# The effects of rhythm control strategies versus rate control strategies for atrial fibrillation and atrial flutter: a systematic review with meta-analysis and Trial Sequential Analysis

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# Abstract

## Background

Atrial fibrillation and atrial flutter may be managed by either a rhythm control strategy or a rate control strategy but the evidence on the clinical effects of these two intervention strategies is unclear. Our objective was to assess the beneficial and harmful effects of rhythm control strategies versus rate control strategies for atrial fibrillation and atrial flutter.

## Methods

We searched CENTRAL, MEDLINE, Embase, LILACS, Web of Science, BIOSIS, Google Scholar, clinicaltrials.gov, TRIP, EU-CTR, Chi-CTR, and ICTRP for eligible trials comparing any rhythm control strategy with any rate control strategy in patients with atrial fibrillation or atrial flutter published before November 2016. Our primary outcomes were all-cause mortality, serious adverse events, and quality of life. Our secondary outcomes were stroke and ejection fraction. We performed both random-effects and fixed-effect meta-analysis and chose the most conservative result as our primary result. We used Trial Sequential Analysis (TSA) to control for random errors. Statistical heterogeneity was assessed by visual inspection of forest plots and by calculating inconsistency ($I^2$) for traditional meta-analyses and diversity ($D^2$) for TSA. Sensitivity analyses and subgroup analyses were conducted to explore the reasons for substantial statistical heterogeneity. We assessed the risk of publication bias in meta-analyses consisting of 10 trials or more with tests for funnel plot asymmetry. We used GRADE to assess the quality of the body of evidence.

## Results

25 randomized clinical trials (n=9354 participants) were included, all of which were at high risk of bias. Meta-analysis showed that rhythm control strategies versus rate control strategies significantly increased the risk of a serious adverse event (risk ratio (RR) 1.10; 95% confidence interval (CI) 1.02 to 1.18; P=0.02; $I^2$ = 12%; 21 trials), but TSA did not confirm this result (TSA-adjusted CI 0.99 to 1.22). The increased risk of a serious adverse event did not seem to be caused by any single component of the composite outcome. Meta-analysis showed that rhythm control strategies versus rate control strategies were associated with better SF-36 physical component score (mean difference (MD) 6.93 points; 95% CI 2.25 to 11.61; P=0.004; $I^2$ = 95%; 8 trials) and ejection fraction (MD 4.20%; 95% CI 0.54 to 7.87; P=0.02; $I^2$ = 79%; 7 trials), but TSA did not confirm these

results. Both meta-analysis and TSA showed no significant differences on all-cause mortality, SF-36 mental component score, Minnesota Living with Heart Failure Questionnaire, and stroke.

## Conclusions

Rhythm control strategies compared with rate control strategies seem to significantly increase the risk of a serious adverse event in patients with atrial fibrillation. Based on current evidence, it seems that most patients with atrial fibrillation should be treated with a rate control strategy unless there are specific reasons (e.g., patients with unbearable symptoms due to atrial fibrillation, patients who are hemodynamically unstable due to atrial fibrillation, or patients who are symptomatic even after adequate rate control) justifying a rhythm control strategy. More randomized trials at low risk of bias and low risk of random errors are needed.

## Systematic review registration

PROSPERO CRD42016051433

# Resumé


## Baggrund

Atrieflimren og atrieflagren kan behandles vha. en strategi med rytmekontrol eller en strategi med frekvenskontrol, men evidensen for de kliniske effekter af disse to strategier er uklar. Vores formål var at undersøge de gavnlige og skadelige effekter af rytmekontrol versus frekvenskontrol i patienter med atrieflimren eller atrieflagren.

## Metode

Vi søgte 8 databaser for publicerede forsøg og 4 databaser for igangværende forsøg i oktober 2016. Vi inkluderede alle randomiserede forsøg der sammenlignede rytmekontrol med frekvenskontrol i patienter med atrieflimren eller atrieflagren. Vores effektmål var død af enhver årsag, alvorlige komplikationer, livskvalitet, apopleksi og uddrivningsfraktionen (EF). Vores primære interessetidspunkt var ved maksimal opfølgning. Vi undersøgte risikoen for systematiske fejl vha. syv bias domæner og risikoen for tilfældige fejl vha. Trial Sequential Analysis. Kvaliteten af evidensen blev vurderet vha. GRADE.

## Resultat

25 randomiserede forsøg (n = 9345 patienter) blev inkluderet. Alle forsøgene havde høj risiko for bias. Meta-analysen for alvorlige komplikationer viste, at rytmekontrol versus frekvenskontrol havde en signifikant øget risiko (relativ risiko (RR) 1.10; 95% konfidensinterval (CI) 1.02 til 1.18; P=0.02; $I^2$ = 12%). Meta-analysen for SF-36 fysisk komponent score (SF-36 PCS) og EF viste henholdsvis, at rytmekontrol versus frekvenskontrol havde en signifikant øget SF-36 PCS (gennemsnitsforskellen (MD) 6.93 point; 95% CI 2.25 til 11.61; P=0.004; $I^2$ = 95%) og EF (MD 4.20%; 95% CI 0.54 til 7.87; P=0.02; $I^2$ = 79%). Meta-analyserne for død af enhver årsag, andre livskvalitetsmålinger og apopleksi viste ingen signifikant forskel mellem de to strategier.

## Konklusion

Rytmekontrol versus frekvenskontrol virker til signifikant at øge risikoen for at få en alvorlig komplikation i patienter med atrieflimren. Baseret på nuværende evidens bør de fleste patienter med atrieflimren behandles med en frekvenskontrol hvis der ikke samtidig er specifikke grunde (fx patienter med uholdbare symptomer grundet atrieflimren, patienter der er hæmodynamiske ustabile grundet deres atrieflimren eller

patienter der selv på optimal frekvenskontrolbehandling er symptomatiske) til at anvende rytmekontrol. Flere randomiserede forsøg med lav risiko for bias og lav risiko for tilfældige fejl er nødvendige.

# Introduction

Atrial fibrillation is the most common arrhythmia of the heart with a prevalence of approximately 2% in the western world [1, 2]. Atrial fibrillation and atrial flutter are both associated with an increased risk of morbidity and death [3-9]. The risks of both cerebral stroke and heart failure are increased nearly fivefold in patients with atrial fibrillation and atrial flutter and about 20% of every stroke may be due to atrial fibrillation [3-8]. Atrial fibrillation and atrial flutter also have a significant impact on healthcare costs and account for approximately 1% of the National Health Service budget in the United Kingdom and approximately 26 billion dollars of annual expenses in the United States [10, 11].

Two different overall intervention strategies may be used for atrial fibrillation and atrial flutter – a rhythm control strategy and a rate control strategy [12, 13]. When using any rhythm control strategy, the aim is to obtain and maintain sinus rhythm, while the overall aim when using any rate control strategy is to lower the ventricular frequency [14].

No former systematic review assessing the effects of rhythm control strategies versus rate control strategies for atrial fibrillation or atrial flutter has searched all relevant databases and has considered both risks of systematic errors and risks of random errors [15-18].

# Methods

We conducted this systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) (S1 Text) [19, 20], and the updated Cochrane methodology used in this systematic review is described in detail in our protocol (S2 Text), which was registered prior to the systematic literature search [18, 21, 22].

## Search strategy and selection criteria

We searched for trials comparing any rhythm control strategy with any rate control strategy in patients with atrial fibrillation or atrial flutter. We searched for eligible trials published before November 2016 in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded on Web of Science, BIOSIS, Google Scholar, clinicaltrials.gov, Trip Medical Database (TRIP), EU Clinical Trial Register (EU-CTR), Chinese Clinical Trial Registry (ChiCTR), and WHO International Clinical Trials Registry Platform (ICTRP) [21]. The search strategy can be found in the supplementary material (S3 Text).

Additionally, we checked the reference lists of relevant publications for any unidentified trials. Trials were included irrespective of trial design, setting, publication status, publication year, language, and the reporting of one of our outcomes.

## Data extraction and risk of bias assessment

Three authors (NJS, JF, EEN) independently selected relevant trials, and four authors (NJS, SS, JF, EEN) extracted data using a standardized data extraction sheet and assessed the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions and Lundh et al. [18, 23]. Any discrepancies were discussed with a fifth review author (JCJ). We attempted to contact trial authors if relevant data were unclear or missing.

## Outcomes and subgroup analysis

Our primary outcomes were all-cause mortality, serious adverse events (as defined by the ICH guidelines) [24], and quality of life. Our secondary outcomes were stroke and ejection fraction. All outcomes were analyzed as proportions of participants in each intervention group except for quality of life and ejection fraction which were both analyzed as continuous outcomes. For all outcomes, we used the trial results reported at maximal follow-up. However, if the trialists reported results at multiple time-points, we used the results reported at the time-point closest to 24 months.

We planned the following subgroup analyses on our primary outcomes:

- comparison of different types of rhythm control interventions;
- comparison of different types of rate control interventions;
- comparison of different mean ages of participants;
- comparison of different durations of atrial fibrillation;
- comparison of different durations of anticoagulation therapy;
- comparison of participants with atrial fibrillation to participants with atrial flutter; and
- comparison of trials only randomizing men to trials only randomizing women.

