## SUPPLEMENTARY METHODS

### Extraction of Individual Patient Data (IPD)

A graphical reconstructive algorithm was used to attain information on survival from atrial tachyarrhythmia recurrence of individual patients. Images of Kaplan-Meier curves from included studies were digitised to obtain step function values and step timings. Survival information of individual patients were then recovered based on the numerical solutions to the inverted Kaplan-Meier product-limit equations and provided risk tables. IPD was reconstructed by KYF. and approved by JJZ and VHT by visual comparisons and by comparing log-rank values of the reconstructed dataset against originally reported values where available.

### Pairwise Comparisons

Pairwise comparisons were first performed between treatment pairs for which data on direct comparisons were available from ≥3 studies. The one-stage Kaplan-Meier method was used to determine atrial tachyarrhythmia recurrence between treatment pairs using semiparametric Cox-based models. To account for between-study heterogeneity, Cox-models with random-effects gamma-frailties and stratification were conducted to determine hazard ratios (HRs) between the 2 compared arms. This was followed by a 2-stage method which pooled hazard ratios (HRs) of individual studies and their 95% confidence intervals (95%CIs) under a random-effects meta-analysis.

### Frequentist Network Meta-Analysis (NMA)

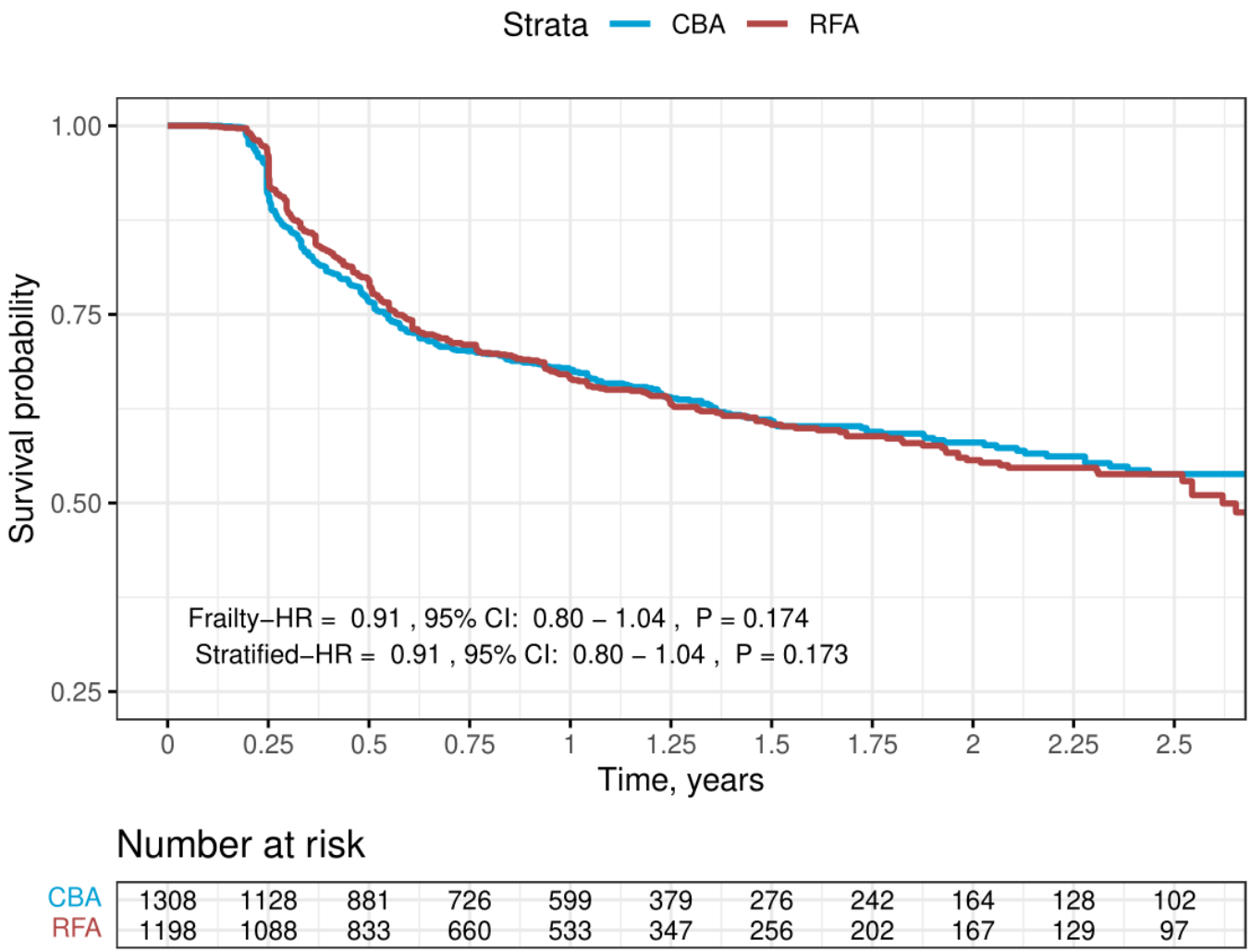
A Frequentist NMA was conducted to compare the treatments of cryoballoon ablation (CBA), radiofrequency ablation (RFA), combined RFA and CBA (RFA + CBA), pulmonary vein ablation catheter (PVAC), laser balloon ablation (LBA), hot balloon ablation (HBA) and antiarrhythmic drugs (AAD). Indirect comparisons were performed using AAD therapy as the common comparator. Natural log-transformed HR estimates for each IPD study and were pooled together in a 2-stage NMA within a Frequentist setting. Treatment strategies were ranked using P-Scores, with higher P-Scores corresponding to greater efficacy, and forest plots comparing NMA-derived HRs of various treatments versus AAD were generated.

### Restricted Mean Survival Time (RMST) Network Meta-Analysis

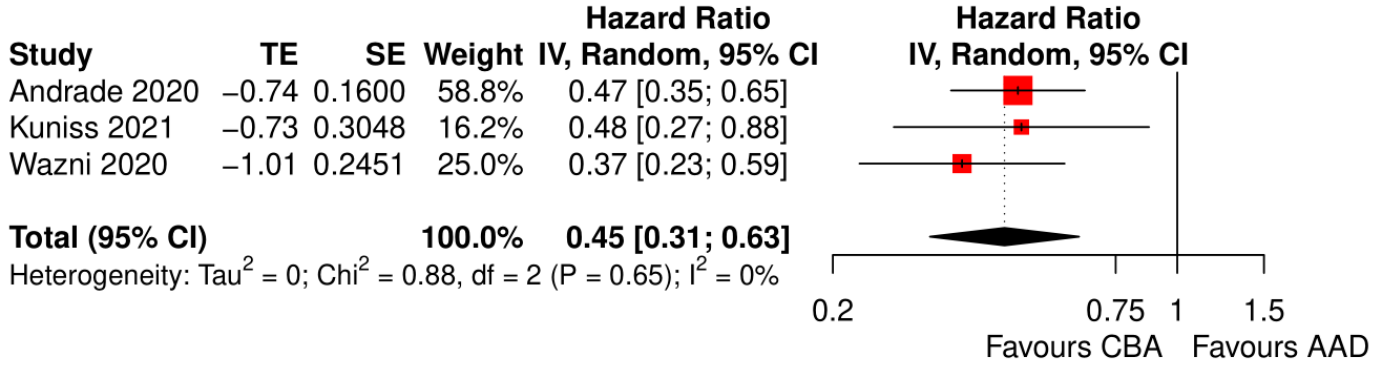
As Cox-based models were used to derive HRs used in the above analyses, the proportional hazards assumption was verified by examining scaled Schoenfeld residuals of the pairwise comparison with the largest number of studies directly reporting this comparison. If the assumption was violated, restricted mean survival time (RMST) for each treatment was also analysed. This non-parametric method models the area under the survival curve at various time horizons. There were 2 parts to this analysis. First, atrial tachyarrhythmia recurrence was modelled at a prespecified epoch of 1 year, with studies following up patients for less than 1 year being excluded from analysis. Mean differences in RMST (RMST-D) and their 95% confidence intervals, derived from pairwise comparisons, were pooled under a Frequentist NMA. Next, the ratio of RMSTs across respective study follow-up durations (RMST-R) was derived and similarly pooled under a Frequentist NMA. As RMST does not utilise HRs and is applicable to nonlinear covariate relationships, it acts as a further sensitivity analysis of the aforementioned NMAs, and provides insight into both the relative short-term and long-term efficacies of various treatments.

