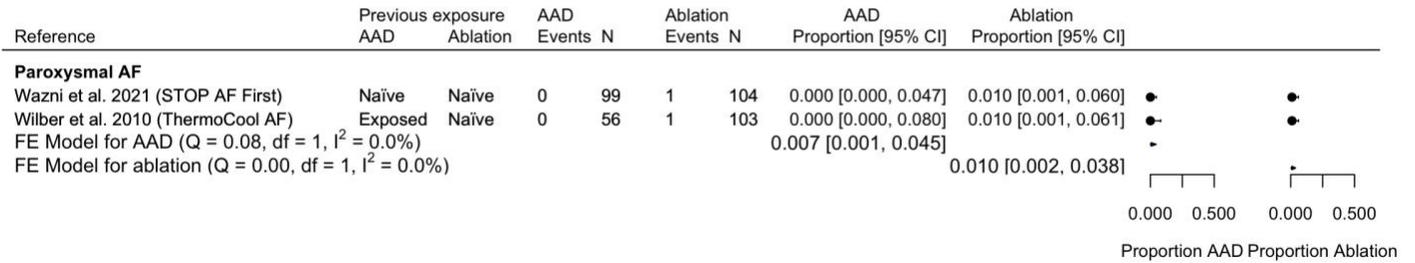
Heart failure incidence



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RR: relative risk.

### A6.5B Forest plot heart failure incidence – proportions

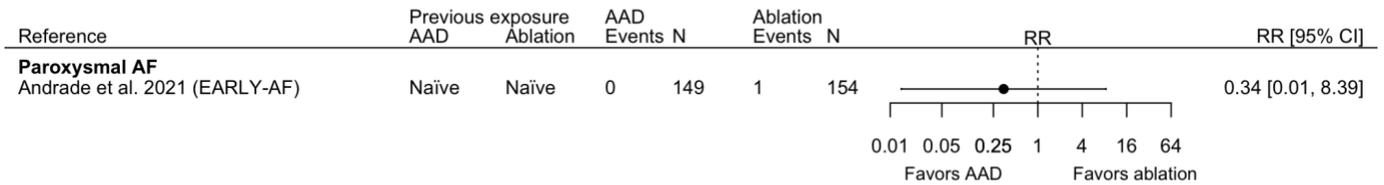
#### Heart failure incidence



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

### A6.6A Forest plot heart failure deterioration – relative risk

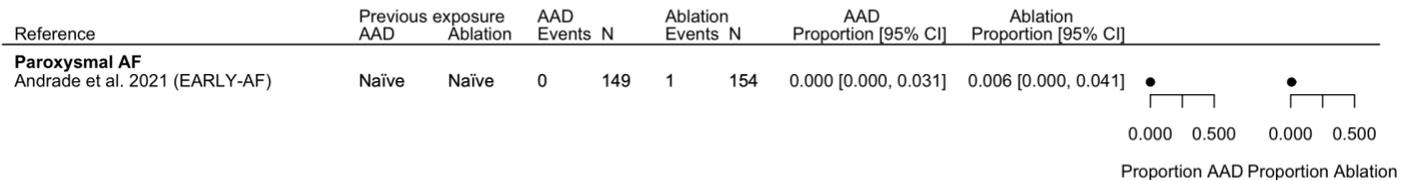
#### Heart failure deterioration



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RR: relative risk.

### A6.6B Forest plot heart failure deterioration – proportions

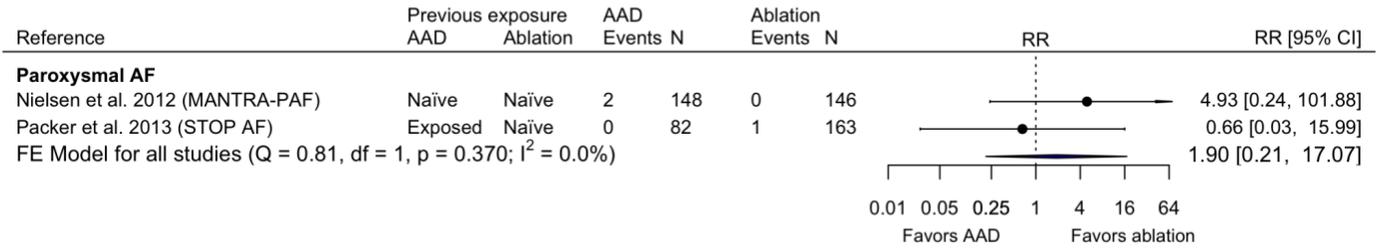
#### Heart failure deterioration



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants.

A6.7A Forest plot heart failure incidence or deterioration – relative risk

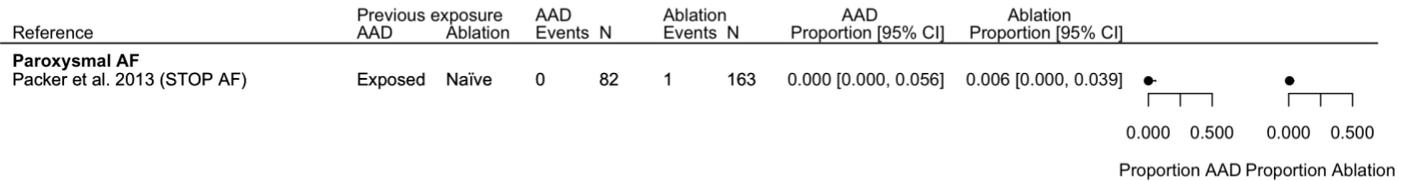
Heart failure incidence or deterioration



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RR: relative risk.

A6.7B Forest plot heart failure incidence or deterioration – proportions

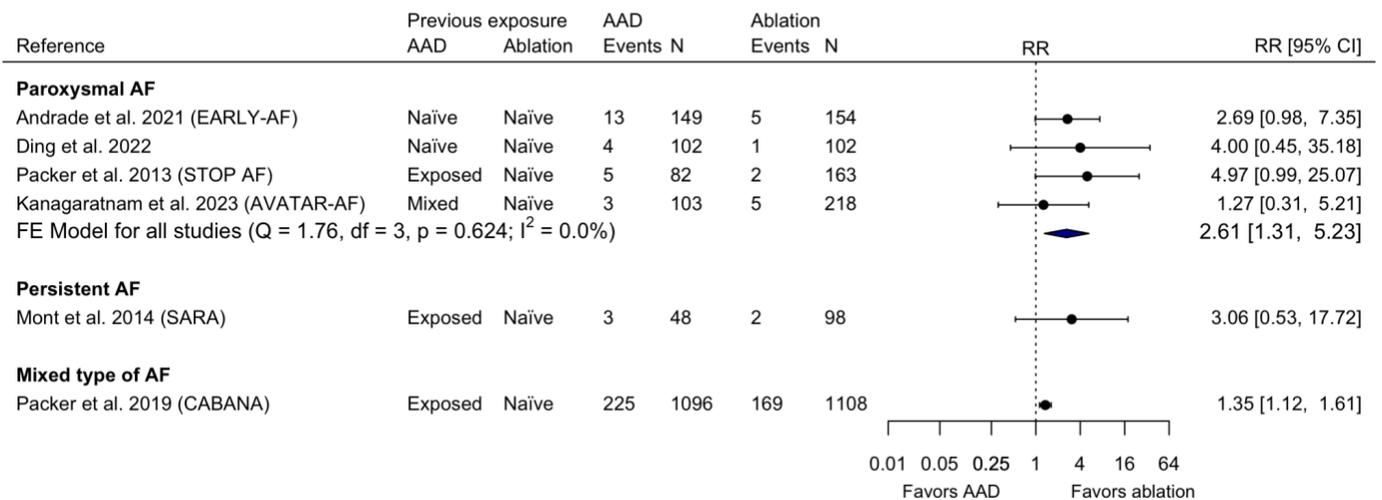
Heart failure incidence or deterioration



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants.

A6.8A Forest plot hospitalization – relative risk

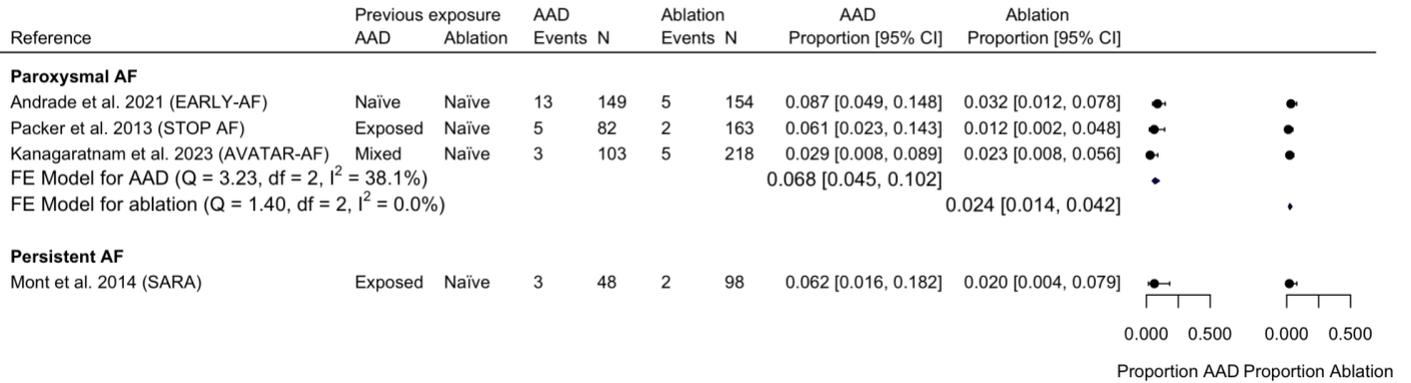
Hospitalization



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RR: relative risk.