Additionally, we performed a post-hoc subgroup analysis:

- comparison of participants with heart failure to participants without heart failure.

## Assessment of statistical and clinical significance

We performed our meta-analyses according to the recommendations stated in the *Cochrane Handbook for Systematic Reviews of Interventions* [18], Keus et al. [17], and the eight-step assessment suggested by Jakobsen et al. [15] for better validation of meta-analytic results in systematic reviews. Review Manager 5 and Stata 15 were used for all meta-analyses [25, 26]. We used risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes. We did not use standardized mean difference (SMD) when analyzing continuous outcomes due to the fact that the outcomes assessed were not homogeneous and the several methodological limitations of using this approach [18]. We performed both random-effects (DerSimonian-Laird model) and fixed-effect meta-analysis with the Mantel-Haenszel method and chose the most conservative result as our primary result [15]. The more conservative result was the result with the highest P value and the widest 95% confidence interval (CI). If there was substantial discrepancy between the results of the two methods, we reported and discussed the results [15]. We used Trial Sequential Analysis (TSA) to control for random errors and reported TSA-adjusted CI if the cumulative Z-curves did not reach the futility area or passed the diversity-adjusted required information size (DARIS) [15, 16, 21, 22, 27-35]. TSA estimates the DARIS (that is the number of participants needed in a meta-analysis to detect or reject a certain intervention effect). When analyzing dichotomous outcomes, we pragmatically anticipated an intervention effect of 15% risk ratio reduction (RRR). When analyzing continuous outcomes, we pragmatically anticipated an intervention effect equal to the MD of the observed SD/2 [36]. Statistical heterogeneity was assessed by visual inspection of forest plots and by calculating inconsistency ($I^2$) for traditional meta-analyses and diversity ($D^2$) for TSA [31]. We calculated the 95% CI of the inconsistency ($I^2$) with the TSA software [27]. Sensitivity analyses and subgroup analyses were conducted to explore the reasons for substantial statistical heterogeneity [15]. We assessed the risk of publication bias in meta-analyses consisting of 10 trials or more with tests for funnel plot asymmetry. We assessed three primary outcomes and, hence, considered a P value of 0.025 or less as the threshold for statistical significance for the primary outcomes [15, 37]. We assessed two secondary outcomes and, hence, considered a P value of 0.033 as the threshold for statistical significance for the secondary outcomes [15, 37]. We used 'best-worst case' analyses and 'worst-best case' analyses to assess the potential impact of missing data (incomplete outcome data bias) [15]. We calculated Bayes factor to show if the meta-analysis results fitted better with the null hypotheses or the anticipated intervention effects [15]. We used GRADE to assess the quality of the body of evidence [15, 38-40].

# Results

## Study characteristics

Our literature search identified a total of 16 952 papers. We included 25 randomized clinical trials with 26 trial comparisons including a total of 9354 participants (Fig 1) [41-96]. All trials were at high risk of bias (S1 Table). All trials included participants with atrial fibrillation and three trials included both participants with atrial fibrillation and flutter [50, 62, 86]. The individual trials used various types of rhythm control interventions and rate control interventions. The rhythm control interventions used were: amiodarone with or without electrical cardioversion (6/26 trial comparisons); not specified (6/26 trial comparisons); electrical cardioversion with antiarrhythmic drug therapy following sinus rhythm restoration (5/26 trial comparisons); catheter ablation (4/26 trial comparisons); antiarrhythmic therapy with or without electrical cardioversion (2/26 trial comparisons); ibutilide (1/26 trial comparisons); propafenone (1/26 trial comparisons); and total endoscopic ablation (1/26 trial comparisons). The rate control interventions used were: beta-blockers, calcium channel blockers, digoxin, or a combination of these (11/26 trial comparisons); not specified (5/26 trial comparisons); AV-node ablation (4/26 trial comparisons); digoxin and/or beta blockers (2/26 trial comparisons); diltiazem (2/26 trial comparisons); beta blockers, calcium channel blockers, digoxin, and/or AV-node ablation (1/26 trial comparisons); and digoxin, carvedilol, and/or bisoprolol (1/26 trial comparisons). We have summarized the inclusion- and exclusion criteria for each included trial in S2 Table and other trial characteristics in S3 Table. Additionally, we have summarized the characteristics of excluded studies [97-102] and characteristics of ongoing trials [103-105] in S3 Table.

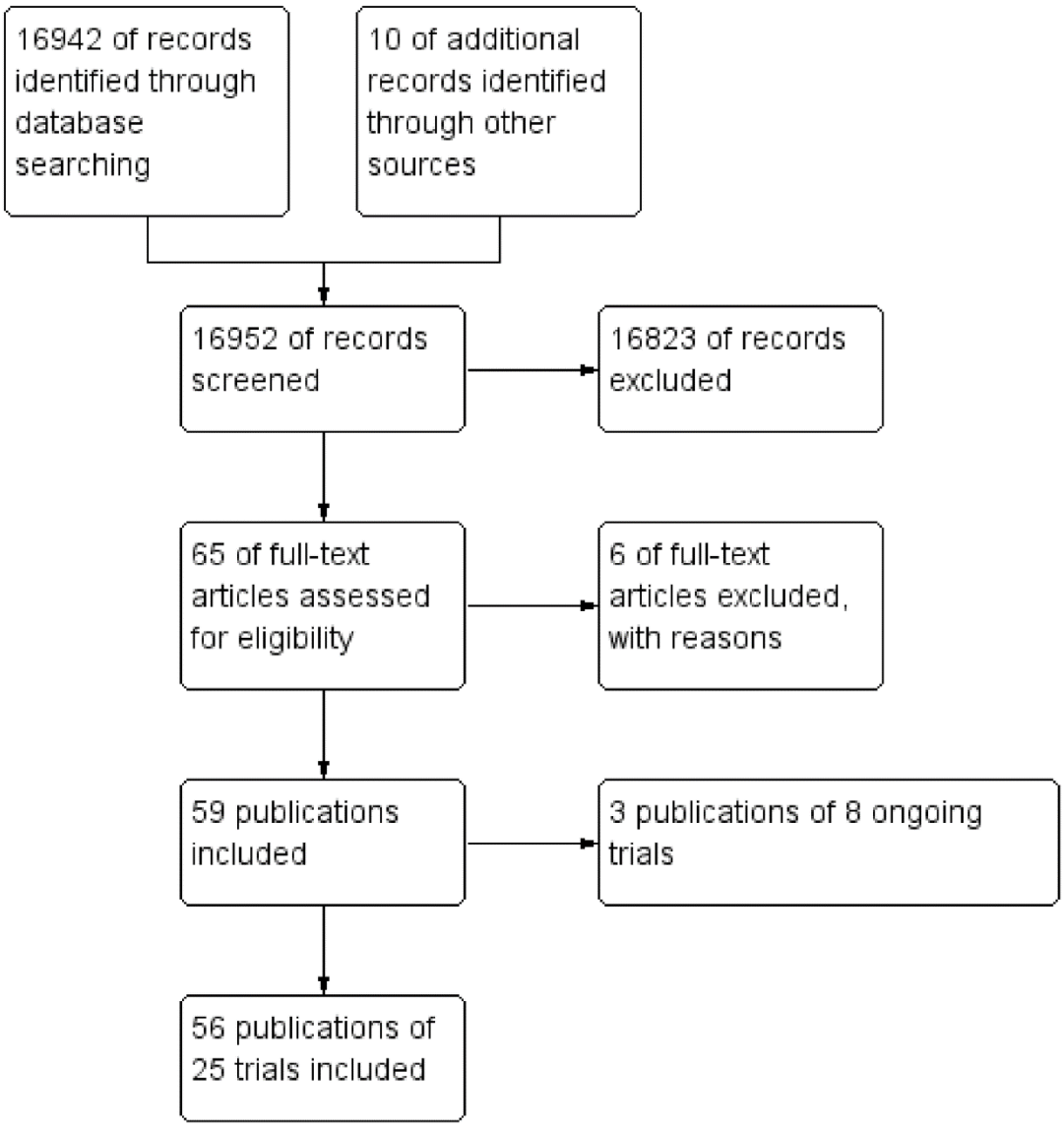


**Fig 1. PRISMA flow diagram.** We screened 16 952 records and included 56 publications of 25 trials in this systematic review.

## All-cause mortality

18 trials randomizing a total of 8668 participants reported all-cause mortality. Meta-analysis showed no significant difference between rhythm control strategies and rate control strategies (RR 1.05; 95% CI 0.95 to 1.16; P=.35; $I^2$=0%; Bayes factor = 3438; Fig 2). Visual inspection of the forest plot showed no signs of heterogeneity (Fig 2). The TSA showed that there was not enough information to confirm or reject a RRR of 15% (TSA-adjusted CI 0.90 to 1.22) (Fig 3). Incomplete outcome data bias alone had the potential to influence the results in the 'worst-best case'-scenario (S1 and S2 Figs). Visual inspection of the funnel plot showed no clear signs of asymmetry (S3 Fig).