**Abbreviations in Supplementary Figures and Tables**
AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; CI: confidence intervals; HBA: hot balloon ablation; HR: hazard ratio; LBA: laser balloon ablation; MD: mean difference; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation; RMST-D: restricted mean survival time difference; RMST-R: restricted mean survival time ratio; SE: standard error of treatment effect; TE: treatment effect

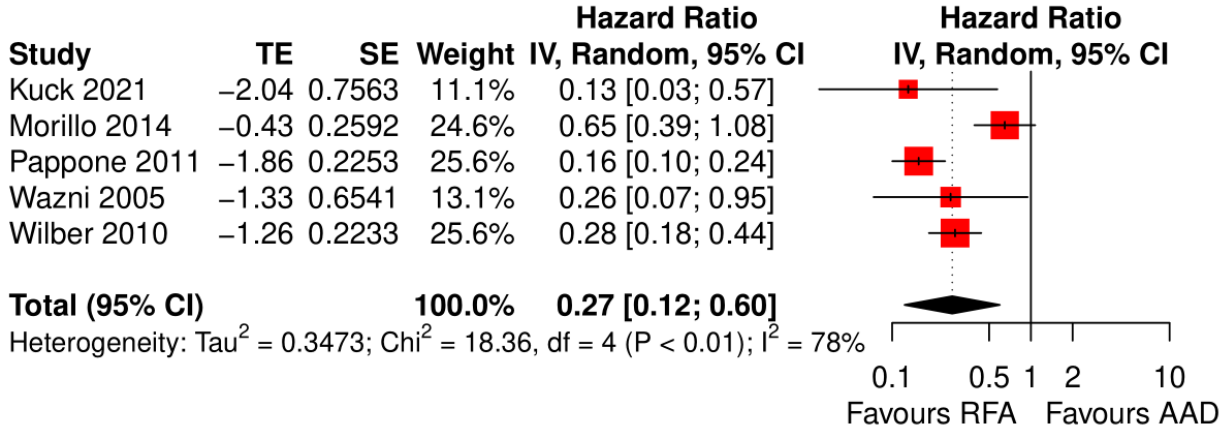
Supplementary Fig S1. Individual patient data one-stage meta-analysis of CBA versus RFA for freedom from atrial arrhythmia.



Supplementary Fig S2. Forest plots of 2-stage meta-analyses of CBA versus AAD for atrial tachyarrhythmia recurrence.



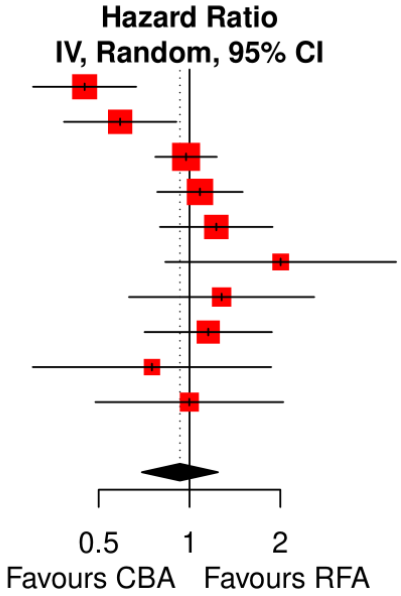

Supplementary Fig S3. Forest plots of 2-stage meta-analyses of RFA versus AAD for atrial tachyarrhythmia recurrence.



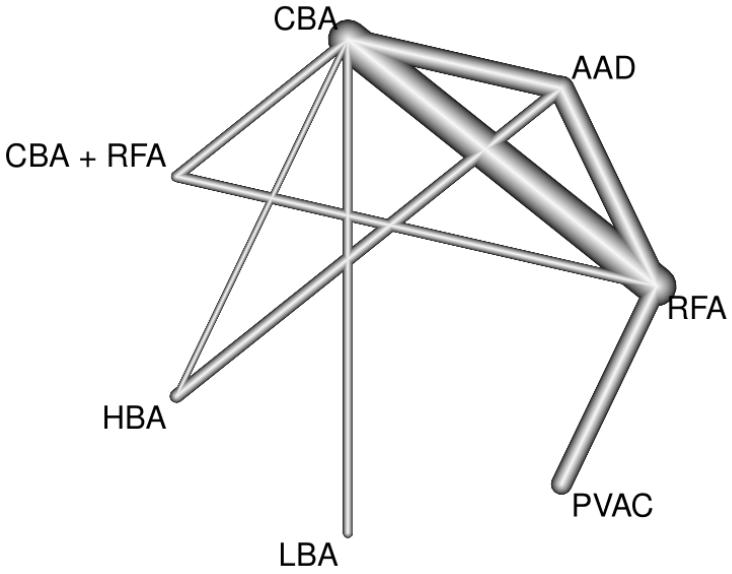
Supplementary Fig S4. Forest plots of 2-stage meta-analyses of CBA versus RFA for atrial tachyarrhythmia recurrence.

| Study | TE | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Ang 2018 | −0.80 | 0.2015 | 12.3% | 0.45 [0.30; 0.67] |
| Buist 2018 | −0.53 | 0.2196 | 11.6% | 0.59 [0.38; 0.91] |
| Kuck 2018 | −0.03 | 0.1202 | 15.4% | 0.97 [0.77; 1.23] |
| Larsen 2020 | 0.08 | 0.1670 | 13.6% | 1.08 [0.78; 1.50] |
| Pak 2021 | 0.20 | 0.2199 | 11.6% | 1.23 [0.80; 1.89] |
| Perez−Castellano 2014 | 0.70 | 0.4498 | 5.5% | 2.00 [0.83; 4.84] |
| Ikenouchi 2018 | 0.24 | 0.3612 | 7.3% | 1.28 [0.63; 2.59] |
| Knecht 2014 | 0.14 | 0.2485 | 10.5% | 1.15 [0.71; 1.88] |
| Matta 2018 | −0.29 | 0.4648 | 5.2% | 0.75 [0.30; 1.87] |
| Tokuda 2016 | −0.00 | 0.3663 | 7.1% | 1.00 [0.49; 2.05] |
| **Total (95% CI)** | | | **100.0%** | **0.93 [0.69; 1.24]** |