A6.8B Forest plot hospitalization – proportions

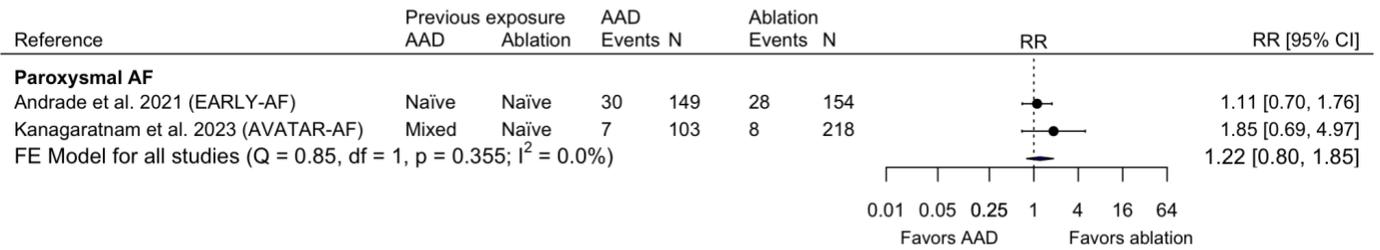
Hospitalization



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

A6.9A Forest plot emergency room visits – relative risk

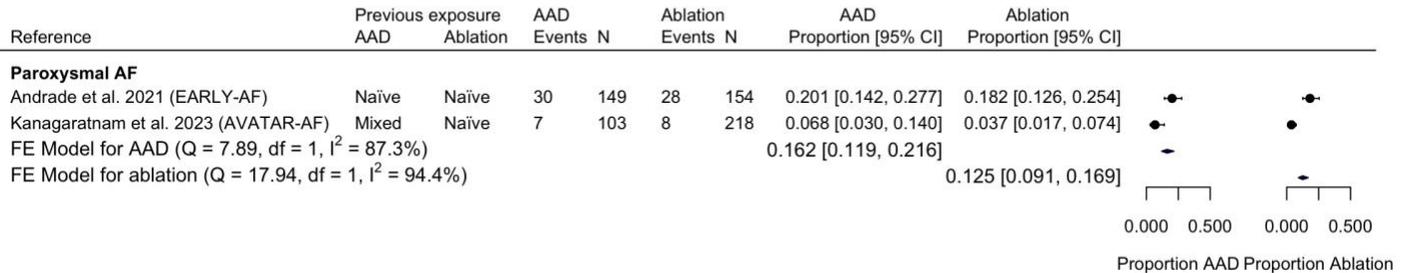
Emergency room visits



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RR: relative risk.

A6.9B Forest plot emergency room visits – proportions

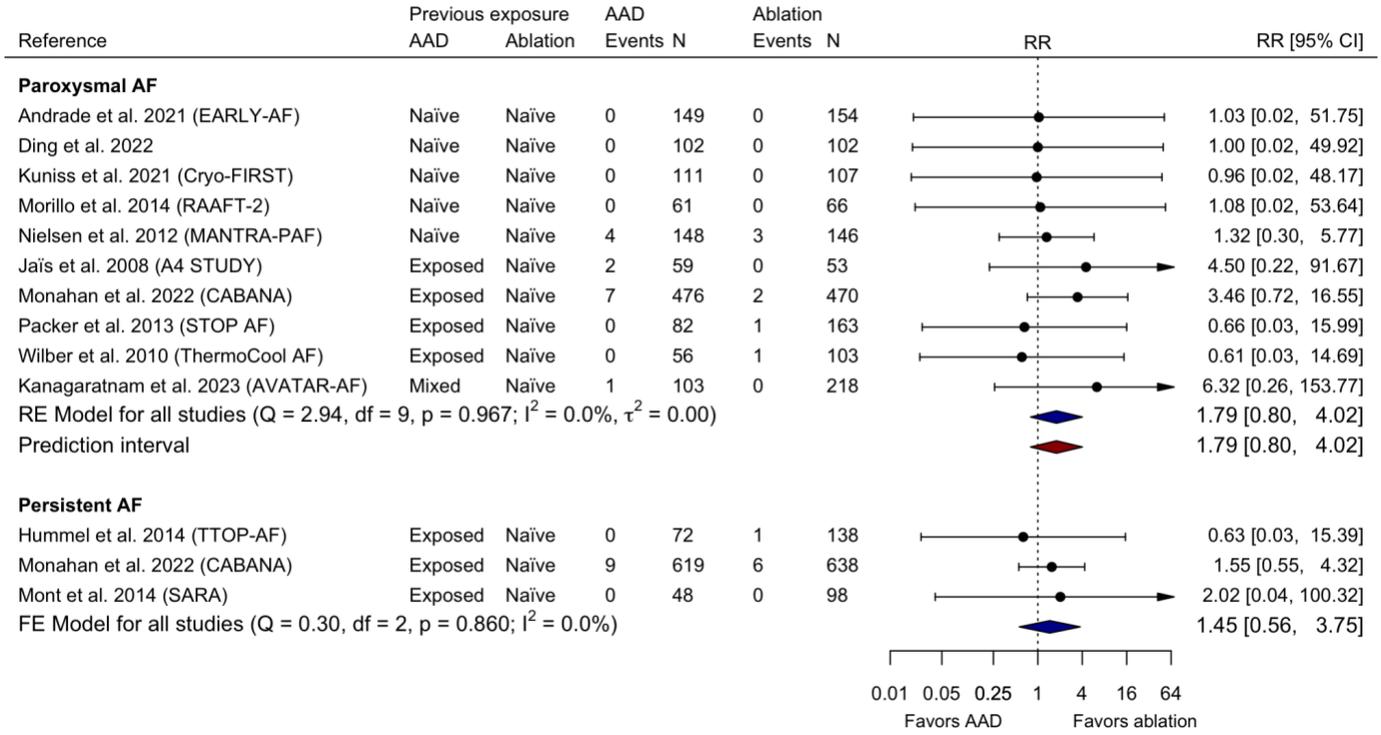
Emergency room visits



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

A6.10A Forest plot all-cause mortality – relative risk

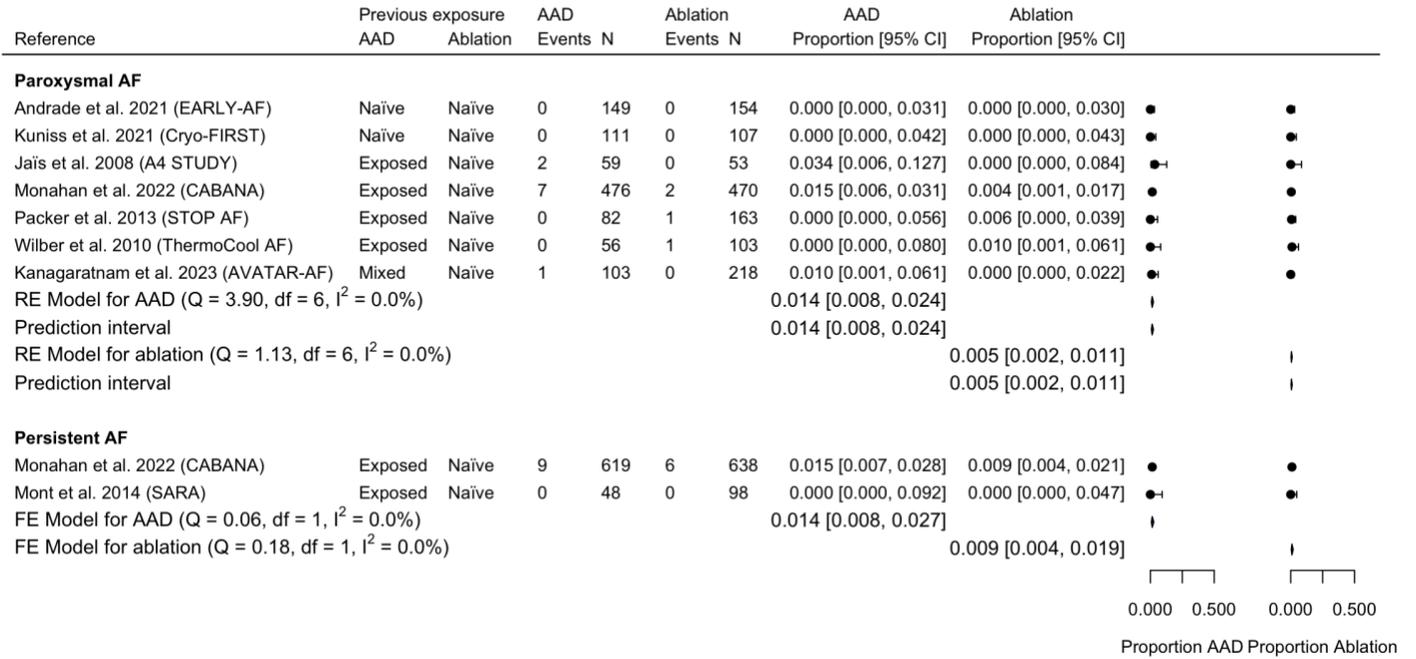
All-cause mortality



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects; RR: relative risk.

A6.10B Forest plot all-cause mortality – proportions

All-cause mortality



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RE: random-effects.

## Appendix 7. Repeat ablation results

### A7.1 Summary of findings

Outcome	Population			Proportion event in catheter ablation treatment group (95% CI)	GRADE rating
	Type of AF	Previous exposure to AADs	Previous exposure to catheter ablation		
<b>Repeat ablation during the blanking period</b>	Paroxysmal	Naïve	Naïve	6/327 (3 studies) 0.024 (0.011 to 0.052)	High
	Paroxysmal	Exposed	Naïve	67/319 (3 studies) 0.223 (0.178 to 0.275)	Low <sup>3</sup>
	Paroxysmal	Mixed	Naïve	20/218 (1 study) 0.092 (0.058 to 0.140)	High
	Mixed	Exposed	Naïve	25/1108 (1 study) 0.023 (0.015 to 0.034)	Moderate <sup>2</sup>
<b>Repeat ablation after the blanking period</b>	Paroxysmal	Naïve	Naïve	19/261 (2 studies) 0.091 (0.059 to 0.138)	Low <sup>3</sup>
	Paroxysmal	Exposed	Naïve	23/174 (2 studies) 0.140 (0.094 to 0.202)	Low <sup>3</sup>
	Paroxysmal	Mixed	Naïve	24/218 (1 study) 0.110 (0.073 to 0.161)	High
<b>Repeat ablation during total follow-up (or unclear)</b>	Paroxysmal	Naïve	Naïve	0/170 (2 studies) 0.007 (0.001 to 0.050)	High
	Paroxysmal	Exposed	Naïve	10/128 (1 study) 0.078 (0.040 to 0.143)	Low <sup>1,2</sup>
	Persistent	Exposed	Naïve	8/98 (1 study) 0.082 (0.038 to 0.159)	High

Note: The (pooled) proportions only include studies with outcome assessment at 52 weeks except for repeat ablation during the blanking period which are for a period of 11-13 weeks. If there was reporting of repeat ablation for participants that crossed over from the AAD treatment group to the catheter ablation group, this number of events and number of participants were included in the total proportion.