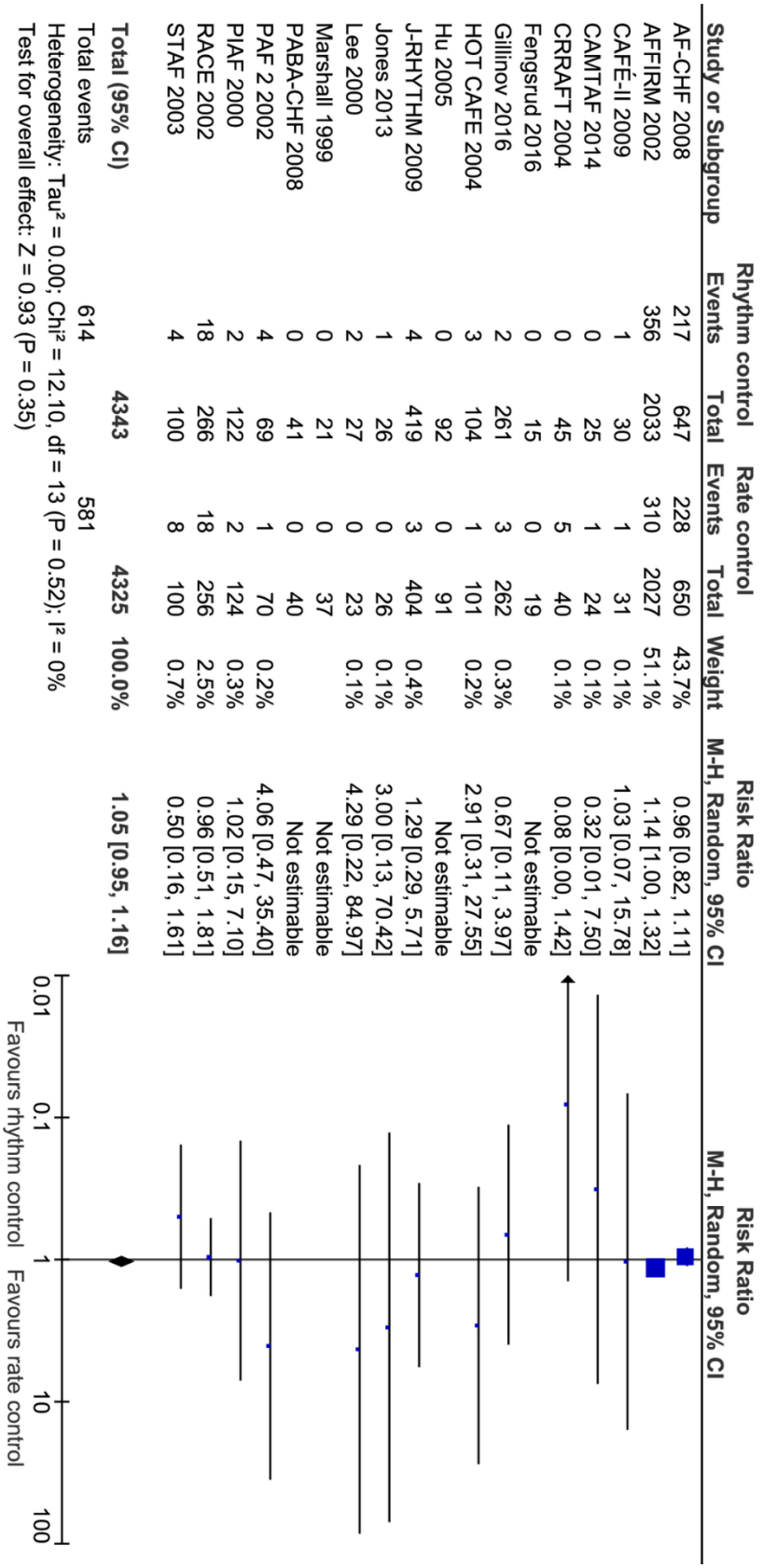


**Fig 2. Forest plot of the meta-analysis of all-cause mortality.** Meta-analysis showed no significant difference between rhythm control strategies and rate control strategies when assessing all-cause mortality.

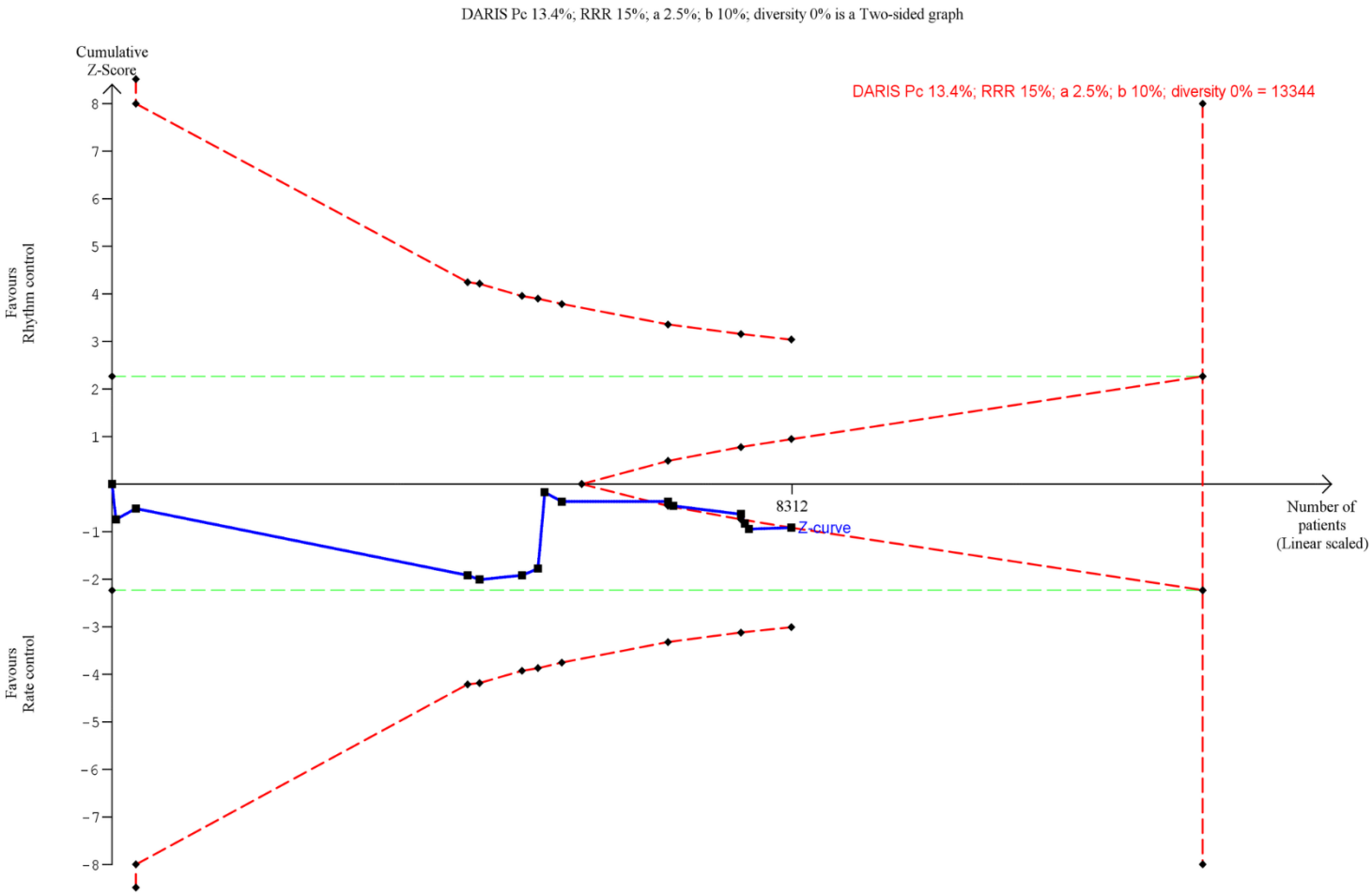


**Fig 3. Trial Sequential Analysis of all-cause mortality.** Trial Sequential Analysis (TSA) showed that there was not enough information to confirm or reject a risk ratio reduction of 15% (TSA-adjusted confidence interval 0.90 to 1.22). The Z-curve (the blue line) does not cross any boundaries.

## Serious adverse events

21 trials randomizing a total of 8789 participants reported the proportion of participants with a serious adverse event. Meta-analysis showed that rhythm control strategies versus rate control strategies significantly increased the risk of a serious adverse event (RR 1.10; 95% CI 1.02 to 1.18; P=0.02; $I^2$=12%; Bayes factor = $1.05^{e9}$; Fig 4). Visual inspection of the forest plot did not show signs of heterogeneity (Fig 4). The TSA showed that there was not enough information to confirm or reject a RRR of 15% (TSA-adjusted CI 0.99 to 1.22) (Fig 5). Incomplete outcome data bias alone had the potential to influence the results in the 'best-worst case'-scenario (S4 and S5 Figs). Visual inspection of the funnel plot showed a bit asymmetry (S6 Fig), but Harbord's test showed no significance (P=0.63).

**Fig 4. Forest plot of the meta-analysis of serious adverse events.** Meta-analysis showed that rhythm control strategies versus rate control strategies significantly increased the risk of a serious adverse event.