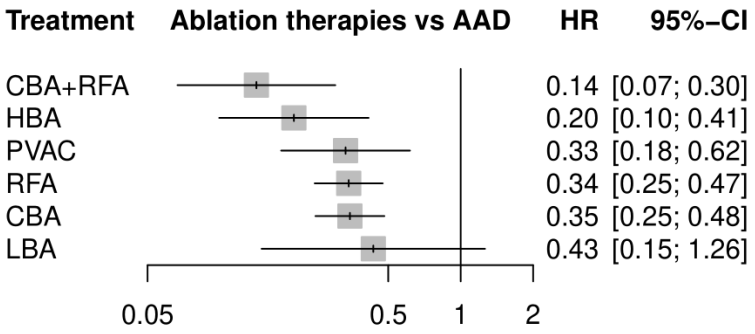
Heterogeneity: $Tau^2 = 0.0893$; $Chi^2 = 24.57$, df = 9 ($P < 0.01$); $I^2 = 63\%$



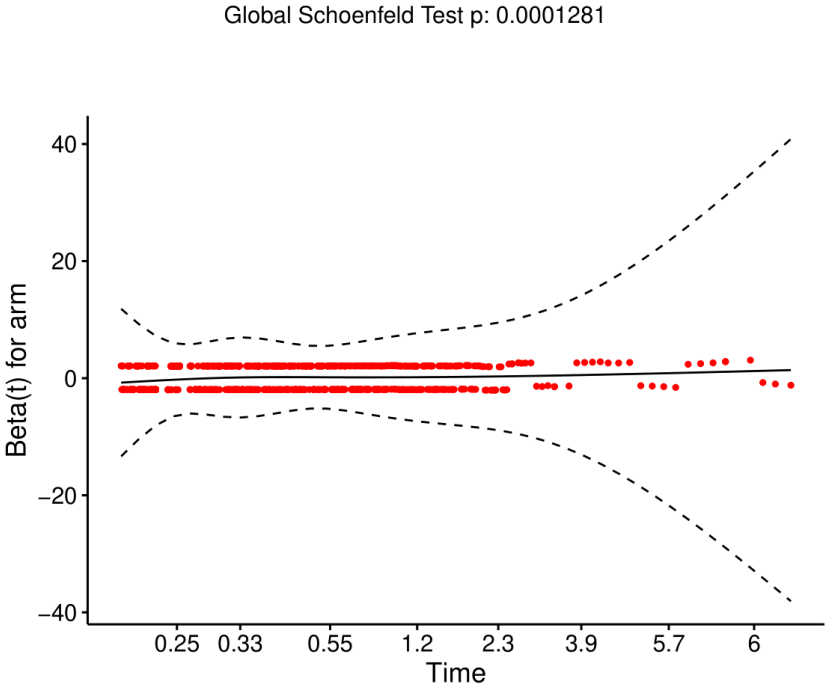

Supplementary Fig S5. Network plot for hazard ratio-based Frequentist network meta-analysis.



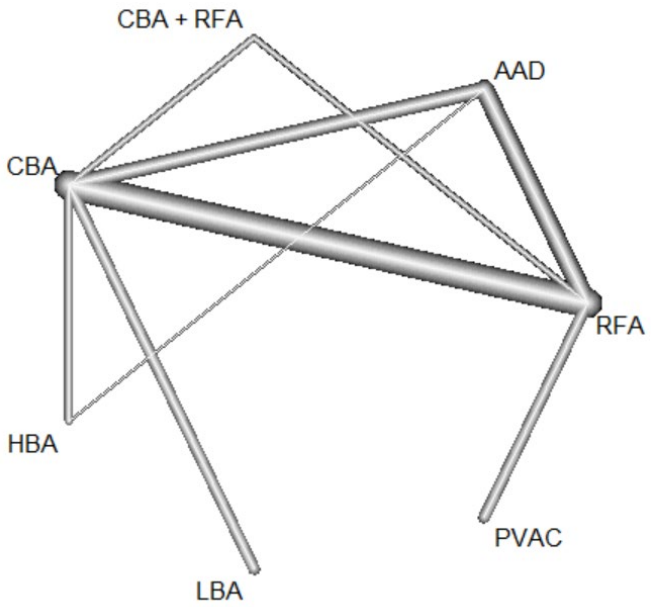
Supplementary Fig S6. Forest plot of various ablation therapies versus AAD in the hazard ratio-based network meta-analysis.



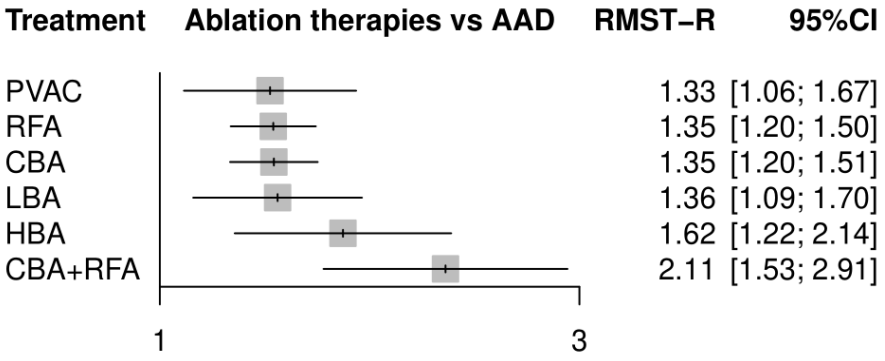

Supplementary Fig S7. Schoenfeld residuals for the CBA versus RFA comparison.



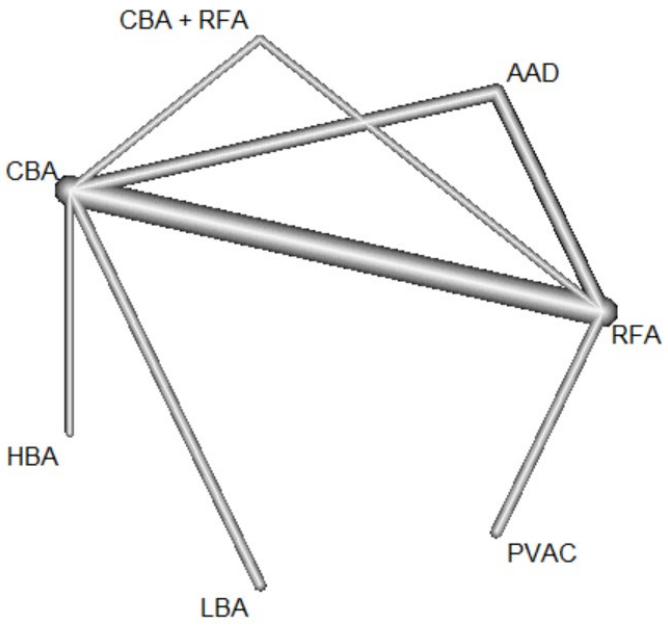
Supplementary Fig S8. Network plot for Frequentist network meta-analysis of RMST-R.