<sup>1</sup> Rated down for risk of bias

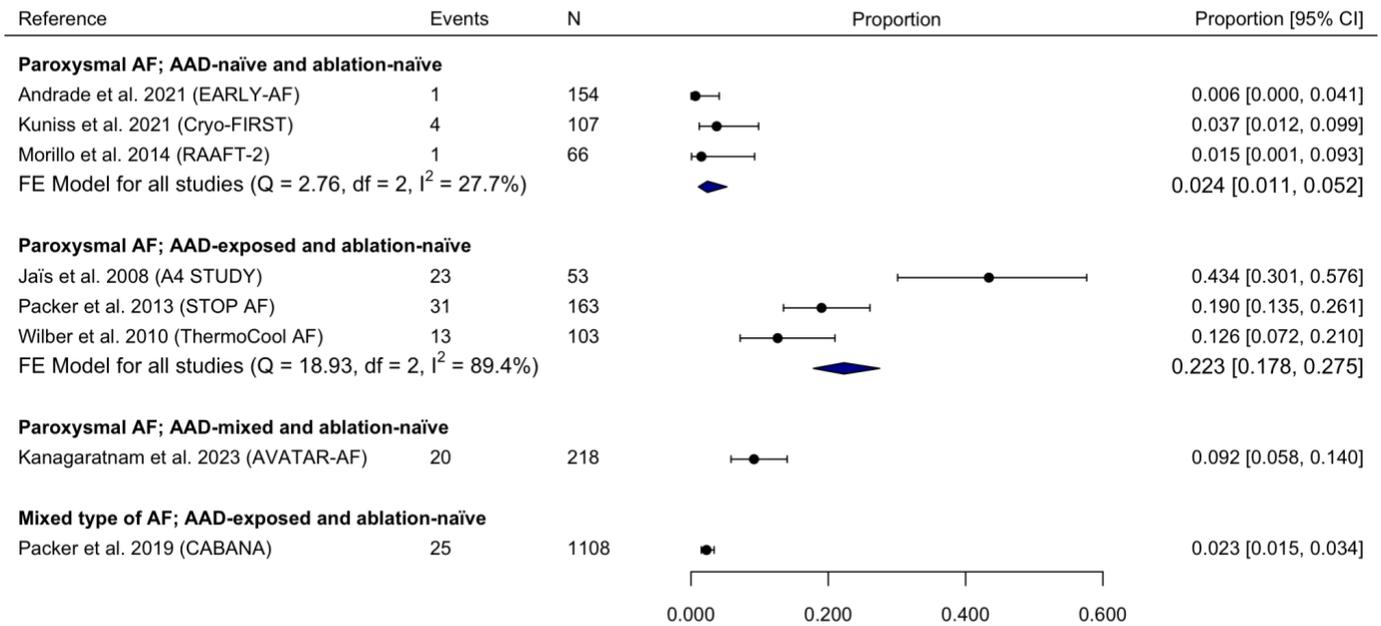
<sup>2</sup> Rated down for indirectness in the population (including studies that only included elderly participants and/or studies that were classified into paroxysmal/persistent AF but did not have >90% of that type)

<sup>3</sup> Rated down twice for inconsistency

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval.

## A7.2 Forest plot repeat ablation during the blanking period

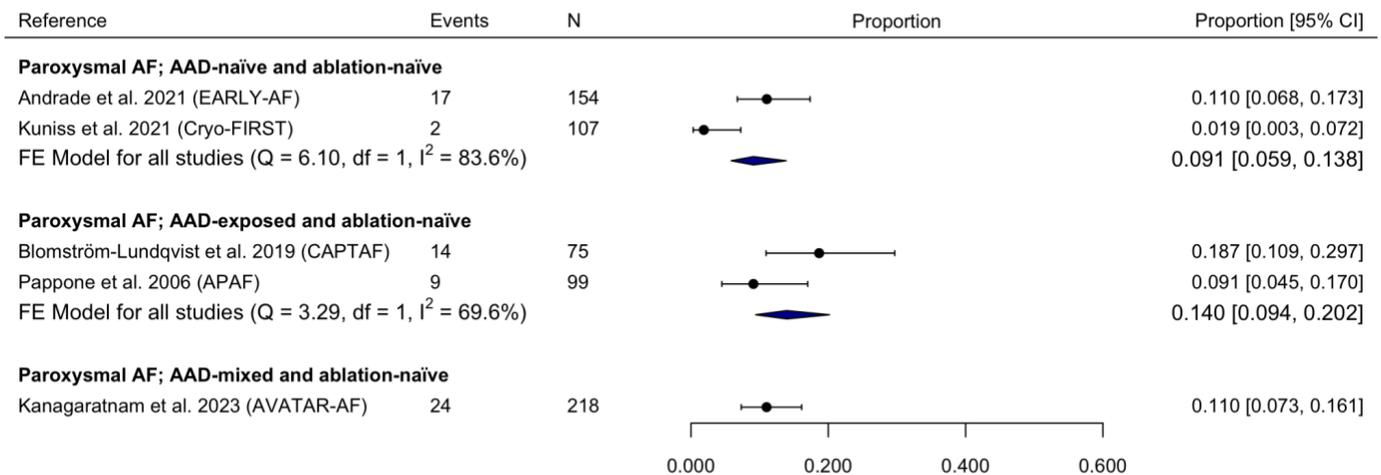
### Repeat ablation during the blanking period



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

## A7.3 Forest plot repeat ablation after the blanking period

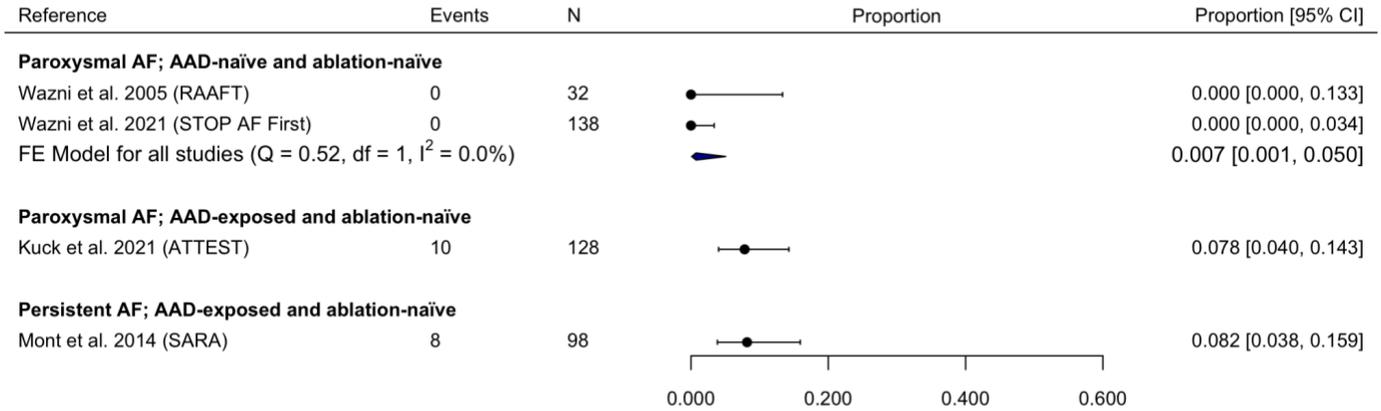
### Repeat ablation after the blanking period



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

### A7.4 Forest plot repeat ablation during the total follow-up (or unclear)

#### Repeat ablation during the total period (or unclear)



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

## Appendix 8. Serious adverse events (both groups) results

### A8.1 Summary of findings

Outcome	Type of AF	Population		Proportions at 52 weeks		Relative risk at any follow-up duration		
		Previous exposure to AADs	Previous exposure to catheter ablation	Proportion event in AAD treatment group (95% CI)	Proportion event in catheter ablation treatment group (95% CI)	Number of studies (number of participants)	Relative risk (95% CI) [95% PI]	GRADE rating
Deep vein thrombosis	All	All	Naïve	0/184 (2 studies) 0.007 (0.001 to 0.047)	1/186 (2 studies) 0.009 (0.002 to 0.042)	2 (370)	0.51 (0.04 to 6.03)	Very low <sup>1,3</sup>
Intracardiac thrombus	All	All	Naïve	-	-	1 (225)	0.28 (0.01 to 6.72)	Very low <sup>1,2,3</sup>
Pulmonary embolism	All	All	Naïve	1/134 (2 studies) 0.011 (0.002 to 0.054)	0/136 (2 studies) 0.008 (0.001 to 0.058)	2 (270)	1.92 (0.16 to 22.60)	Very low <sup>1,3</sup>
Thromboembolism	All	All	Naïve	-	-	1 (149)	1.01 (0.06 to 15.90)	Very low <sup>1,2,3</sup>
Ventricular tachyarrhythmia	All	All	Naïve	0/99 (1 study) 0.000 (0.000 to 0.047)	1/104 (1 study) 0.010 (0.001 to 0.060)	1 (203)	0.35 (0.01 to 8.49)	Very low <sup>1,3</sup>
Ventricular tachycardia	All	All	Naïve	3/187 (2 studies) 0.018 (0.006 to 0.055)	1/186 (2 studies) 0.009 (0.002 to 0.044)	6 (1064)	1.35 (0.39 to 4.73) [0.39 to 4.73]	Very low <sup>1,3</sup>
Life-threatening/ major bleeding	Paroxysmal	All	All	1/82 (1 study) 0.012 (0.001 to 0.075)	3/163 (1 study) 0.018 (0.005 to 0.057)	2 (449)	0.73 (0.10 to 5.15)	Very low <sup>1,3</sup>
	Persistent	All	All	-	-	1 (210)	9.52 (0.46 to 195.71)	Very low <sup>1,3</sup>
	Mixed	All	All	-	-	1 (2204)	1.01 (0.64 to 1.59)	Very low <sup>1,2,3</sup>

Note: The (pooled) proportions only include studies with outcome assessment at 52 weeks, the relative risk only contains studies with mean and measure of spread.

<sup>1</sup> Rated down for risk of bias

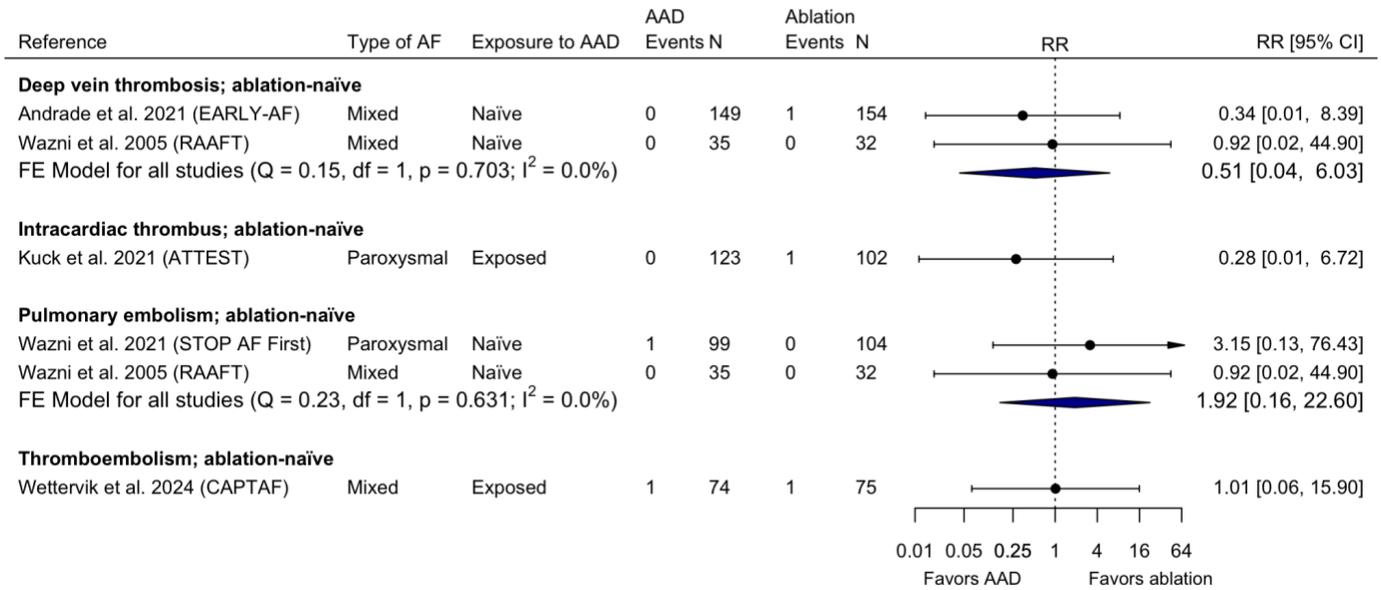
<sup>2</sup> Rated down for indirectness in the population (including studies that only included elderly participants and/or studies that were classified into paroxysmal/persistent AF but did not have >90% of that type)

<sup>3</sup> Rated down twice for imprecision

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; PI: prediction interval.