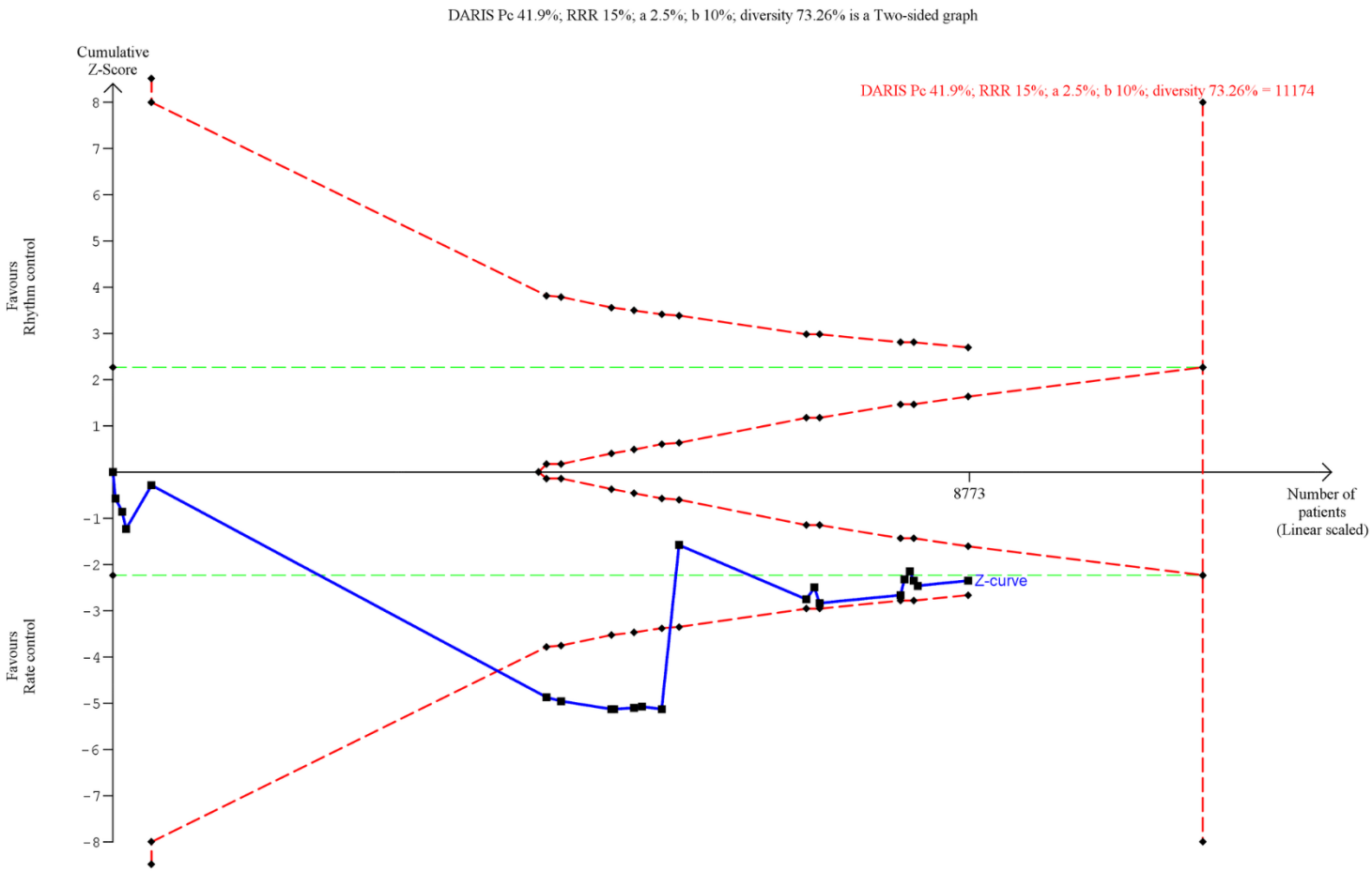


**Fig 5. Trial Sequential Analysis of serious adverse events.** Trial Sequential Analysis (TSA) of serious adverse events showed that there was not enough information to confirm or reject a RRR of 15% (TSA-adjusted confidence interval 0.99 to 1.22). The Z-curve (the blue line) does not cross any boundaries.

We have summarized the specific types of serious adverse events in each trial in S4 Table.

We did not include hospitalization for non-acute electrical cardioversion or hospitalization for elective antiarrhythmic drug loading as a serious adverse event, as readmission for non-acute electrical cardioversion and readmission for elective antiarrhythmic drug loading in most trials was mandated by the individual trial protocols (see 'Discussion').

The four primary components of the composite outcome serious adverse event (excluding all-cause mortality and stroke) were myocardial infarction, heart failure, ventricular tachycardia, and hospitalization (excluding hospitalization for non-acute electrical cardioversion and hospitalization for elective antiarrhythmic drug loading). Meta-analysis of either myocardial infarction, heart failure, ventricular tachycardia, or hospitalization (excluding hospitalization for non-acute electrical cardioversion and hospitalization for elective antiarrhythmic drug loading) showed no significant difference between rhythm control strategies and rate control strategies (S7-S10 Figs).

## Subgroup analysis for all-cause mortality and serious adverse events

All the planned tests for subgroup differences when analyzing both all-cause mortality (S11-S15 Figs) and serious adverse events (S16-S20 Figs) showed no significant differences. Two of the planned subgroup analyses (comparison of participants with atrial fibrillation to those with atrial flutter; and comparison of trials only randomizing men to trials only randomizing women) were not possible to conduct due to lack of relevant data. The post hoc subgroup analysis (comparison of participants with heart failure to participants without heart failure) also showed no significant differences when analyzing all-cause mortality (S21 Fig) and serious adverse events (S22 Fig).

## Quality of life

Quality of life was only assessed in 13 out of 24 trials and different assessment scales were used, including SF-36, Minnesota Living with Heart Failure Questionnaire, Kansas City Cardiomyopathy Questionnaire, Psychological General Well-Being Index, and Mental Health Inventory. All trials reported standard deviations for their analyses. Hence, we did not need to impute standard deviations.

Only data from SF-36 physical component score, SF-36 mental component score, and Minnesota Living with Heart Failure Questionnaire could be used in meta-analyses. The only meta-analysis showing a statistically significant result was the analysis of the results of SF-36 physical component score (MD 6.93 points in favor

of the rhythm control group; 95% CI 2.25 to 11.61; P=0.004; $I^2$=95%; Bayes factor = 0.022; Fig 6). However, both visual inspection of the forest plot (Fig 6) and the statistical tests showed considerable heterogeneity ($I^2$=95%), and the TSA showed that there was not enough information to confirm or reject a MD of 4.81 points (TSA-adjusted CI -3.16 to 17.02) (Fig 7). Furthermore, incomplete outcome data bias alone had the potential to influence the results (S23 and S24 Figs). The remaining meta-analyses (analysis of SF-36 mental component score and Minnesota Living with Heart Failure Questionnaire) showed no significant differences (S25 and S26 Figs), and the TSAs showed that there was not enough information to confirm or reject our anticipated intervention effects (S27 Fig). We have summarized all these results in Table 1.

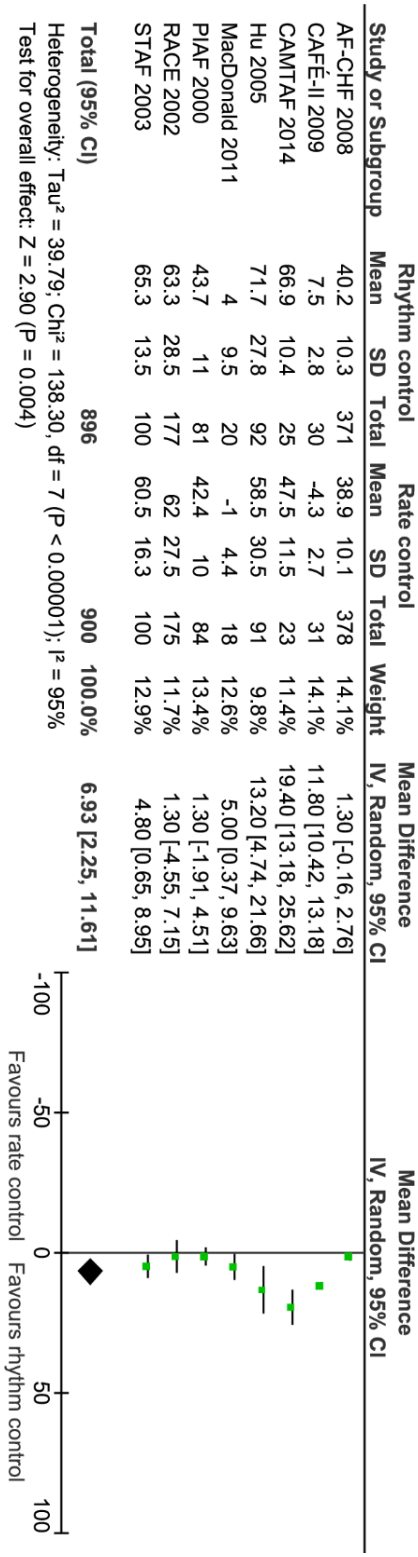


**Fig 6. Forest plot of the meta-analysis of quality of life (the Short Form (36) physical component score (SF-36 PCS)).** Meta-analysis showed that rhythm control strategies versus rate control strategies significantly increased the quality of life measured by SF-36 PCS.