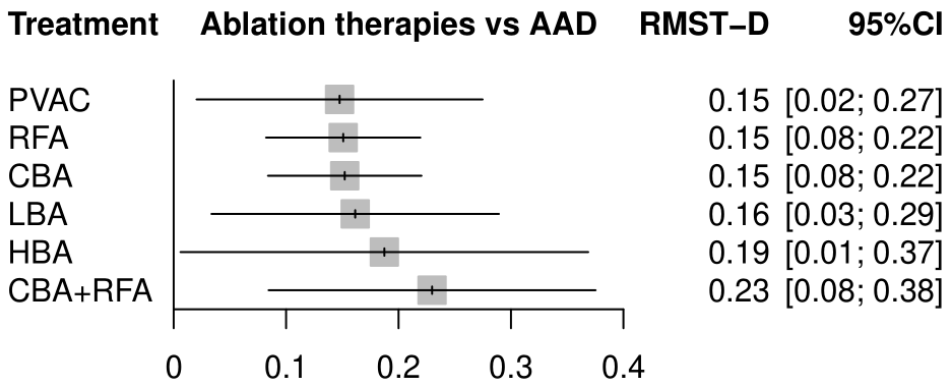

Supplementary Fig S9. Forest plot of RMST-R for freedom from atrial tachyarrhythmia in various ablation modalities compared to antiarrhythmic drugs.



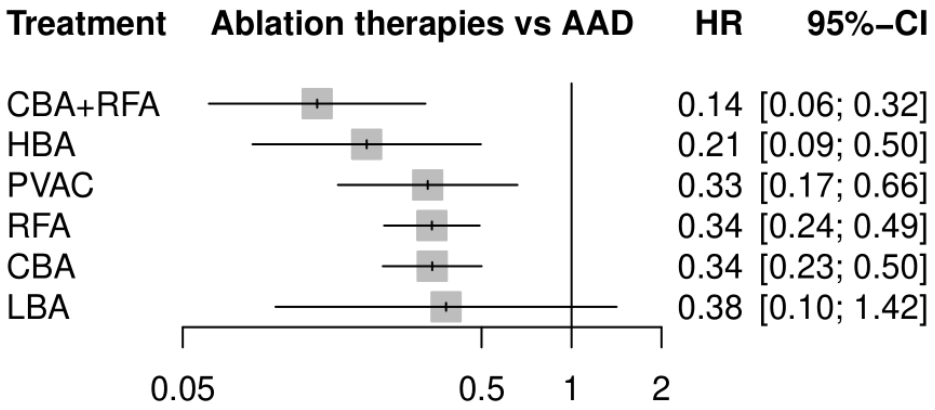
Supplementary Fig S10. Network plot for Frequentist network meta-analysis of RMST-D.



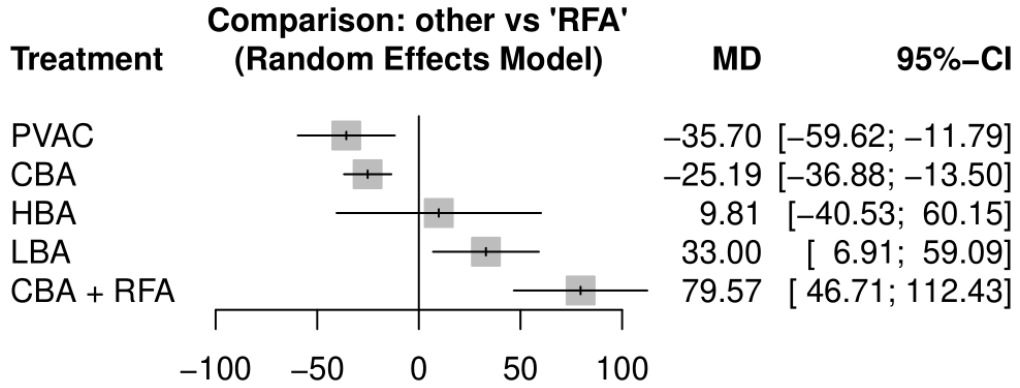

Supplementary Fig S11. Forest plot of RMST-D for freedom from atrial tachyarrhythmia in various ablation modalities compared to antiarrhythmic drugs at an epoch of 1 year.



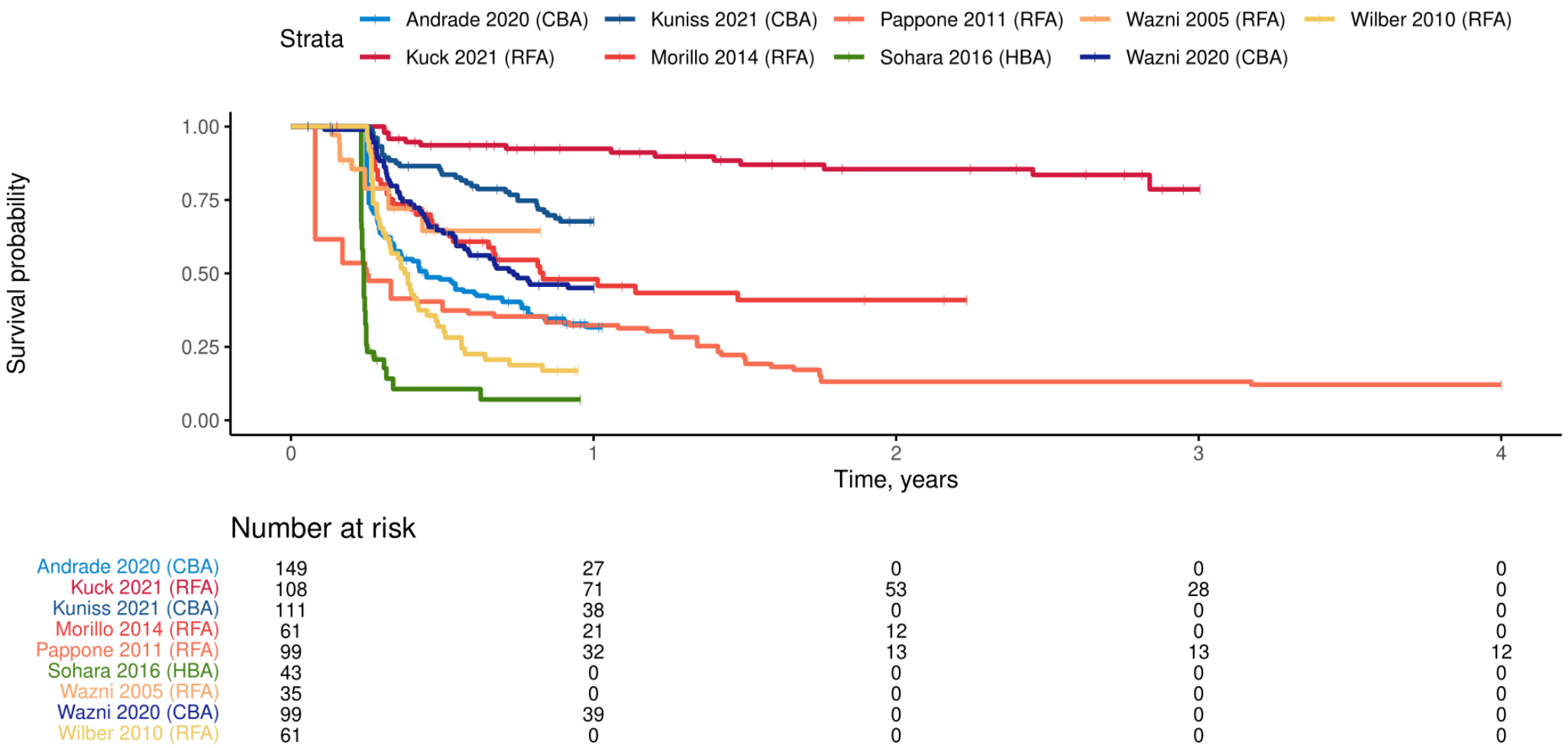
Supplementary Fig S12. Forest plot of various ablation therapies versus AAD in a sensitivity Frequentist network meta-analysis.