A8.2A Thrombosis/embolism – relative risk

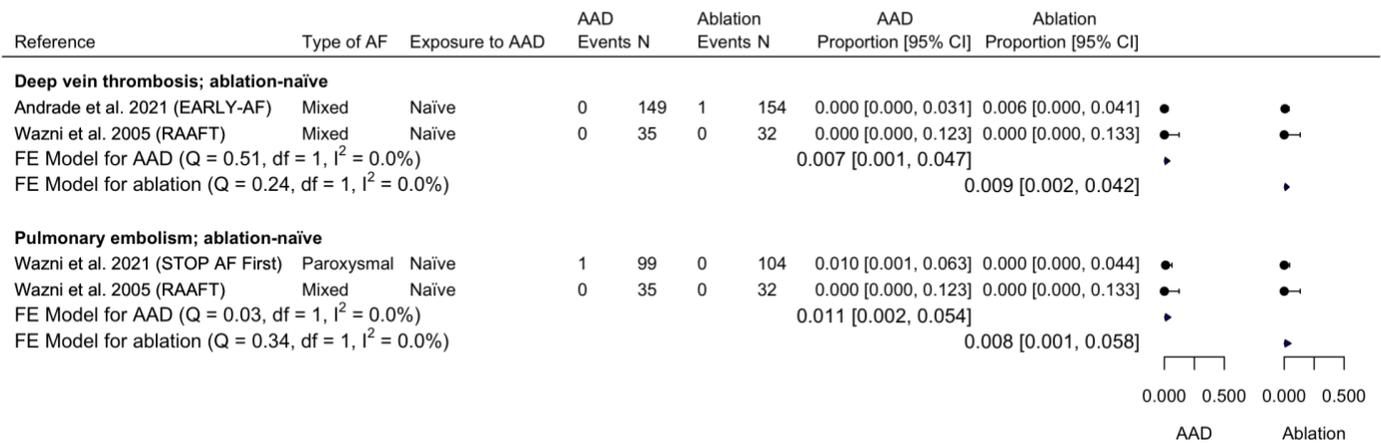
Thrombosis/embolism



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RR: relative risk.

A8.2B Thrombosis/embolism – proportions

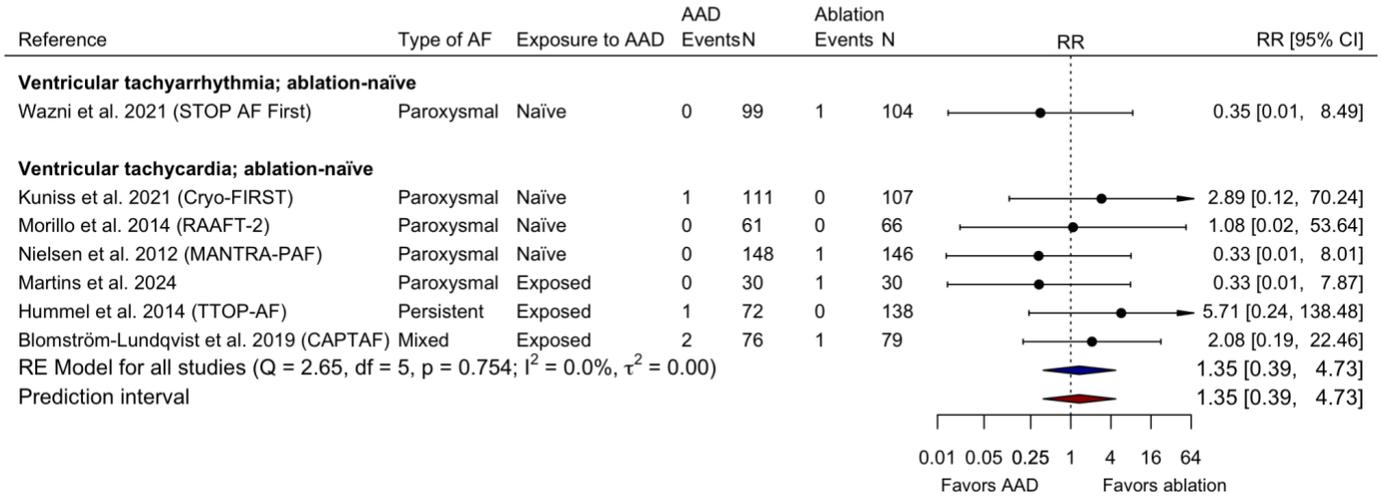
Thrombosis/embolism



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

A8.3A Ventricular tachycardia/arrhythmia – relative risk

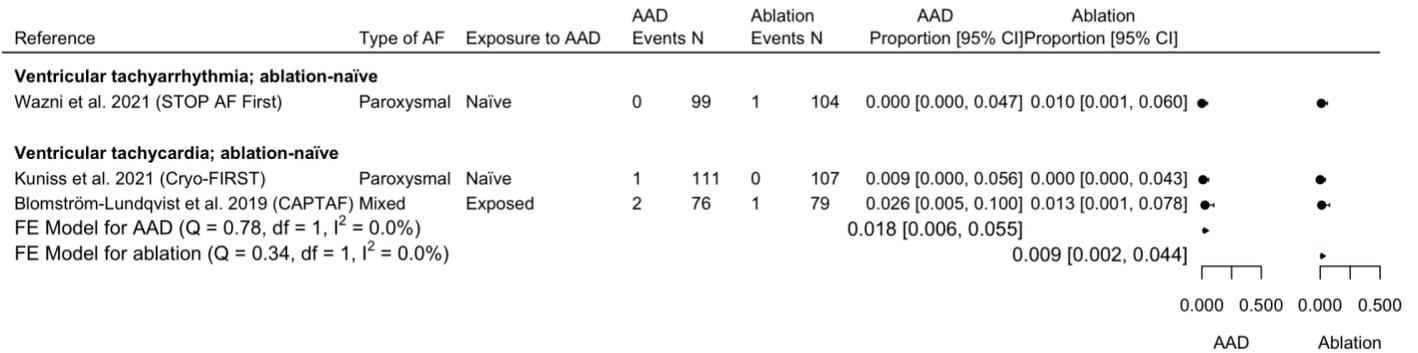
Ventricular tachycardia/-arrhythmia



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RE: random-effects; RR: relative risk.

A8.3B Ventricular tachycardia/arrhythmia – proportions

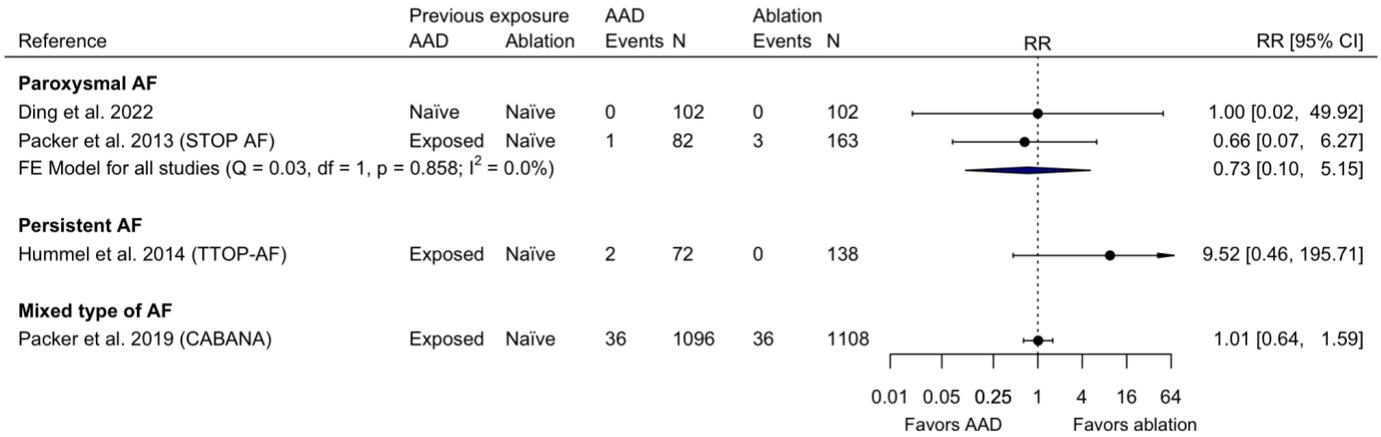
Ventricular tachycardia/-arrhythmia



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

A8.4A Forest plot life-threatening/major bleeding – relative risk

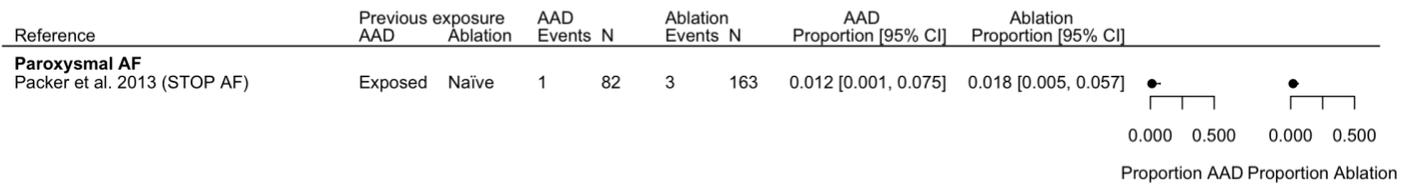
Life-threatening/major bleeding



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants; RR: relative risk.

A8.4B Forest plot life-threatening/major bleeding – proportions

Life-threatening/major bleeding



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants.