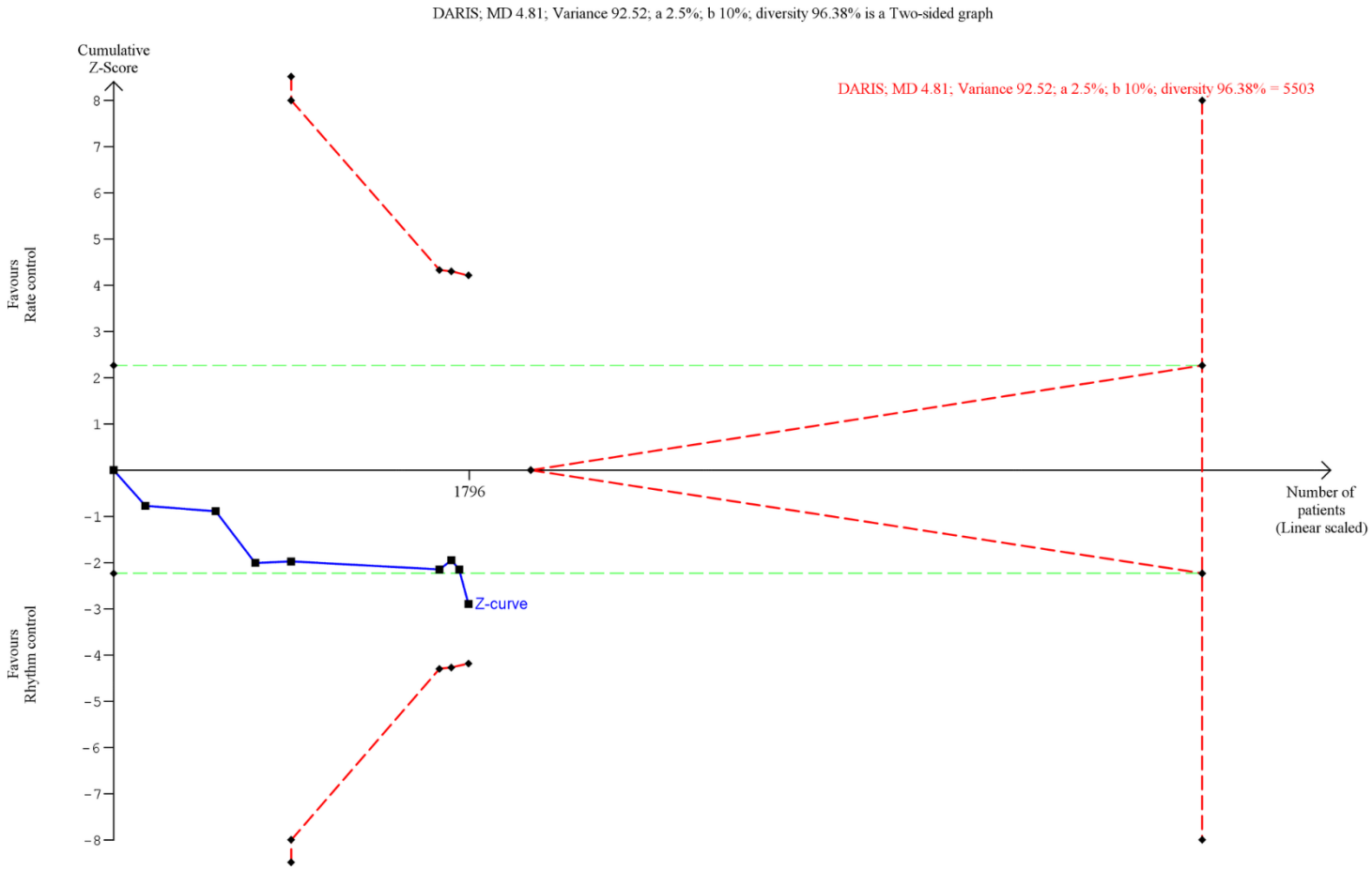


**Fig 7. Trial Sequential Analysis of quality of life (the Short Form (36) physical component score (SF-36 PCS)).** Trial Sequential Analysis showed that there was not enough information to confirm or reject a mean difference of 4.81 points (TSA-adjusted confidence interval -3.16 to 17.02). The Z-curve (the blue line) does not cross any boundaries.

**Table 1. Quality of life, results for each type of scale.**

| | Trials | Participants | Mean difference (points) | 95% confidence interval (CI) | Trial Sequential Analysis - adjusted CI | P-value | $I^2$ | Bayes factor | Best-worst case scenario (MD [95% CI]) | Worst-best case scenario (MD [95% CI]) |
|---|---|---|---|---|---|---|---|---|---|---|
| **SF-36 mental component score** | 8 | 1796 | 3.33 | -0.75 to 7.41 | -4.47 to 11.13 | 0.11 | 93% | 0.35 | 8.16 [5.45 to 10.87] | -1.25 [-8.55 to 6.04] |
| **Minnesota Living With Heart Failure Questionnaire** | 6 | 404 | -7.13 | -16.19 to 1.94 | - | 0.12 | 95% | 3.73 | -8.51 [-17.84 to 0.82] | -5.41 [-14.55 to 3.73] |
| **Kansas City Cardiomyopathy Questionnaire** | 1 | 38 | 1.50 | -9.78 to 12.78 | - | 0.79 | - | - | - | - |
| **Psychological General Well-Being Index** | 1 | 56 | -8.9 | -18.16 to 0.36 | - | 0.06 | - | - | - | - |
| **Mental Health Inventory** | 1 | 56 | -0.4 | -2.1 to 1.3 | - | 0.64 | - | - | - | - |

# Stroke

13 trials randomizing a total of 8114 participants reported the proportion of participants with stroke. Meta-analysis showed no significant difference between rhythm control strategies versus rate control strategies (RR 1.04; 95% CI 0.78 to 1.38; P=.78; $I^2$=9%; Fig 8). Visual inspection of the forest plot did not show signs of heterogeneity (Fig 8). The TSA showed that there was not enough information to confirm or reject a RRR of 15% (TSA-adjusted CI 0.33 to 3.28) (Fig 9). Incomplete outcome data bias alone did not have the potential to influence the results (S28 and S29 Figs).

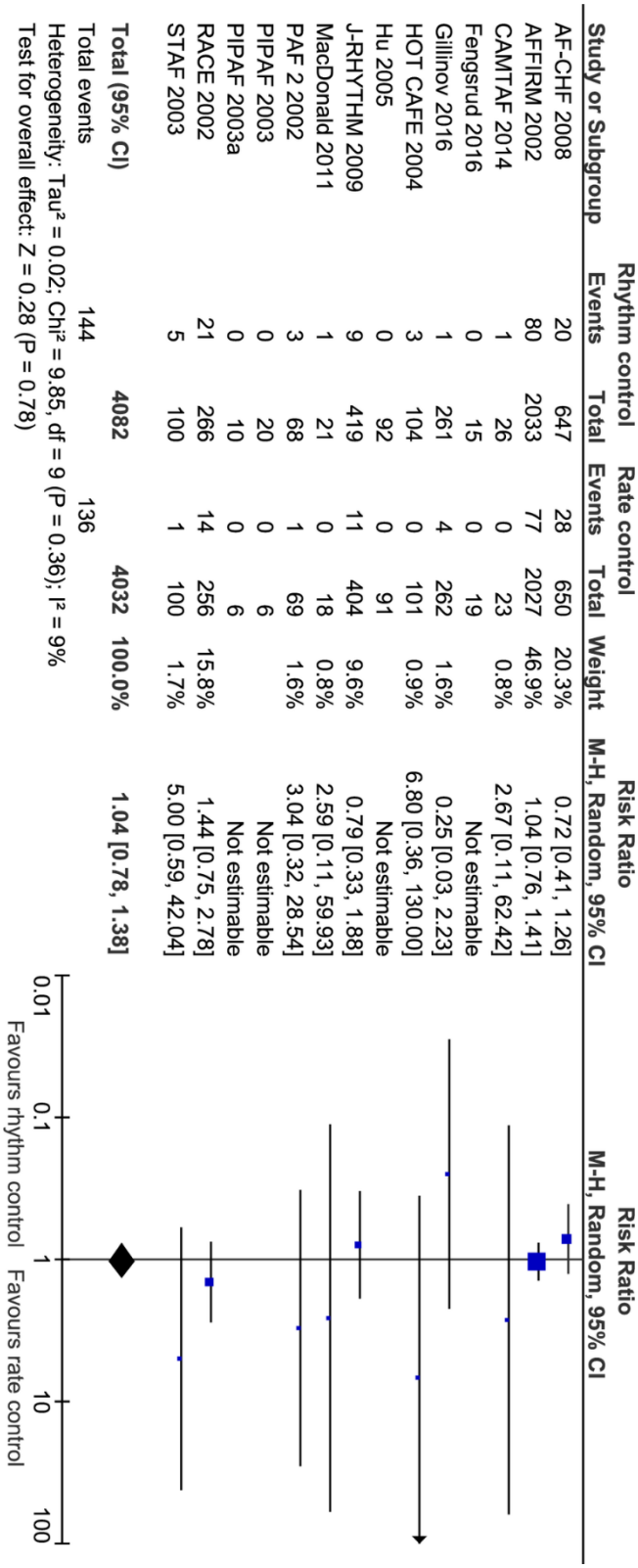


**Fig 8. Forest plot of the meta-analysis of stroke.** Meta-analysis showed no significant difference between rhythm control strategies and rate control strategies when assessing stroke.