Supplementary Fig S13. Forest plot of procedural time for various ablation therapies versus AAD in a Frequentist network meta-analysis.

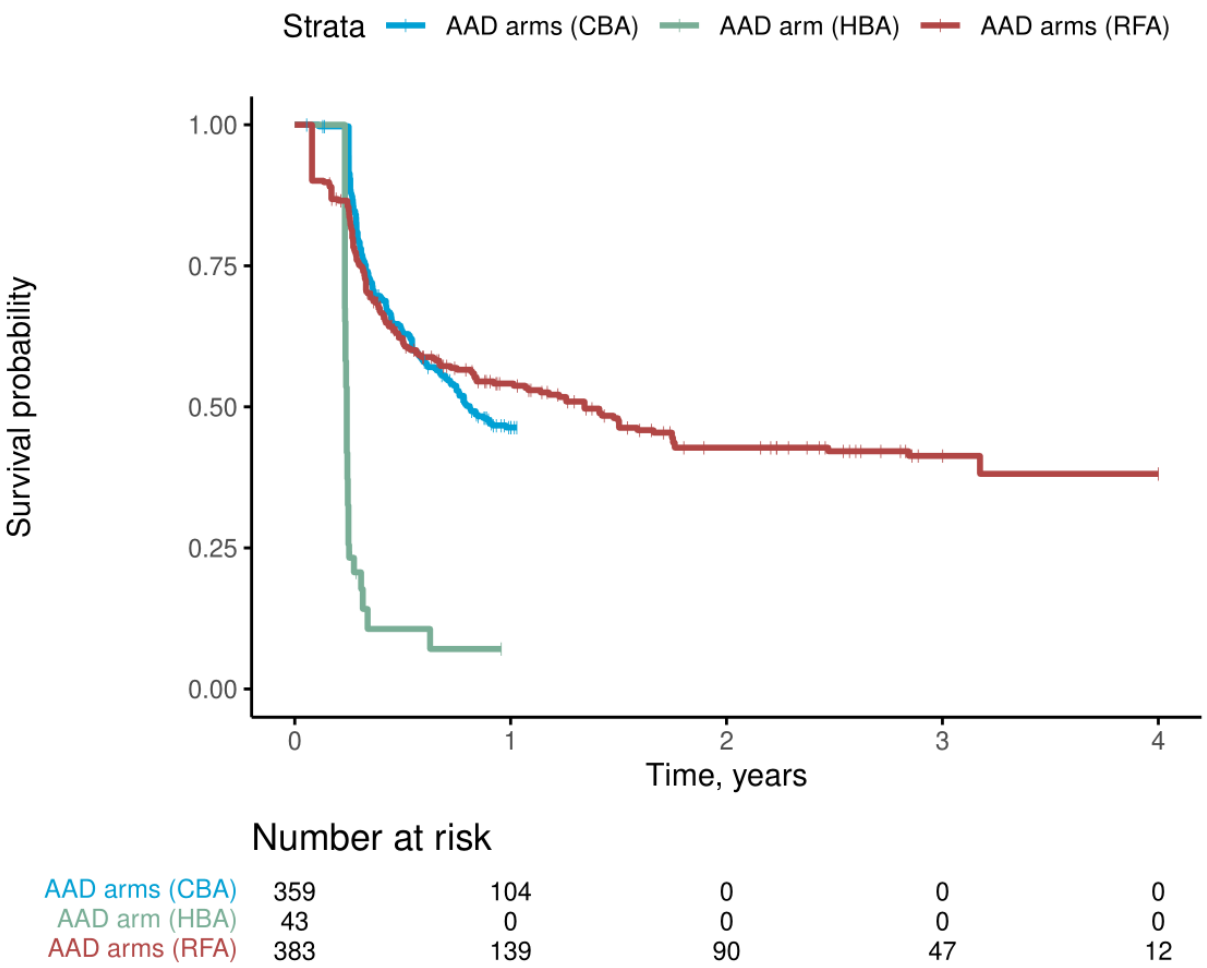


Supplementary Fig S14. Kaplan-Meier plot of atrial arrhythmia recurrence in the antiarrhythmic drug arms of respective studies.




Studies comparing AAD versus CBA are colored with a blue palette, while studies comparing RFA versus AAD are colored with a red palette. The study comparing HBA versus AAD is colored green.

Supplementary Fig S15. Kaplan-Meier plot of AAD arms, grouped by treatment modality which they were compared against in respective studies.



**SUPPLEMENTARY TABLES**

Supplementary Table S1. Full search phrases used for the respective database

| **PubMed** | 302 articles |
|---|---|
| ((atrial fibrillation[MeSH Terms] OR afib) AND paroxysmal) AND (ablation) AND (cryoballoon OR cryoablation OR radiofrequency OR laser OR PVAC OR mesh OR nmarq) AND (random* OR propensity) NOT ((animals [mh] NOT humans [mh])) NOT (systematic[sb] OR Editorial[pt] OR Meta-Analysis[pt]) | |
| **EMBASE** | 267 articles |
| ('atrial fibrillation'/exp OR 'afib') AND paroxysmal AND ablation AND ('cryoballoon'/exp OR cryoablation:ti,ab,kw OR 'radiofrequency'/exp OR radiofrequency:ti,ab,kw OR laser:ti,ab,kw OR pvac OR mesh OR nmarq) AND (random OR randomised OR randomised OR propensity) NOT ([animals]/lim NOT [humans]/lim) AND ([article]/lim OR [article in press]/lim) AND [humans]/lim | |
| **Web of Science** | 222 articles |
| AB = (((atrial fibrillation OR afib) AND paroxysmal) AND (ablation) AND (cryoballoon OR cryoablation OR radiofrequency OR laser OR PVAC OR mesh OR nmarq) AND (random OR randomized OR randomised OR propensity)) OR TI = (((atrial fibrillation OR afib) AND paroxysmal) AND (ablation) AND (cryoballoon OR cryoablation OR radiofrequency OR laser OR PVAC OR mesh OR nmarq) AND (random OR randomised OR randomised OR propensity)) OR KP = (((atrial fibrillation OR afib) AND paroxysmal) AND (ablation) AND (cryoballoon OR cryoablation OR radiofrequency OR laser OR PVAC OR mesh OR nmarq) AND (random OR randomized OR randomised OR propensity)) OR SU = (((atrial fibrillation OR afib) AND paroxysmal) AND (ablation) AND (cryoballoon OR cryoablation OR radiofrequency OR laser OR PVAC OR mesh OR nmarq) AND (random OR randomised OR randomised OR propensity)) | |
| **Cochrane Controlled Register of Trials CENTRAL** | 9 articles |
| #1 MeSH descriptor: [Atrial Fibrillation] explode all trees 4923<br>#2 MeSH descriptor: [Catheter Ablation] explode all trees 1546<br>#3 cryoballoon 323<br>#4 MeSH descriptor: [Cryosurgery] explode all trees365<br>#5 MeSH descriptor: [Radiofrequency Ablation] explode all trees 1611<br>#6 MeSH descriptor: [Laser Therapy] explode all trees 4358<br>#7 mesh ablation 239<br>#8 nmarq 12<br>#9 #3 OR #4 OR #5 OR #6 OR #7 OR #8 6611<br>#10 random 82411<br>#11 randomized 1218340<br>#12 propensity 4532<br>#13 #10 OR #11 #12 85714<br>#14 #1 AND #2 AND #9 AND #13 9 | |