## Appendix 9. Serious adverse events (only for catheter ablation) results

### A9.1 Summary of findings

Outcome	Population			Proportion event in catheter ablation treatment group (95% CI) [95% PI]	GRADE rating
	Type of AF	Previous exposure to AADs	Previous exposure to catheter ablation		
Atrio-oesophageal fistula	All	All	Naïve	0/1882 (7 studies) 0.003 (0.001 to 0.008) [0.001 to 0.008]	High
Pericardial tamponade	All	All	Naïve	24/2405 (10 studies) 0.013 (0.008 to 0.021) [0.005 to 0.033]	High
	All	All	Exposed	3/120 (1 study) 0.025 (0.006 to 0.077)	High
Pericardial tamponade or pericardial effusion	All	All	Naïve	2/87 (1 study) 0.023 (0.004 to 0.088)	High
Pericardial tamponade or pericardial effusion (drainage warranted)	All	All	Naïve	1/190 (1 study) 0.005 (0.000 to 0.033)	High
Pericarditis	All	All	Naïve	6/724 (5 studies) 0.011 (0.005 to 0.025) [0.005 to 0.025]	High
Perimyocarditis	All	All	Naïve	1/200 (1 study) 0.005 (0.000 to 0.032)	High
Phrenic nerve injury	All	All	Naïve	1/1036 (2 studies) 0.003 (0.001 to 0.012)	Low <sup>1,2</sup>
Phrenic nerve palsy	All	All	Naïve	33/579 (4 studies) 0.084 (0.060 to 0.116)	Low <sup>3</sup>
Phrenic nerve palsy (persistent)	All	All	Naïve	4/228 (1 study) 0.018 (0.006 to 0.047)	High
Phrenic nerve paralysis	All	All	Naïve	8/579 (4 studies) 0.021 (0.011 to 0.041)	High
Pneumothorax	All	All	Naïve	1/1006 (1 study) 0.001 (0.000 to 0.006)	Moderate <sup>1</sup>
Pulmonary vein stenosis	All	All	Naïve	27/2286 (11 studies) 0.016 (0.008 to 0.032) [0.002 to 0.099]	Moderate <sup>2</sup>

Note: If there was reporting of repeat ablation for participants that crossed over from the AAD treatment group to the catheter ablation group, this number of events and number of participants were included in the total proportion.

<sup>1</sup> Rated down for indirectness in the population (including studies that only included elderly participants and/or studies that were classified into paroxysmal/persistent AF but did not have >90% of that type)

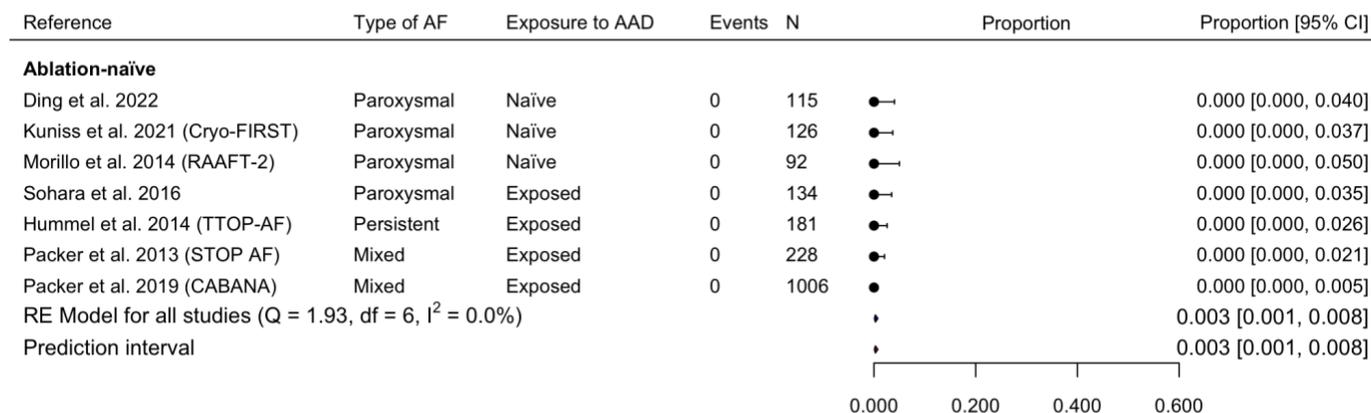
<sup>2</sup> Rated down for inconsistency

<sup>3</sup> Rated down twice for inconsistency

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; PI: prediction interval.

## A9.2 Forest plot atrio-oesophageal fistula

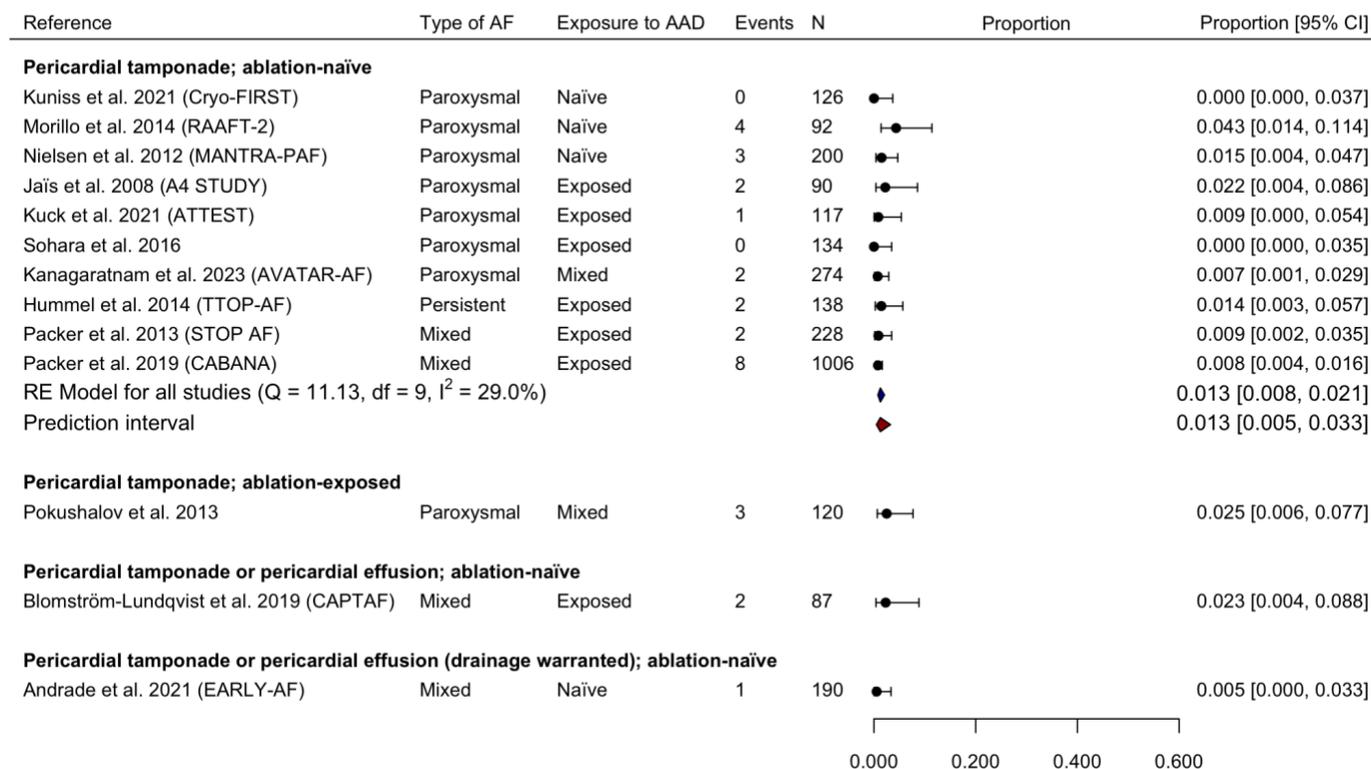
### Atrio-oesophageal fistula



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RR: random-effects.

## A9.3 Forest plot pericardial tamponade/effusion

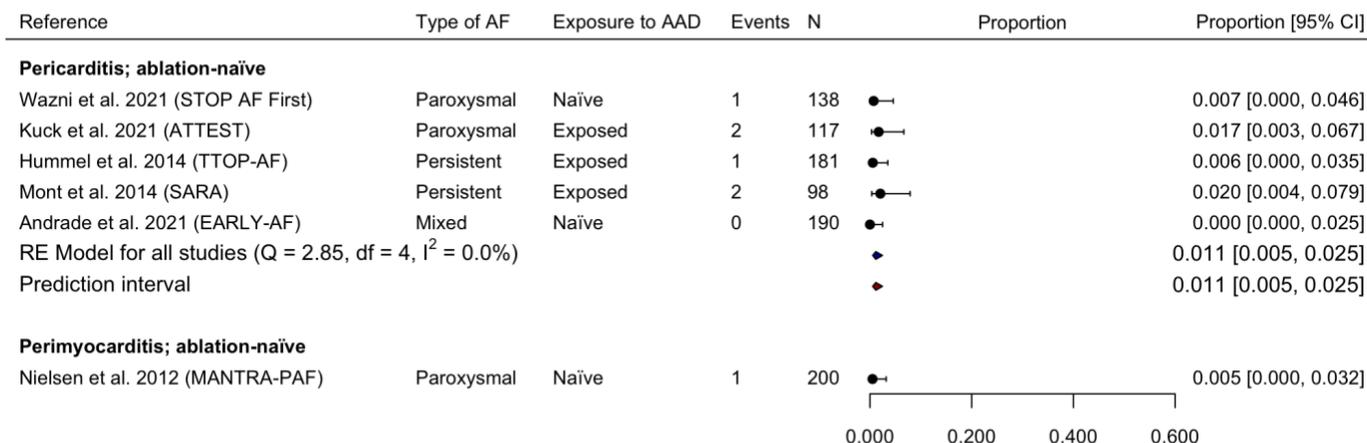
### Pericardial tamponade and effusion



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RE: random-effects.