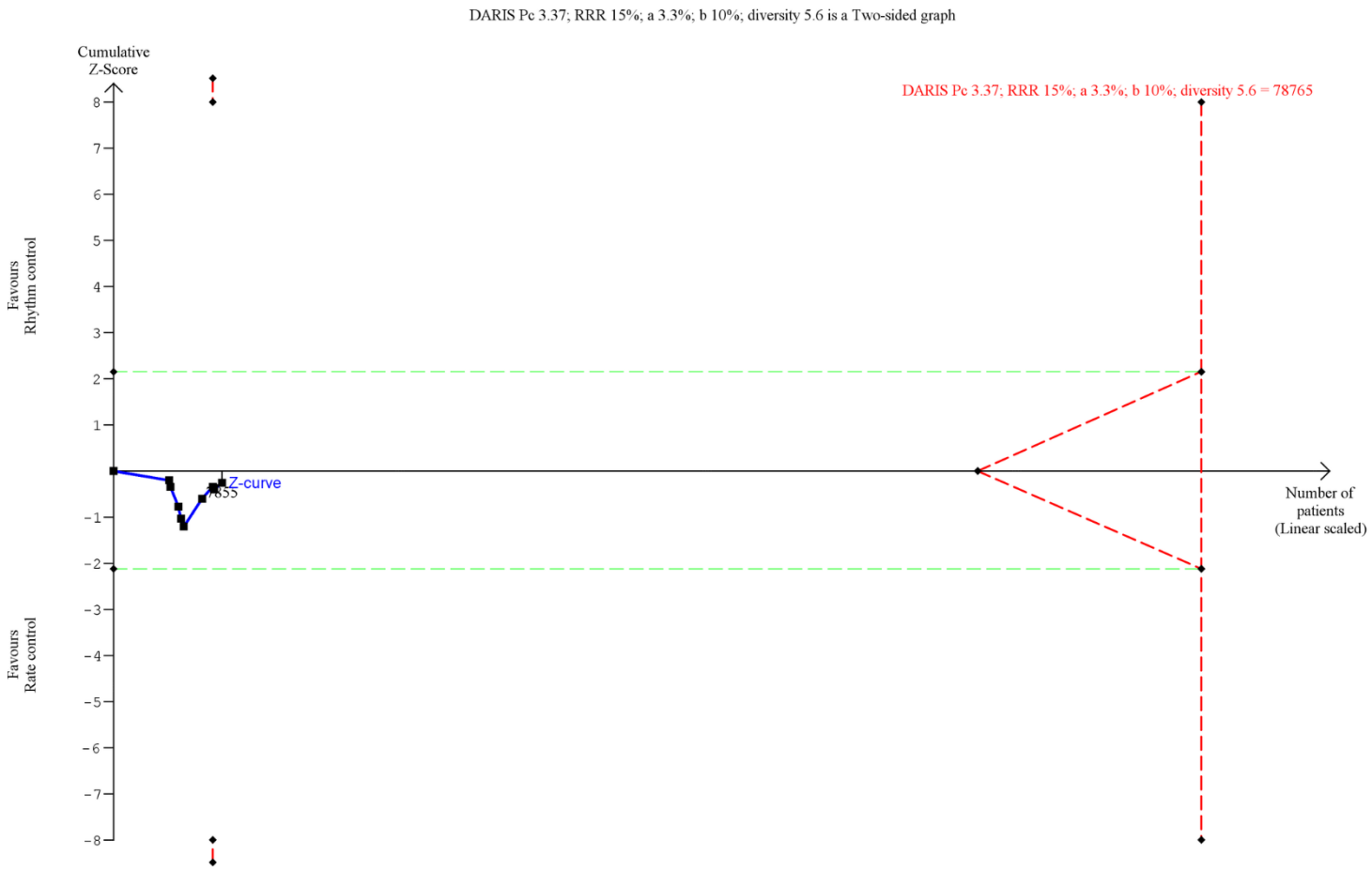


**Fig 9. Trial Sequential Analysis of stroke.** Trial Sequential Analysis (TSA) showed that there was not enough information to confirm or reject a risk ratio reduction of 15% (TSA-adjusted confidence interval 0.33 to 3.28). The Z-curve (the blue line) does not cross any boundaries.

## Ejection fraction

Seven trials randomizing a total of 428 participants assessed the effects of rhythm control strategies versus rate control strategies on ejection fraction. Meta-analysis showed that rhythm control strategies versus rate control strategies significantly increased the mean ejection fraction (MD 4.20%; 95% CI 0.54 to 7.87; P=0.02; $I^2$=79%; Fig 10). Visual inspection of the forest plot showed some signs of heterogeneity (Fig 10). The TSA showed that there was not enough information to confirm or reject a MD of 4.20% (TSA-adjusted CI -2.37 to 10.77) (Fig 11). Incomplete outcome data bias alone had the potential to influence the results in the 'worst-best case' scenario (S30 and S31 Figs).

**Fig 10. Forest plot of the meta-analysis of ejection fraction.** Meta-analysis showed that rhythm control strategies versus rate control strategies significantly increased the ejection fraction.

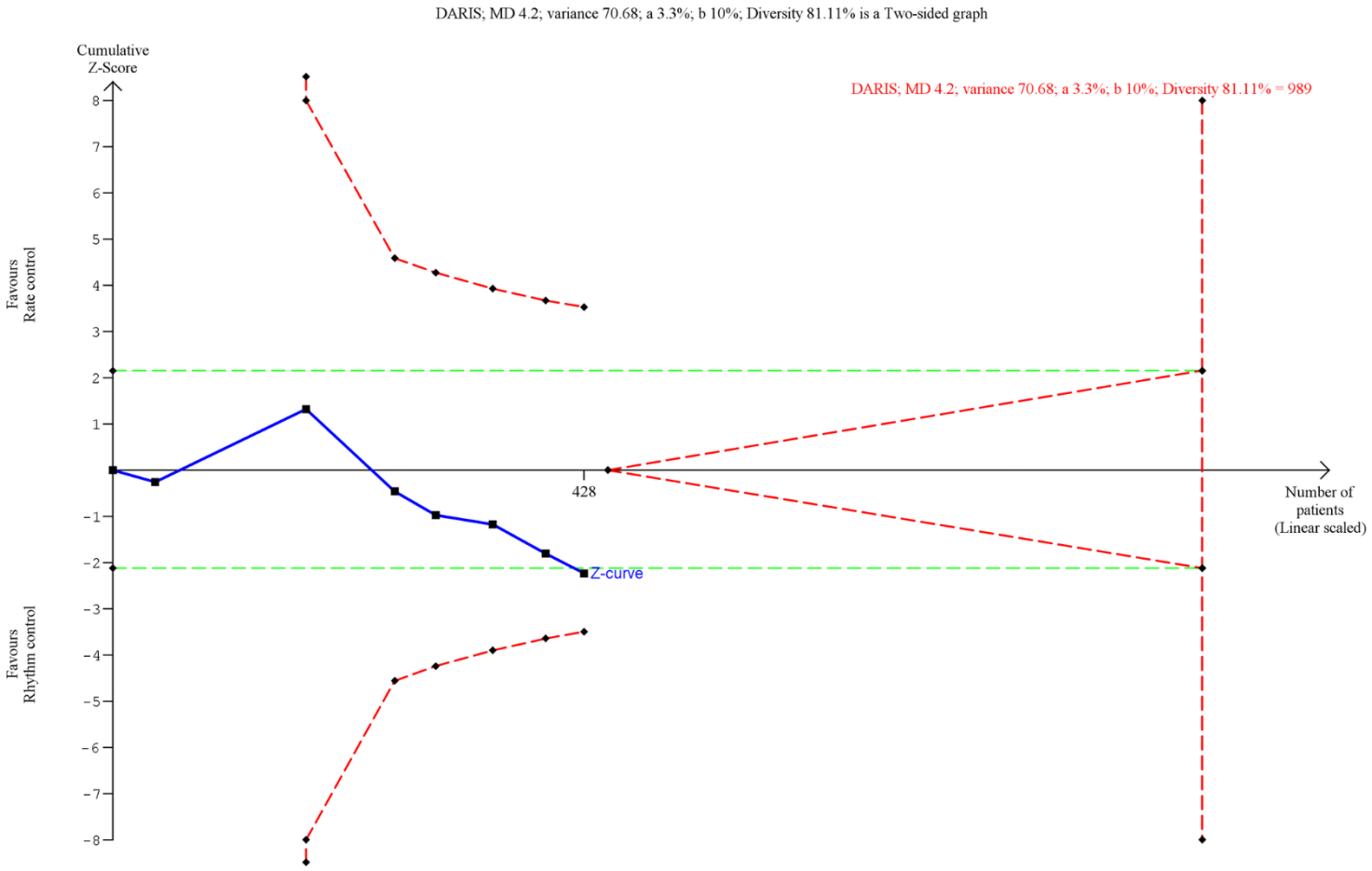


**Fig 11. Trial Sequential Analysis of ejection fraction.** Trial Sequential Analysis (TSA) showed that there was not enough information to confirm or reject a mean difference of 4.20% (TSA-adjusted confidence interval -2.37 to 10.77). The Z-curve (the blue line) does not cross any boundaries.