Date searched: 29 October 2021

Supplementary Table S2. Baseline characteristics of participants in included studies

| Study | Arm | No. of participants (males) | Age, years[a] | Diabetes mellitus (%) | Hypertension (%) | Previous stroke/TIA | AF duration, years[a] | LVEF, % | LA diameter, mm[a] | Baseline beta-blocker use (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Ang 2018 Cryo vs RF | 1G CBA | 67 (48) | 55.7 | 4 (6.0) | 25 (37) | 5 (7.5) | NR | NR | 43.0 | NR |
| | Non-CF RFA | 67 (42) | 60.7 | 5 (7.5) | 21 (31) | 6 (9.0) | NR | NR | 42.4 | NR |
| | CBA + RFA | 69 (40) | 58.9 | 5 (7.2) | 26 (38) | 26 (38) | NR | NR | 42.6 | NR |
| Buist 2018 | 2G CBA | 133 (92) | 59.7±9.9 | 14 (11) | 57 (43) | 8 (6.0) | 4.9±5.9 | NR | NR | NR |
| | CF RFA | 136 (99) | 58.2±10.8 | 9 (17) | 52 (39) | 10 (7.4) | 5.1±6.1 | NR | NR | NR |
| Kuck 2018 Fire & Ice | 1G/2G/AG CBA | 374 (221) | 59.9±9.8 | 37 (9.9) | 215 (58) | 16 (4.3) | 4.6±5.1 | NR | 40.6±6.5 | 235 (63) |
| | CF/Non-CF RFA | 376 (236) | 60.1±9.2 | 22 (5.9) | 221 (59) | 14 (3.7) | 4.7±5.3 | NR | 40.6±5.8 | 253 (67) |
| Larsen 2020 CIRCA Dose | 2G CBA | 231 (152) | 58.9 | 19 (8.2) | 80 (35) | 12 (5.2) | NR | 59.3 | 36.3 | NR |
| | CF RFA | 115 (79) | 58.6±9.2 | 10 (8.7) | 40 (35) | 4 (3.5) | NR | 59.1±6.6 | 37.4±8.5 | NR |
| Pak 2021 CRAFT | 2G CBA | 156 (108) | 60.8±11.3 | 35 (11) | 80 (51) | 12 (7.7) | 1.2 [0.7-3.0] | 65.2±6.1 | 38.8±5.6 | NR |
| | HPSD RFA | 156 (116) | 59.0±10.4 | 18 (11) | 71 (45) | 17 (11) | 1.4 [0.7-3.2] | 65.9±6.3 | 39.6±5.6 | NR |
| Perez-Castellano 2014 COR | 1G CBA | 25 (17) | 58 [45-62] | 4 (16) | 6 (24) | NR | NR | NR | 42 [39-47] | NR |
| | Non-CF RFA | 25 (22) | 56 [40-61] | 2 (8.0) | 8 (32) | NR | NR | NR | 42 [38-45] | NR |
| Ikenouchi 2018 | 2G CBA | 99 (60) | 77.7±2.4 | 14 (14) | 71 (72) | 12 (12) | NR | 67±9 | 35±7 | NR |
| | CF/non-CF RFA | 99 (58) | 77.6±2.2 | 15 (15) | 66 (67) | 18 (18) | NR | 68±10 | 37±9 | NR |
| Knecht 2014 BEAT-AF | 1G CBA | 71 (53) | 58.6±10.6 | 0 | 31 (44) | NR | 5.6±5.8 | 58.9±6.6 | 39.5±6.0 | 42 (59) |
| | CF RFA | 71 (55) | 57.8±11.2 | 0 | 34 (48) | NR | 4.8±5.8 | 58.8±6.5 | 39.2±5.3 | 41 (58) |
| Matta 2018 | 2G CBA | 46 (38) | 59±9 | 3 (6.5) | 21 (46) | 1 (2.2) | 4.3±4.8 | 61±6 | NR | 24 (52) |
| | CF RFA | 46 (36) | 59±9 | 3 (6.5) | 21 (46) | 0 | 4.8±4.3 | 61±5 | NR | 26 (57) |
| Tokuda 2016 | 2G CBA | 123 (106) | 57.9±9.7 | 9 (7.3) | 38 (31) | NR | NR | 64.6±4.9 | 36.6±4.5 | NR |
| | CF RFA | 123 (107) | 58.0±9.1 | 9 (7.3) | 42 (34) | NR | NR | 64.7±5.2 | 36.4±5.9 | NR |
| Andrade 2020 EARLY AF | 2G CBA | 154 (112) | 57.7±12.3 | NR | 57 (37) | 4 (2.6) | 1.0 [0-3.0] | 59.6±7.0 | 39.5±5.0 | 85 (55) |
| | AAD | 149 (102) | 59.5±10.6 | NR | 55 (36) | 5 (3.4) | 1.0 [0-4.0] | 59.8±7.6 | 38.1±6.5 | 92 (62) |
| Kuniss 2021 Cryo FIRST | 2G CBA | 107 (76) | 50.5±13.1 | 1 (0.9) | 33 (30) | 0 | 0.7±1.5 | 62.8±5.4 | 46.8±8.2 | 54 (51) |
| | AAD | 111 (72) | 54.1±13.4 | 4 (3.6) | 40 (36) | 0 | 0.8±2.1 | 63.7±5.4 | 47.7±6.3 | 56 (51) |
| Wazni 2020 STOP AF | 2G CBA | 104 (63) | 60.4±11.2 | 15 (14) | 58 (56) | 2 (1.9) | 1.3±2.5 | 60.9±6.0 | 38.7±5.7 | 6 (5.8) |
| | AAD | 99 (57) | 61.6±11.2 | 17 (17) | 57 (58) | 3 (3.0) | 1.3±2.3 | 61.6±5.9 | 38.2±5.4 | 9 (9.1) |
| Kuck 2021 ATTEST | CF/non-CF RFA | 128 (54) | 67.8±4.8 | 12 (10) | 120 (94) | 12 (9.4) | 4.3 (1.6-52) | 61.8±5.8 | 42.1±6.1 | NR |
| | AAD | 127 (53) | 67.6±4.6 | 14 (11) | 123 (97) | 8 (6.3) | 4.2 (2.1-31) | 62.3±5.2 | 43.4±5.6 | NR |
| Morillo 2014 RAAFT 2 | Non-CF RFA | 66 (51) | 56.3±9.3 | 1 (1.5) | 28 (42) | 3 (4.6) | NR | 61.4±4.8 | 40±5.0 | 40 (61) |
| | AAD | 61 (45) | 54.3±11.7 | 4 (6.6) | 27 (44) | 4 (6.6) | NR | 60.8±7.0 | 43±5.0 | 36 (59) |
| Pappone 2011 APAF | Non-CF RFA | 99 (69) | 55±10 | 5 (5.1) | 55 (56) | NR | 6±4 | 60±8 | 40±6 | NR |
| | AAD | 99 (64) | 57±10 | 4 (4.0) | 56 (56) | NR | 6±6 | 61±6 | 38±6 | NR |
| Wazni 2005 | Non-CF RFA | 33 | 53±8 | NR | 8 (25) | NR | 0.4±0.2 | 53±4 | 41±8 | 19 (57) |
| | AAD | 37 | 54±8 | NR | 10 (28) | NR | 0.4±0.2 | 54±6 | 42±7 | 23 (62) |
| Wilber 2010 | Non-CF RFA | 106 (73) | 55.5 [53.7-57.3] | 10 (9.5) | 51 (49) | 3 (2.9) | 5.4 [4.3-6.5] | 62.3 [60.4-64.3] | 40.0 [38.9-41.1] | 36 (34) |
| | AAD | 61 (38) | 56.1 [52.9-59.4] | 7 (12) | 30 (49) | 1 (1.6) | 6.2 [4.6-7.9] | 62.7 [60.7-64.7] | 40.5 (39.0-41.9) | 22 (36) |
| Suruga 2021 | HBA | 30 (25) | 63±11 | 8 (27) | 18 (60) | 2 (6.7) | NR | 64±9 | 40±4.6 | 10 (33) |
| | 2G CBA | 30 (26) | 64±10 | 5 (17) | 11 (37) | 1 (3.3) | NR | 66±6 | 39±5.7 | 12 (40) |
| Sohara 2016 | HBA | 100 (80) | 58.8±10.4 | 3 (3.0) | 51 (51) | NR | 5.3±6.8 | 66.7±6.1 | 38.3±5.6 | NR |
| | AAD | 43 (35) | 61.0±10.0 | 4 (9.3) | 24 (56) | NR | 4.6±4.6 | 66.5±6.5 | 38.3±4.9 | NR |
| Chun 2021 | LBA | 100 (54) | 66.5±9.4 | 12 (12) | 68 (68) | 4 (4.0) | NR | 61.5±5.6 | 39.8±5.2 | NR |
| | 2G CBA | 100 (58) | 65.0±9.2 | 12 (12) | 65 (65) | 2 (2.0) | NR | 61.5±6.1 | 39.1±5.3 | NR |
| Yano 2021 | LBA | 37 (21) | 72 [59-79] | 10 (27) | 26 (70) | 5 (14) | NR | 70 [65-74] | 43 [40-46] | 17 (46) |
| | 2G CBA | 37 (22) | 74 [62-79] | 5 (14) | 20 (54) | 5 (14) | NR | 71 [67-74] | 42 [39-45] | 11 (30) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Gal 2014 | PVAC | 230 (174) | 56.6±10.3 | 13 (5.7) | 90 (39) | 16 (7.0) | 7.9±5.0 | NR | 41.7±4.7 | NR |
| | Non-CF RFA | 230 (173) | 56.1±.9.8 | 17 (7.4) | 71 (31) | 9 (3.9) | 8.6±5.2 | NR | 40.6±4.9 | NR |
| McCready 2014 | PVAC | 94 (58) | 62±11 | 3 (3.2) | 26 (28) | 2 (2.2) | NR | 62±11 | 39±5 | 47 (50) |
| | Non-CF RFA | 94 (58) | 58±12 | 6 (6.4) | 23 (24) | 3 (3.2) | NR | 64±6 | 38±7 | 51 (54) |