## A9.4 Forest plot peri(myo)carditis

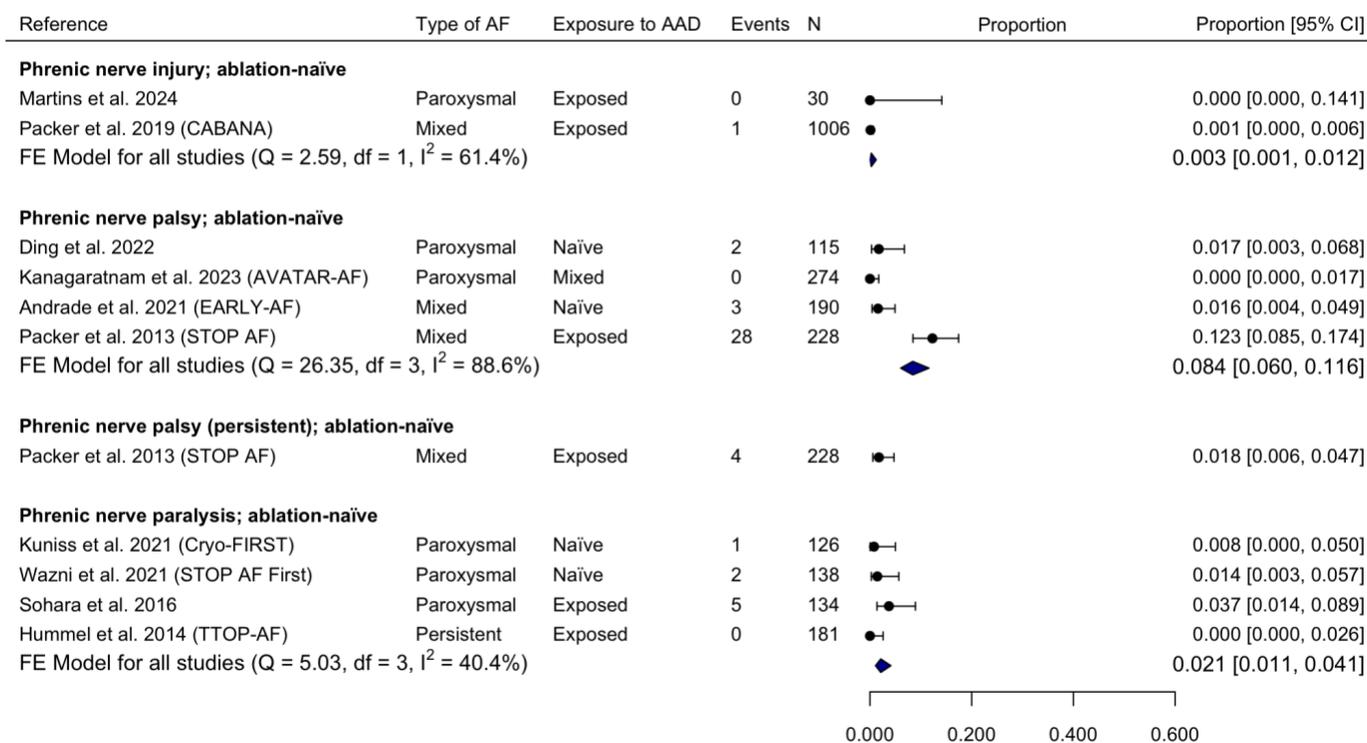
### Pericarditis and perimyocarditis



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RE: random-effects.

## A9.5 Forest plot phrenic nerve injury/palsy/paralysis

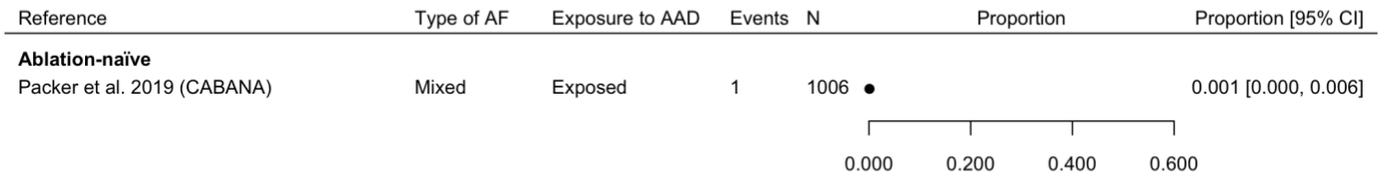
### Phrenic nerve injury, palsy, paralysis



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants.

### A9.6 Forest plot pneumothorax

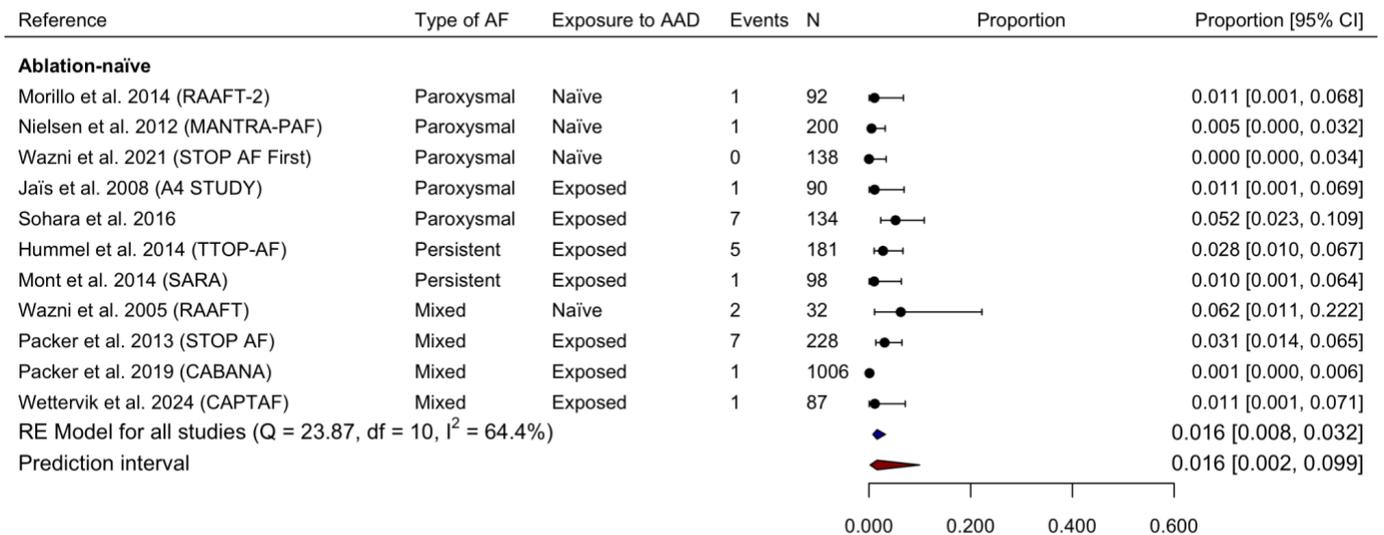
#### Pneumothorax



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants.

### A9.7 Forest plot pulmonary vein stenosis

#### Pulmonary vein stenosis



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants; RE: random-effects.

## Appendix 10. Medication side-effects results

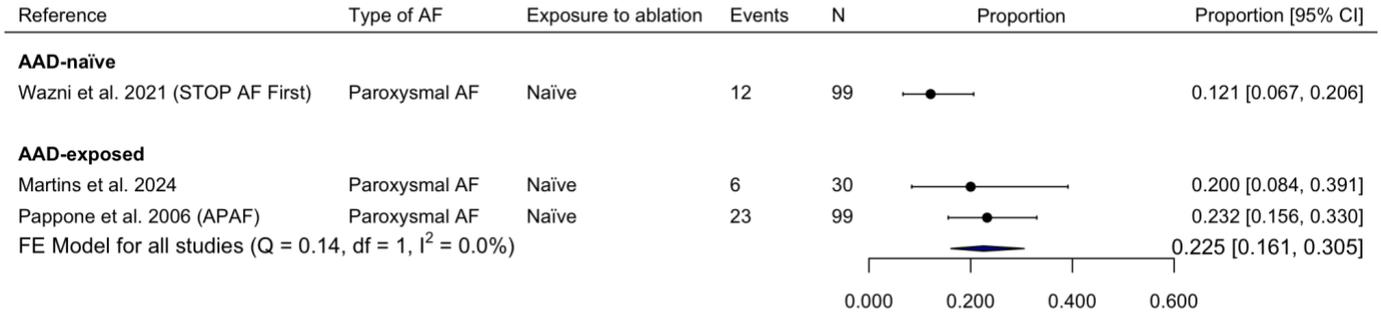
### A10.1 Summary of findings

Outcome	Population			Proportion event in AAD treatment group (95% CI)	GRADE rating
	Type of AF	Previous exposure to AADs	Previous exposure to catheter ablation		
<b>Discontinuations due to side-effects</b>	All	Naïve	All	12/99 (1 study) 0.121 (0.067 to 0.206)	High
	All	Exposed	All	29/129 (2 studies) 0.225 (0.161 to 0.305)	High
<b>Diarrhea</b>	All	Naïve	All	2/99 (1 study) 0.020 (0.004 to 0.078)	High
<b>Eructation</b>	All	Naïve	All	1/99 (1 study) 0.010 (0.001 to 0.063)	High
<b>Presyncope</b>	All	Naïve	All	6/248 (2 studies) 0.027 (0.012 to 0.060)	High
<b>Syncope</b>	All	Naïve	All	4/359 (3 studies) 0.013 (0.005 to 0.033)	High
<b>Anxiety</b>	All	Naïve	All	1/99 (1 study) 0.010 (0.001 to 0.063)	High
<b>Dizziness</b>	All	Naïve	All	3/99 (1 study) 0.030 (0.008 to 0.092)	High
<b>Dyspnea</b>	All	Naïve	All	3/99 (1 study) 0.030 (0.008 to 0.092)	High
<b>Erectile dysfunction</b>	All	Naïve	All	2/248 (2 studies) 0.008 (0.002 to 0.032)	High
<b>Fatigue</b>	All	Naïve	All	2/99 (1 study) 0.020 (0.004 to 0.078)	High
<b>Joint pain</b>	All	Naïve	All	2/149 (1 study) 0.013 (0.002 to 0.053)	High

Note: The (pooled) proportions only include studies with outcome assessment at 52 weeks.  
Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval.