We have summarized our main results in the Summary of Findings table (Table 2).

**Table 2. Summary of Findings table.**

| Summary of Findings table | | | | | | |
|---|---|---|---|---|---|---|
| **Outcomes** | **Anticipated absolute effects** | | **Relative effect (Trial Sequential Analysis-adjusted confidence interval)** | **№ of participants (trials)** | **Quality of the evidence (GRADE)** | **Comments** |
| | **Risk with rhythm control strategy** | **Risk with rate control strategy** | | | | |
| All-cause mortality | 141 per 1000 | 134 per 1000 | 1.05 (0.90 to 1.12) | 8668 (18 trials) | ⊕⊖⊖⊖ - Very low quality of evidence caused by risk of bias (-2) and imprecision (-1). | Trial Sequential Analysis showed that there was not enough information to confirm or reject a RRR of 15% or more. All trials had high risk of bias, mostly because of 'blinding of participants and personnel', 'incomplete outcome data bias', and 'for-profit bias'. |
| Serious adverse events | 462 per 1000 | 419 per 1000 | 1.10 (0.99 to 1.22) | 8789 (21 trials) | ⊕⊖⊖⊖ - Very low quality of evidence caused by risk of bias (-2) and imprecision (-1). | Trial Sequential Analysis showed that there was not enough information to confirm or reject a RRR of 15% or more. All trials had high risk of bias, mostly because of 'blinding of participants and personnel', 'incomplete outcome data bias', and 'for-profit bias'. |
| Quality of life | Quality of life showed a significant effect of rhythm control versus rate control on the SF-36 physical component score (MD 6.93, Trial Sequential Analysis-adjusted confidence interval -3.16 to 17.0). | | | 1796 (8 trials) for SF-36 physical component score | ⊕⊖⊖⊖ - Very low quality of evidence caused by risk of bias (-2), imprecision (-1), and inconsistency (-1). | Trial Sequential Analysis for all 3 meta-analyses showed that there was not enough information to confirm or reject our anticipated intervention effects. All trials had high risk of bias, mostly because of 'blinding of participants and personnel', 'incomplete outcome data bias', and 'for-profit bias'. All meta-analysis had high levels of heterogeneity. However, the differences were mostly between low and high intervention effects (i.e., not very serious inconsistency). |
| | The meta-analyses of SF-36 mental component score showed nonsignificant results (MD 3.33, Trial Sequential Analysis-adjusted confidence interval -4.47 to 11.1). | | | 1796 (8 trials) for SF-36 mental component score | | |
| | The meta-analysis of Minnesota Living With Heart Failure Questionnaire showed nonsignificant results (MD -7.13, 95% CI -16.2 to 1.94). | | | 404 (6 trials) for Minnesota Living With Heart Failure Questionnaire | | |
| Stroke | 35 per 1000 | 34 per 1000 | 1.04 (0.33 to 3.28) | 8114 (13 trials) | ⊕⊖⊖⊖ - Very low quality of evidence caused by risk of bias (-2), imprecision (-1), and publication bias (-1). | Trial Sequential Analysis showed that there was not enough information to confirm or reject a RRR of 15% or more. All trials had high risk of bias, mostly because of 'blinding of participants and personnel', 'incomplete outcome data bias', and 'for-profit bias'. |

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| Ejection fraction | Rhythm control strategies versus rate control strategies significantly increased the mean ejection fraction (MD 4.20, Trial Sequential Analysis-adjusted confidence interval -2.37 to 10.8). | 428 (7 trials) | ⊕⊖⊖⊖ - Very low quality of evidence caused by risk of bias (-2), imprecision (-1), and inconsistency (-1). | Trial Sequential Analysis showed that there was not enough information to confirm or reject our anticipated intervention effects. All trials had high risk of bias, mostly because of 'blinding of participants and personnel', 'incomplete outcome data bias', and 'for-profit bias'. All meta-analysis had high levels of heterogeneity. However, the differences were mostly between low and high intervention effects (i.e., not very serious inconsistency). |

Table 2 legend: Summary of Findings table based on GRADE [15, 38-40]. The Summary of Findings table summarizes our main results and use five GRADE criteria (risk of bias; inconsistency of results; indirectness of evidence; imprecision; and publication bias) to assess the quality of the body of evidence.

# Discussion

We included 25 trials randomizing a total of 9354 participants with 26 comparisons of rhythm control strategies versus rate control strategies. All trials and outcome results were at high risk of bias and the quality of the evidence according to GRADE was 'very low' (see Summary of Findings table (Table 2)).

## Statement of principal findings

The meta-analysis of serious adverse events showed that rhythm control strategies versus rate control strategies significantly increased the risk of serious adverse events by approximately 10%, but TSA did not confirm this result. The increased risk of a serious adverse event did not seem to be driven by a particular component of the composite outcome. The meta-analyses of quality of life (SF-36 physical component score) and ejection fraction both showed a statistically significant effect in favor of the rhythm control group. However, TSAs showed that we did not have enough information to confirm or reject our anticipated intervention effects and the clinical relevance of an increase of 6.93 points on SF-36 physical component score and an increase of 4.20% in ejection fraction is questionable. No significant differences between rhythm control strategies and rate control strategies were found when assessing all-cause mortality, quality of life assessed by SF-36 mental component score, quality of life assessed by Minnesota Living with Heart Failure Questionnaire, or stroke – and all corresponding TSAs showed that there was not enough information to confirm or reject our anticipated intervention effects.

## Strengths and limitations of the systematic review

Our review has several strengths. We included more participants than any previous review which gives us increased power and precision to detect any significant difference between our compared treatment strategies [21, 22]. We followed our protocol which was registered prior to the systematic literature search [21, 22]. Data were double-extracted by independent authors minimizing the risk of inaccurate data-extraction, and we assessed the risk of bias in all trials according to Cochrane [18]. We used GRADE to assess the quality of the evidence [38-40], TSA to assess the risks of random errors [15, 16, 21, 22, 27-35], the eight-step assessment suggested by Jakobsen et al. to assess if the thresholds for significance were crossed [15], and sensitivity analyses (best-worst and worst-best) to test the potential impact of incomplete outcome data bias. Hence, this systematic review considered both risks of random errors and risks of systematic errors which adds further robustness to our results and conclusions. Another strength of our review is that we pragmatically accepted any rhythm control strategy and any rate control strategy – our results may therefore guide a clinician when choosing between the treatment strategies. The main result of this review is the apparent increased risk of a serious adverse event when using rhythm control strategies and the statistical heterogeneity of this meta-analysis result was low ($I^2$=12%). Hence, the included trials seem to show very similar results which increase the validity of the meta-analysis result.

As mentioned in the results section, we did not plan to include hospitalization for non-acute electrical cardioversion or hospitalization for elective antiarrhythmic drug loading as a serious adverse event, but it might be argued that any hospitalization ought to be considered a serious adverse event [24]. If we had included hospitalization for non-acute electrical cardioversion and hospitalization for elective antiarrhythmic drug loading, which in multiple trials were mandated by their protocol, the increased risk of a serious adverse event in the rhythm control group would be even greater. A post hoc meta-analysis confirmed this assumption (S32 Fig). Our results after excluding hospitalization for non-acute electrical cardioversion and hospitalization for elective antiarrhythmic drug loading as a serious adverse event were still significant which also increase the validity of our results.

Our review also has several limitations. All trials were at high risk of bias and especially the risk of incomplete blinding of participants and personnel and for-profit bias might bias our review results. Our assessment of especially publication bias was also uncertain, as a relatively low number of trials were included. Furthermore, some of the performed meta-analyses had considerable statistical heterogeneity. Hence, publication bias and heterogeneity might further bias our results. Large meta-epidemiological studies have shown that high risks of bias tend to overestimate benefits and underestimate harms of experimental interventions [106-112]. We hypothesized that the rhythm control strategy in most trials may be regarded as the experimental group and that the risk of a serious adverse event when using rhythm control strategies

might be even higher than our results show due to the risk of bias. When assessing the overall quality of the available evidence, GRADE assessment showed that the quality of the evidence was 'very low' for all outcomes, mostly due to risk of bias, imprecision, and inconsistency (see Summary of Findings table (Table 2)). Another limitation of our present review is the use of a composite outcome such as serious adverse events. A potential limitation when using composite outcomes is that each component of a composite outcome (in this case serious adverse events) will not necessarily have similar degrees of severity and will not be affected similarly by the interventions [113]. 'True' differences in severity between compared groups might therefore not be reflected in review results when using composite outcomes [113]. Several of the included trials did not specify the type of serious adverse events but it was, e.g., often just reported that a given patient was hospitalized (S4 Table). Hence, it was difficult to assess severity differences between the compared groups when assessing risks of serious adverse events. We believe that the clinical relevance of the outcome 'serious adverse events' and the resulting increased statistical power when using serious adverse events as an outcome justifies the use of serious adverse events as a primary outcome, but the interpretative limitations ought to be considered. A further limitation of our review is that we considered rhythm control strategies and rate control strategies as two goal-oriented intervention strategies. Due to widely varying interventions within the two groups, we were not able to assess the effects of each single intervention. However, even though the specific treatment elements of both rhythm control strategies and rate control strategies differed across trials (S3 Table), our results on both all-cause mortality and serious adverse events showed very limited statistical heterogeneity and test for subgroup differences showed no significant differences. Furthermore, our results show an averaged effect and if certain specific treatment elements have beneficial effects that differ from our overall meta-analysis results then other treatment elements must have more harmful effects. Nevertheless, it might be that certain single treatment elements have effects that are not shown by our analyses. The results on quality of life and ejection fraction had very large degrees of statistical heterogeneity and were especially at high risk of selective outcome reporting bias. Accordingly, these results should be interpreted with great caution.