[a] Reported as mean ± standard deviation, median [interquartile range] or mean

1G: first-generation; 2G: second-generation; AAD: antiarrhythmic drugs; AF: atrial fibrillation; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; CF: contact-force; HBA: hot balloon ablation; HPSD: high-power short duration; LA: left atrium; LBA: laser balloon ablation; LVEF: left ventricular ejection fraction; NR: not reported; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Studies: Refer to REFERENCES

Supplementary Table S3. Summary of all serious adverse effects and selected adverse effects in included studies

| Study | Arm | Total serious adverse effects | Permanent phrenic nerve palsy | Cardiac tamponade | Stroke/TIA | Death |
|---|---|---|---|---|---|---|
| Ang 2018 Cryo vs RF | CBA | NR | NR | NR | NR | 2 |
| | RFA | NR | NR | NR | NR | 1 |
| | CBA + RFA | NR | NR | NR | NR | 2 |
| Buist 2018 | CBA | 8 | 0 | NR | 0 | 0 |
| | RFA | 9 | 0 | NR | 1 | 0 |
| Kuck 2018 Fire & Ice | CBA | 40 | 1 | 1 | 3 | 2 |
| | RFA | 51 | 0 | 5 | 3 | 0 |
| Larsen 2020 CIRCA Dose | CBA | 15 | 3 | 0 | 2 | 0 |
| | RFA | 6 | 0 | 1 | 0 | 0 |
| Pak 2021 CRAFT | CBA | 6 | 3 | 0 | NR | 0 |
| | RFA | 1 | 0 | 1 | NR | 0 |
| Perez-Castellano 2014 COR | CBA | 1 | NR | NR | NR | 0 |
| | RFA | 1 | NR | NR | NR | 0 |
| Ikenouchi 2018 | CBA | 12 | 4 | 2 | 0 | 0 |
| | RFA | 16 | 0 | 6 | 1 | 0 |
| Knecht 2014 BEAT-AF | CBA | 3 | 0 | 1 | 0 | 0 |
| | RFA | 3 | 0 | 1 | 0 | 0 |
| Matta 2018 | CBA | 3 | 0 | 0 | NR | 0 |
| | RFA | 2 | 0 | 0 | NR | 0 |
| Tokuda 2016 | CBA | 3 | NR | NR | NR | 0 |
| | RFA | 2 | NR | NR | NR | 0 |
| Andrade 2020 EARLY AF | CBA | 15 | 3 | 0 | 0 | 0 |
| | AAD | 27 | 0 | 1 | 1 | 0 |
| Kuniss 2021 Cryo FIRST | CBA | 42 | 0 | 0 | 1 | 0 |
| | AAD | 56 | 1 | 0 | 0 | 0 |
| Wazni 2020 STOP AF | CBA | 22 | 0 | NR | 0 | 0 |
| | AAD | 16 | 0 | NR | 0 | 0 |
| Kuck 2021 ATTEST | RFA | 12 | NR | 1 | 0 | 0 |
| | AAD | 6 | NR | 0 | 1 | 0 |
| Morillo 2014 RAAFT 2 | RFA | 6 | NR | 4 | 0 | 0 |
| | AAD | 3 | NR | 0 | 0 | 0 |
| Pappone 2011 APAF | RFA | 5 | NR | 0 | 1 | NR |
| | AAD | NR | NR | 0 | 0 | NR |
| Wazni 2005 | RFA | NR | NR | NR | 0 | NR |
| | AAD | NR | NR | NR | 0 | NR |
| Wilber 2010 | RFA | 5 | NR | NR | NR | 1 |
| | AAD | 5 | NR | NR | NR | 0 |
| Suruga 2021 | HBA | NR | NR | NR | NR | 0 |
| | CBA | NR | NR | NR | NR | 0 |
| Sohara 2016 | HBA | 14 | 5 (3.7) | 0 | NR | 0 |
| | AAD | 2 | 0 | 0 | NR | 0 |
| Chun 2021 | LBA | 1 | 0 | 0 | 1 | 0 |
| | CBA | 0 | 0 | 0 | 0 | 0 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Yano 2021 | LBA | 1 | 1 | 1 | 0 | 0 |
| | CBA | 1 | 1 | 0 | 0 | 0 |
| Gal 2014 | PVAC | 3 | NR | NR | 0 | NR |
| | RFA | 11 | NR | NR | 0 | NR |
| McCready 2014 | PVAC | 4 | NR | 3 | 0 | NR |
| | RFA | 2 | NR | 0 | 2 | NR |

AAD: antiarrhythmic drugs; AF: atrial fibrillation; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA: laser balloon ablation; NR: not reported; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation; TIA: transient ischemic attack