## A10.2 Forest plot discontinuations due to side-effects

### Discontinuations due to side-effects



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants

## A10.3 Forest plot gastrointestinal side-effects

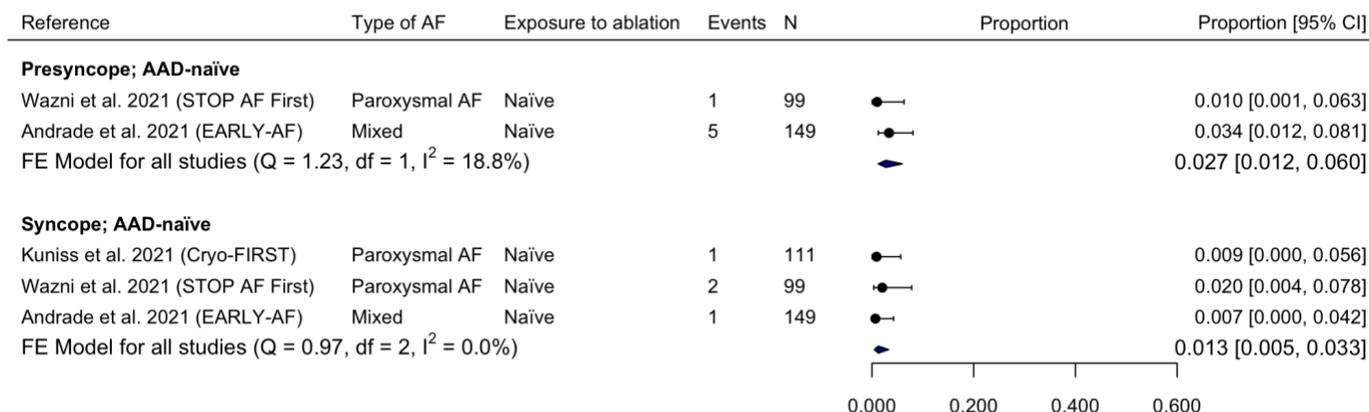
### Gastrointestinal side-effects



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; N: total number of participants

## A10.4 Forest plot (pre)syncope

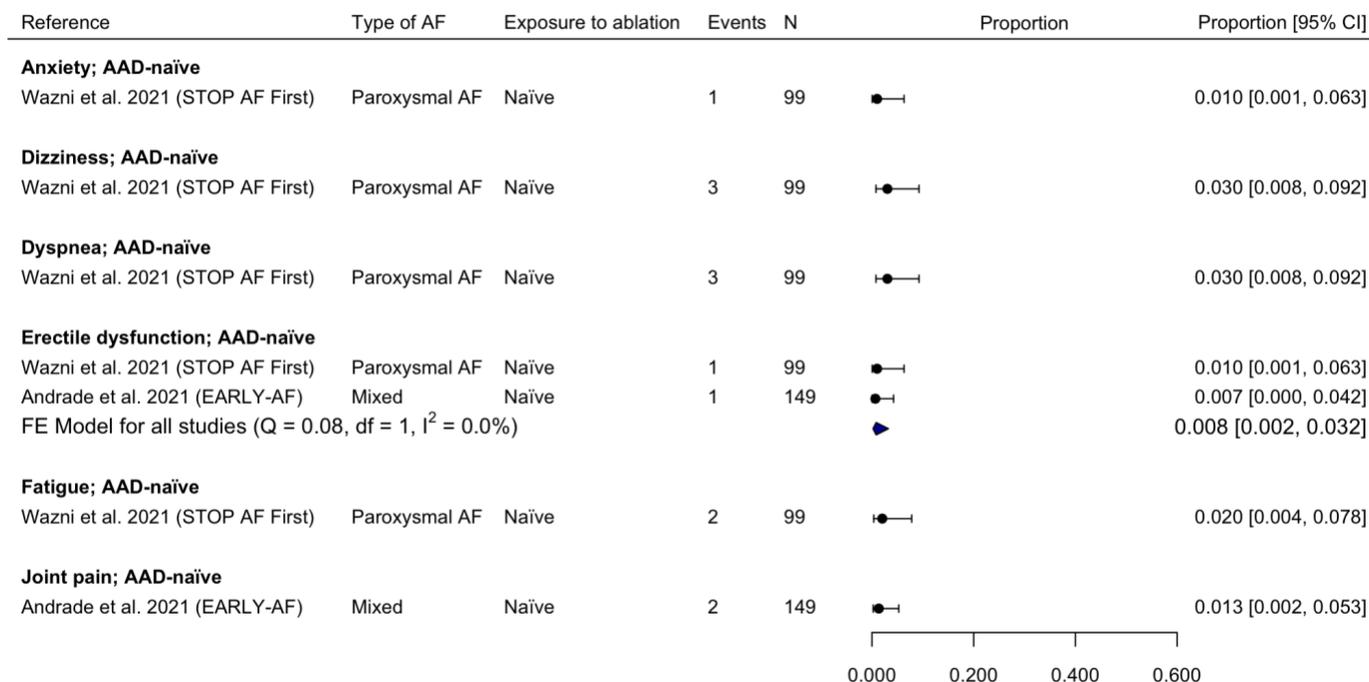
### (Pre)syncope



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants

## A10.5 Forest plot other side-effects

### Other side-effects



Abbreviations: AAD: anti-arrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; N: total number of participants

## Appendix 11. Quality of life results

### A11.1 Summary of findings

Outcome	Population			Number of studies (number of participants)	Mean difference (95% CI) [95% PI]	GRADE rating (Target of certainty)
	Type of AF	Previous exposure to AADs	Previous exposure to catheter ablation			
<b>AFEQT Total score<sup>1</sup></b>	Paroxysmal	All	All	5 (1770)	-7.10 (-10.58 to -3.63) [-13.20 to -1.01]	Low <sup>7,10</sup>
	Persistent	All	All	1 (1038)	-4.30 (-6.28 to -2.32)	Low <sup>7,8</sup>
<b>EQ-5D Index<sup>2</sup></b>	Paroxysmal	All	All	4 (935)	-0.03 (-0.04 to -0.01)	Moderate <sup>7</sup> (No clinically important effect)
	Mixed	All	All	1 (2204)	-0.02 (-0.03 to -0.01)	Low <sup>7,8</sup> (No clinically important effect)
<b>EQ-5D VAS<sup>3</sup></b>	Paroxysmal	All	All	6 (1360)	-3.63 (-5.97 to -1.28) [-7.12 to -0.13]	Moderate <sup>7</sup> (No clinically important effect)
	Mixed	All	All	1 (2204)	-4.40 (-5.81 to -2.99)	Low <sup>7,8</sup> (No clinically important effect)
<b>SF-36 MCS<sup>4</sup></b>	Paroxysmal	All	All	6 (1070)	-1.96 (-3.80 to -0.13) [-4.55 to 0.62]	Moderate <sup>7</sup> (No clinically important effect)
<b>SF-36 PCS<sup>5</sup></b>	Paroxysmal	All	All	6 (1070)	-2.09 (-3.82 to -0.35) [-4.68 to 0.50]	Moderate <sup>7</sup> (No clinically important effect)
<b>SF-36 physical functioning<sup>6</sup></b>	Paroxysmal	All	All	8 (1297)	-7.86 (-13.51 to -2.22) [-24.38 to 8.66]	Very low <sup>7,9,10</sup>
	Mixed	All	All	2 (2300)	-4.70 (-17.81 to 8.41)	Low <sup>7,10</sup> (No clinically important effect)

<sup>1</sup> AFEQT Total score ranges from 0 to 100, where 0 indicates complete disability and 100 indicates no disability

<sup>2</sup> EQ-5D Index ranges from -0.59 to 1, where 0 equals death and 1 indicates perfect health

<sup>3</sup> EQ-5D VAS ranges from 0 to 100, where 0 is the 'worst health you can imagine' and 100 'the best health you can imagine'

<sup>4</sup> SF-36 MCS ranges from 0 to 100, where 0 is the worst health and 100 is the best health

<sup>5</sup> SF-36 PCS ranges from 0 to 100, where 0 is the worst health and 100 is the best health

<sup>6</sup> SF-36 physical functioning ranges from 0 to 100, where 0 is the worst health and 100 is the best health

<sup>7</sup> Rated down for risk of bias

<sup>8</sup> Rated down for indirectness in the population (including studies that only included elderly participants and/or studies that were classified into paroxysmal/persistent AF but did not have >90% of that type)

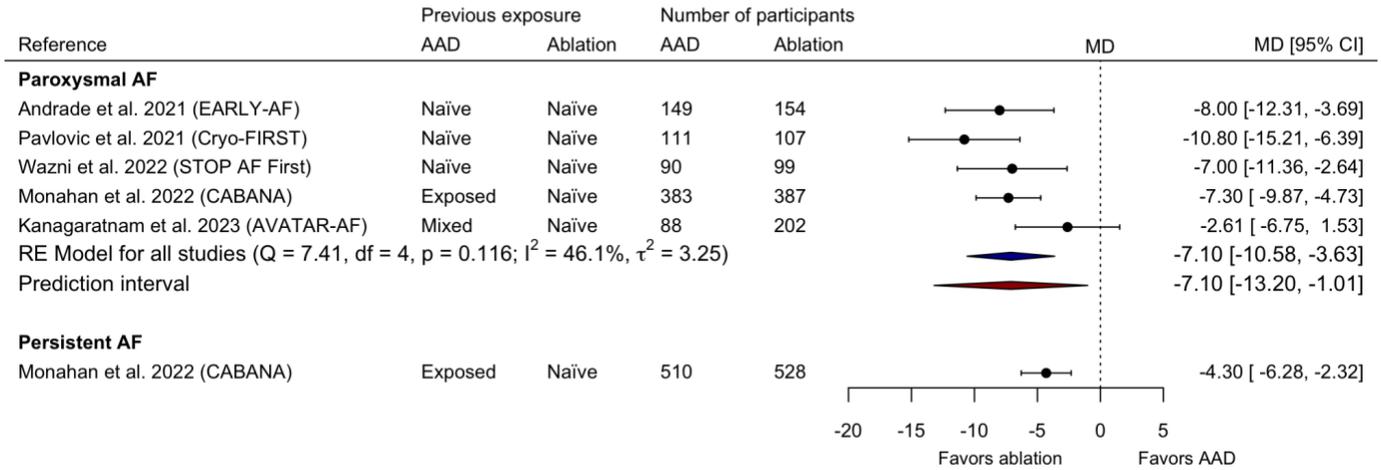
<sup>9</sup> Rated down twice for inconsistency

<sup>10</sup> Rated down for imprecision

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; AFEQT: atrial fibrillation effect on quality-of-life; CI: confidence interval; EQ-5D: EuroQol 5 dimensions; MCS: mental component summary score; PCS: physical component summary score; SF-36: 36-item short-form health survey; VAS: visual analogue scale.

A11.2 Forest plot AFEQT Total score

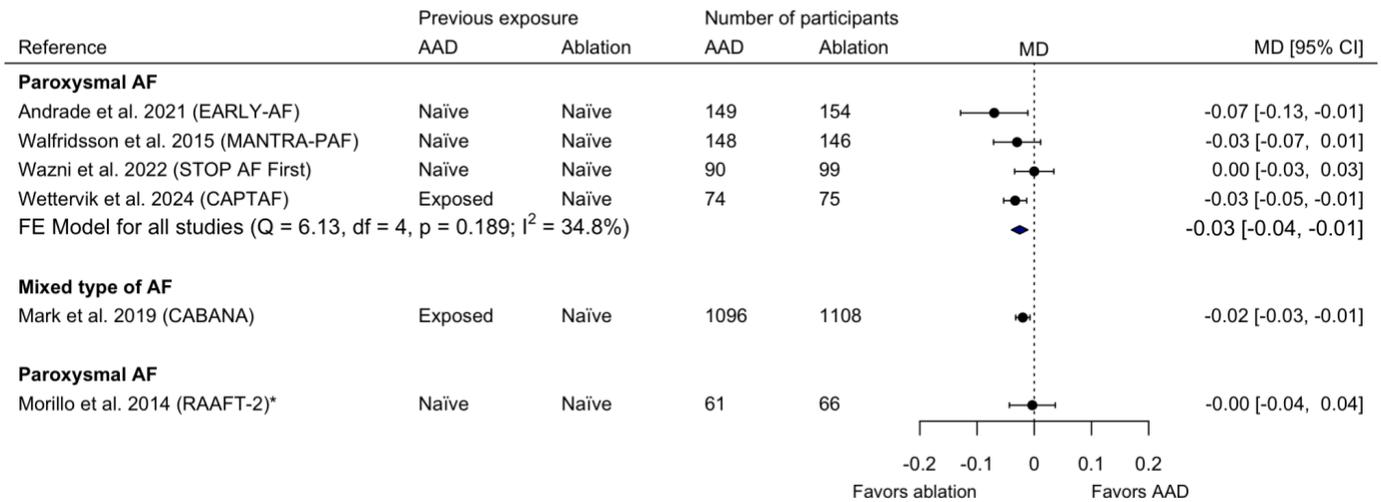
Quality of life - AFEQT



Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; AFEQT: atrial fibrillation effect on quality-of-life; CI: confidence interval; df: degrees of freedom; MD: mean difference; RE: random-effects.