Studies: Refer to REFERENCES

Supplementary Table S4. Risk-of-bias analysis of included studies

| Cochrane Risk-of-Bias tool for randomised controlled trials | | | | | | |
|---|---|---|---|---|---|---|
| **Study** | **Randomisation process** | **Deviations from intended interventions** | **Missing outcome data** | **Measurement of the outcome** | **Selection of the reported result** | **Overall** |
| Ang 2018 Cryo vs RF | + | + | + | + | + | + |
| Buist 2018 | + | + | + | + | + | + |
| Kuck 2018 Fire & Ice | + | + | + | + | + | + |
| Larsen 2020 CIRCA Dose | + | + | + | + | + | + |
| Pak 2021 CRAFT | + | + | + | + | + | + |
| Perez-Castellano 2014 COR | + | + | + | + | + | + |
| Andrade 2020 EARLY AF | + | + | + | + | + | + |
| Kuniss 2021 Cryo FIRST | + | + | + | + | + | + |
| Wazni 2020 STOP AF | + | + | + | + | + | + |
| Kuck 2021 ATTEST | + | + | + | + | + | + |
| Morillo 2014 RAAFT 2 | + | + | + | + | + | + |
| Pappone 2011 APAF | + | + | + | + | + | + |
| Wazni 2005 | + | + | + | + | + | + |
| Wilber 2010 | + | + | + | + | + | + |
| Sohara 2016 | + | ! | + | + | + | + |
| Chun 2021 | + | + | + | + | + | + |
| Gal 2014 | + | + | + | + | + | + |

| | | | | | | |
|---|---|---|---|---|---|---|
| McCready 2014 | + | + | + | + | + | + |

**Newcastle-Ottawa Scale for non-randomised trials**

| Study ID | Selection | Comparability | Exposure | Total |
|---|---|---|---|---|
| Ikenouchi 2018 | *** | ** | *** | **8** |
| Knecht 2014 BEAT-AF | *** | ** | *** | **8** |
| Matta 2018 | *** | ** | *** | **8** |
| Tokuda 2016 | *** | ** | *** | **8** |
| Suruga 2021 | *** | ** | *** | **8** |
| Yano 2021 | *** | ** | *** | **8** |

Studies: Refer to REFERENCES

Supplementary Table S5. League table comparing hazard ratios of various treatments in the Frequentist network meta-analysis of RMST-R

| | | | | | | |
|---|---|---|---|---|---|---|
| AAD | | | | | | |
| **0.47 (0.34-0.65)** | CBA + RFA | | | | | |
| **0.74 (0.66-0.83)** | **1.57 (1.16-2.12)** | CBA | | | | |
| **0.62 (0.47-0.82)** | 1.31 (0.87-1.96) | 0.83 (0.64-1.09) | HBA | | | |
| **0.73 (0.59-0.92)** | **1.55 (1.09-2.22)** | 0.99 (0.82-1.20) | 1.19 (0.86-1.64) | LBA | | |
| **0.75 (0.60-0.94)** | **1.58 (1.10-2.28)** | 1.01 (0.82-1.25) | 1.21 (0.86-1.70) | 1.02 (0.77-1.36) | PVAC | |
| **0.74 (0.66-0.83)** | **1.57 (1.16-2.13)** | 1.00 (0.92-1.09) | 1.20 (0.91-1.58) | 1.01 (0.82-1.24) | 0.99 (0.82-1.21) | RFA |

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA, laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Bold values indicate significance

Supplementary Table S6. League table comparing hazard ratios of various treatments in the Frequentist network meta-analysis of RMST-D

| | | | | | | |
|---|---|---|---|---|---|---|
| AAD | | | | | | |
| **-0.23 (-0.38; -0.08)** | CBA + RFA | | | | | |
| **-0.15 (-0.22; -0.08)** | 0.08 (-0.05; 0.21) | CBA | | | | |
| **-0.19 (-0.37; -0.01)** | 0.04 (-0.17; 0.26) | -0.04 (-0.20; 0.13) | HBA | | | |
| **-0.16 (-0.29; -0.03)** | 0.07 (-0.10; 0.24) | -0.01 (-0.12; 0.10) | 0.03 (-0.17; 0.23) | LBA | | |
| **-0.15 (-0.27; -0.02)** | 0.08 (-0.09; 0.25) | 0.00 (-0.11; 0.12) | 0.04 (-0.16; 0.24) | 0.01 (-0.15; 0.17) | PVAC | |
| **-0.15 (-0.22; -0.08)** | 0.08 (-0.05; 0.21) | 0.00 (-0.05; 0.05) | 0.04 (-0.14; 0.21) | 0.01 (-0.11; 0.13) | -0.00 (-0.11; 0.10) | RFA |

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA, laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Bold values indicate significance

Supplementary Table S7. League table comparing mean differences between various treatments in the sensitivity Frequentist network meta-analysis

| | | | | | | |
|---|---|---|---|---|---|---|
| CBA+RFA | | | | | | |
| **0.41 (0.19-0.90)** | CBA | | | | | |
| **0.41 (0.19-0.90)** | 1.00 (0.73-1.37) | RFA | | | | |
| 0.68 (0.20-2.30) | 1.66 (0.63-4.33) | 1.65 (0.64-4.29) | HBA | | | |
| 0.37 (0.08-1.63) | 0.90 (0.26-3.16) | 0.90 (0.25-3.28) | 0.54 (0.11-.64) | LBA | | |
| 0.43 (0.16-1.13) | 1.04 (0.53-2.01) | 1.03 (0.57-1.86) | 0.62 (0.20-1.92) | 1.15 (0.28-4.78) | PVAC | |
| **0.14 (0.06-0.32)** | **0.34 (0.23-0.50)** | **0.34 (0.24-0.49)** | **0.21 (0.09-0.50)** | 0.38 (0.10-1.42) | **0.33 (0.17-0.66)** | AAD |

AAD: antiarrhythmic drugs; CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA, laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Supplementary Table S8. League table comparing mean differences between various treatments in the Frequentist network meta-analysis of procedural time

| | | | | | |
|---|---|---|---|---|---|
| CBA (P=0.828) | | | | | |
| **-104.8 (-138; -72.0)** | CBA + RFA (P=0.004) | | | | |
| -35.0 (-84.0; 14.0) | **69.8 (10.8; 129)** | HBA (P=0.455) | | | |
| **-58.2 (-81.5; -34.9)** | **46.6 (6.4; 86.8)** | -23.2 (-77.4; 31.0) | LBA (P=0.239) | | |
| 10.5 (-16.1; 37.1) | **115.3 (74.6; 156)** | 45.5 (-10.2; 101) | **68.7 (33.3;104)** | PVAC (P=0.945) | |
| **-25.2 (-36.9; -13.5)** | **79.6 (46.7;112)** | 9.8 (-40.5; 60.2) | **33.0 (6.9; 59.1)** | **-35.7 (-59.6; -11.8)** | RFA (P=0.523) |

CBA: cryoballoon ablation; CBA + RFA: combined cryoballoon plus radiofrequency ablation; HBA: hot balloon ablation; LBA, laser balloon ablation; PVAC: pulmonary vein ablation catheter; RFA: radiofrequency ablation

Bold values indicate significance

P-scores, indicated next to their corresponding ablation therapies, are used as a measure of treatment efficacy in network meta-analyses, with higher P-scores corresponding to higher treatment efficacy. In this case, a higher P-score indicates a lower procedural time.