A11.3 Forest plot EQ-5D Index

Quality of life - EQ-5D Index

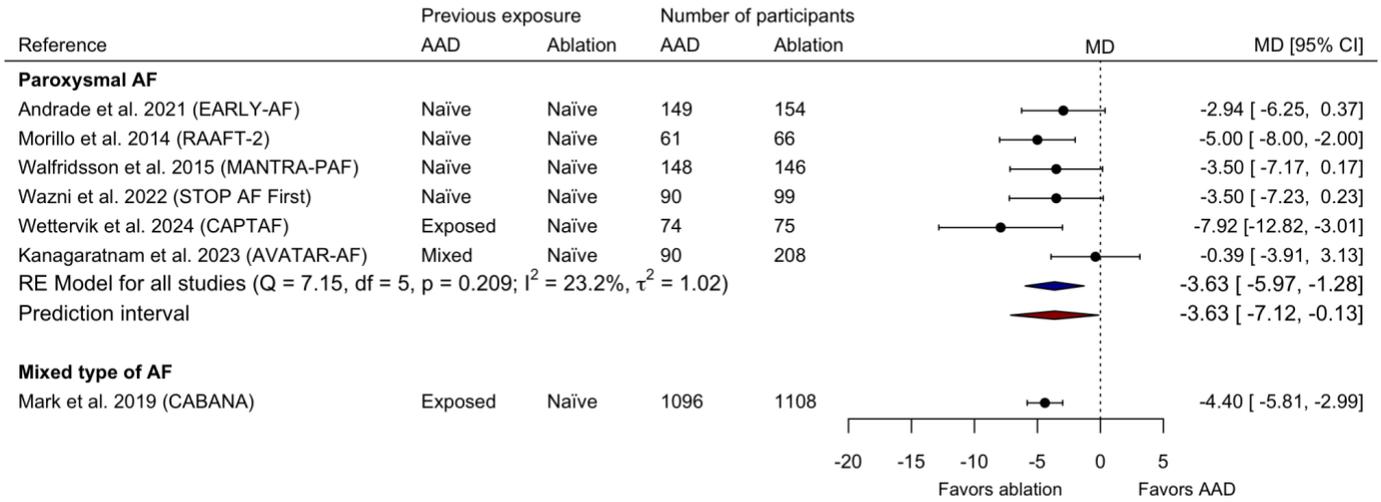


\*Morillo et al. 2014 reports EQ-5D Tariff score instead of EQ-5D Index and is therefore not pooled.

Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; EQ-5D: EuroQol five dimensions; MD: mean difference; RE: random-effects.

A11.4 Forest plot EQ-5D VAS

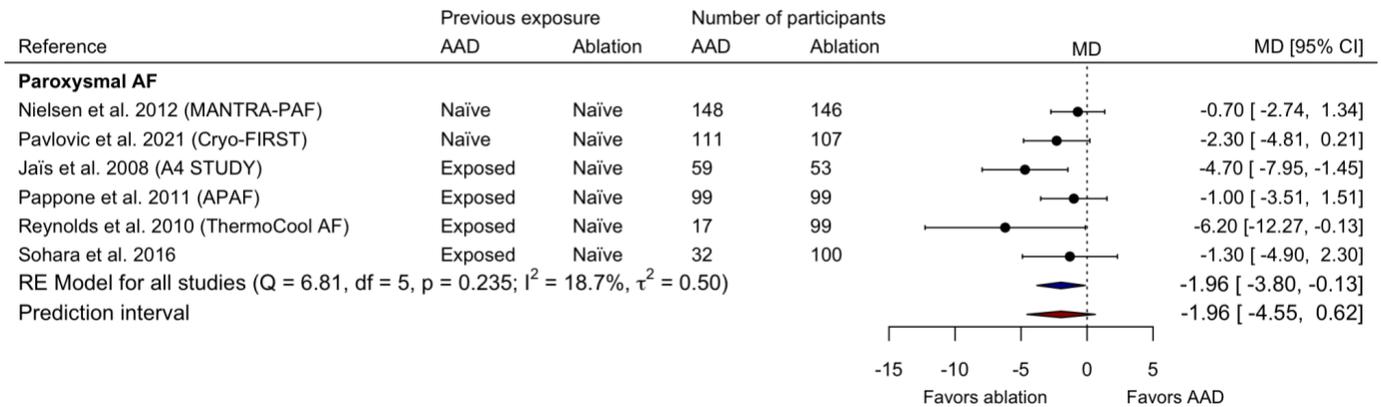
Quality of life - EQ-5D VAS



Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; EQ-5D: EuroQol five dimensions; MD: mean difference; RE: random-effects; VAS: visual analogue scale.

A11.5 Forest plot SF-36 MCS

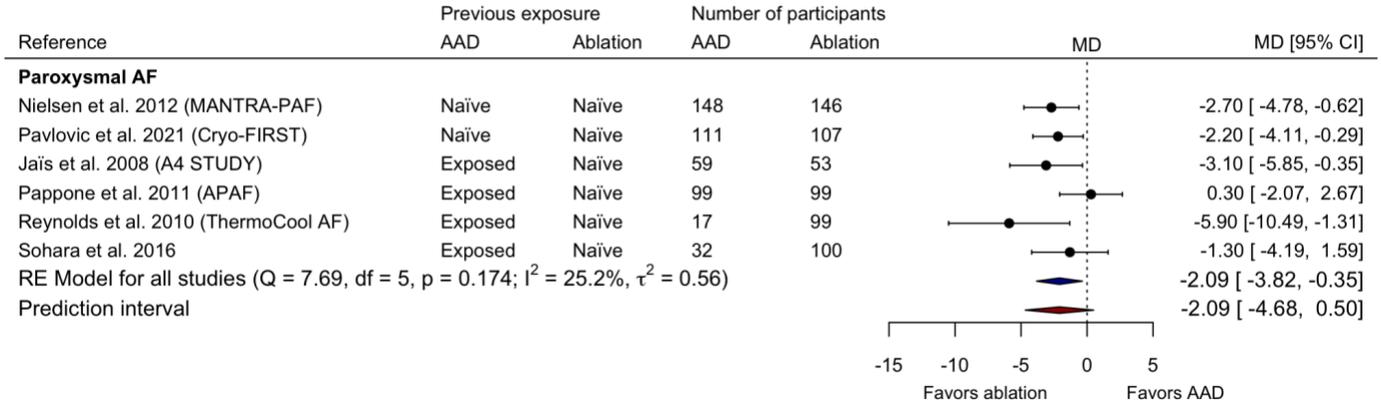
Quality of life - SF-36 MCS



Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; MCS: mental component summary score; MD: mean difference; RE: random-effects; SF-36: 36-item short-form health survey.

A11.6 Forest plot SF-36 PCS

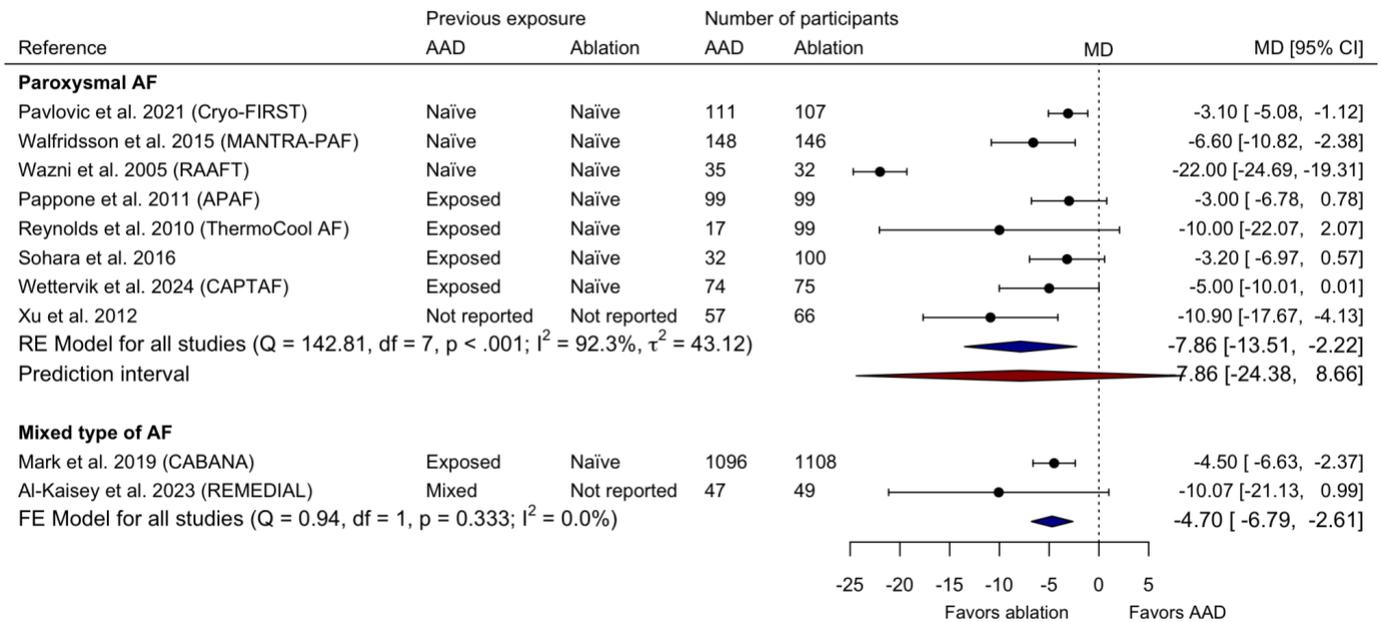
Quality of life - SF-36 PCS



Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; MCS: physical component summary score; MD: mean difference; RE: random-effects; SF-36: 36-item short-form health survey.

A11.2 Forest plot SF-36 physical functioning

Quality of life - SF-36 Physical functioning



Abbreviations: AAD: antiarrhythmic drugs; AF: atrial fibrillation; CI: confidence interval; df: degrees of freedom; FE: fixed-effects; MCS: mental component summary score; MD: mean difference; RE: random-effects; SF-36: 36-item short-form health survey.