The higher risk of a serious adverse event in the rhythm control group might be caused by incorrect use of anticoagulation therapy in the rhythm control group, i.e., physicians might avoid prescribing appropriate anticoagulation therapy if the patient has obtained sinus rhythm. We performed several subgroup analyses comparing trials with different recommendations for anticoagulation therapy (anticoagulation therapy until sinus rhythm for at least 4 weeks compared to anticoagulation therapy until sinus rhythm for at least 12 weeks compared to anticoagulation therapy until end of follow-up) (S20 Fig). No subgroup differences were found. Additionally, we found no difference between rhythm control strategies and rate control strategies when assessing stroke and the point estimate was very close to 1.00 (1.04) (Fig 8). If the participants in the

rhythm control group had received insufficient anticoagulation therapy, we would have expected a higher risk of stroke in the rhythm control group.

## Strengths and limitations in relation to other systematic reviews and observational studies

We have identified multiple systematic reviews of randomized clinical trials assessing the effects of rhythm control strategies versus rate control strategies in patients with atrial fibrillation or atrial flutter [114-121]. The most recent review, made by Al-Khatib et al., was published in 2014 [114]. They included 16 trials randomizing 7608 participants and showed comparable efficacy of rhythm control strategies and rate control strategies [114]. The other previous reviews showed similar findings [115-119, 121], except Testa et al. who showed that rhythm control strategies versus rate control strategies significantly increased the risk of the combined outcome of all-cause mortality and stroke by OR at 1.15 [120]. However, their meta-analysis only included five trials randomizing 5239 participants [120]. We did not plan to assess this composite outcome but a post hoc meta-analysis assessing this composite outcome did not show any significant difference between rhythm control strategies and rate control strategies (S33 Fig). Our present review is the first systematic review of randomized clinical trials showing that rhythm control strategies versus rate control strategies significantly increases the risk of a serious adverse event. Furthermore, no clinically significant beneficial effect of rhythm control strategies versus rate control strategies was found.

We have also identified multiple observational studies assessing the effects of rhythm control strategies versus rate control strategies in patients with atrial fibrillation or atrial flutter [122-125], but these studies showed conflicting results. Comparable to our findings, Noheria et al. included 6988 participants and showed comparable efficacy of rhythm control strategies and rate control strategies when assessing all-cause mortality, heart failure, and stroke, but rhythm control strategies significantly increased the risk of cardiovascular hospitalizations [122]. Contrary to our findings, Ionescu-Ittu et al. included 26 130 participants and showed comparable efficacy of the strategies when assessing all-cause mortality within four years of treatment onset, but five and eight years after treatment onset rate control strategies significantly increased the risk of dying [123]. Furthermore, Camm et al. included 5604 participants and showed that rhythm control strategies were superior to rate control strategies when assessing cardiovascular mortality, stroke, and heart failure, but inferior when assessing hospitalization for arrhythmia [124]. A fourth study, Purmah et al., included 1391 participants and showed comparable efficacy of the strategies when assessing all-cause mortality [125]. The different results between these observational studies might be caused by, e.g., different

inclusion- and exclusion criteria, baseline confounding factors, and confounding by unmeasured variables [113, 126]. Accordingly, observational studies may or may not support our findings.

## Comparison to current guidelines and recent narrative reviews

Current guidelines and recent narrative reviews recommend that a rate control strategy should be used in most patients, while a rhythm control strategy is indicated only to improve symptoms in patients who remain symptomatic on adequate rate control therapy [12, 13, 127-129]. Our results confirm this recommendation and further indicate that rhythm control strategies seem to be more harmful than rate control strategies without any meaningful beneficial effect of rhythm control strategies. Nevertheless, January et al. reports that a rhythm control strategy might be favored in specific patient subgroups. We performed several relevant subgroup analyses and found no significant differences. Moreover, no randomized clinical trial has investigated the effect of rhythm control strategies versus rate control strategies in young patients, and the other subgroup analyses had limited data. Hence, we were not able to investigate if specific patient subgroups differed compared to our main results.

## The possible contribution of ongoing trials

We identified eight ongoing trials (see S3 Table) that might contribute to the current evidence on rhythm control strategies versus rate control strategies for atrial fibrillation [103-105]. These ongoing trials will contribute to the evidence on all-cause mortality, hospitalization, stroke, quality of life, and ejection fraction. Furthermore, AFARC-LVF (NCT02509754), EAST-AFNET 4 [103], and RAFT-AF [105] will focus on the effect of catheter ablation as a rhythm control strategy. These three trials will provide evidence on whether or not catheter ablation is superior to rate control. All ongoing and future trials should be conducted with low risk of systematic error and low risk of random errors, and ought to be designed and reported according to the SPIRIT and CONSORT guidelines [130, 131].

# Conclusions

There might be specific reasons why certain patients with atrial fibrillation ought to be offered a rhythm control strategy aiming at obtaining and maintaining sinus rhythm (e.g., patients with unbearable symptoms due to atrial fibrillation, patients who are hemodynamically unstable due to atrial fibrillation, or patients who are symptomatic even after adequate rate control). Nevertheless, a rhythm control strategy often includes multiple interventions (e.g., antiarrhythmic therapy, electrical cardioversion, etc.) and our results show that

rhythm control strategies seem to offer more harm than benefit in patients with atrial fibrillation. We conclude that more randomized clinical trials with low risk of bias and low risk of play of chance are needed, but based on current evidence, it seems that most patients with atrial fibrillation should be treated with a rate control strategy unless there are specific reasons justifying a rhythm control strategy.

# Differences between the protocol and the review

We changed our subgroup “age of participants: 0 to 59 years, 60-79 years, and above 80 years” to “mean age of the participants: 0 to 59 years, 60-79 years, and above 80 years”, as the former was not possible to conduct due to lack of data.

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# Supporting information

**S1 Text. PRISMA Checklist.**

**S2 Text. Prepublished protocol for this systematic review.**

**S3 Text. Search strategy for MEDLINE (OVIDSP; 1946 to October 2016).**

**S1 Fig. Forest plot of 'best-worst case' scenario for all-cause mortality.**

**S2 Fig. Forest plot of 'worst-best case' scenario for all-cause mortality.**

**S3 Fig. Funnel plot of all-cause mortality.**

**S4 Fig. Forest plot of 'best-worst case' scenario for serious adverse events.**

**S5 Fig. Forest plot of 'worst-best case' scenario for serious adverse events.**

**S6 Fig. Funnel plot for serious adverse events.**

**S7 Fig. Forest plot for myocardial infarction.**

**S8 Fig. Forest plot for heart failure.**

**S9 Fig. Forest plot for ventricular tachycardia.**

**S10 Fig. Forest plot for hospitalization (excluding hospitalization for non-acute electrical cardioversion and hospitalization for elective antiarrhythmic drug loading).**

**S11 Fig. Forest plot of the comparison of different types of rhythm control interventions for all-cause mortality.**

**S12 Fig. Forest plot of the comparison of different types of rate control interventions for all-cause mortality.**

**S13 Fig. Forest plot of the comparison of trials with different mean ages for all-cause mortality.**

**S14 Fig. Forest plot of the comparison of different durations of atrial fibrillation for all-cause mortality.**

**S15 Fig. Forest plot of the comparison of different durations of anticoagulation therapy for all-cause mortality.**

**S16 Fig. Forest plot of the comparison of different types of rhythm control interventions for serious adverse events.**

**S17 Fig. Forest plot of the comparison of different types of rate control interventions for serious adverse events.**

**S18 Fig. Forest plot of the comparison of trials with different mean ages for serious adverse events.**

**S19 Fig. Forest plot of the comparison of trials with different durations of atrial fibrillation for serious adverse events.**

**S20 Fig. Forest plot of the comparison of trials with different durations of anticoagulation therapy for serious adverse events.**

**S21 Fig. Forest plot of the comparison of participants with heart failure to participants without heart failure for all-cause mortality.**

**S22 Fig. Forest plot of the comparison of participants with heart failure to participants without heart failure for serious adverse events.**

**S23 Fig. Forest plot of 'best-worst case' scenario for quality of life (SF-36 physical component score).**

**S24 Fig. Forest plot of 'worst-best case' scenario for quality of life (SF-36 physical component score).**

**S25 Fig. Forest plot for quality of life (SF-36 mental component score).**

**S26 Fig. Forest plot for quality of life (Minnesota Living With Heart Failure Questionnaire).**

**S27 Fig. Trial Sequential Analysis for Quality of life (SF-36 mental component score).**

**S28 Fig. Forest plot of 'best-worst case' scenario for stroke.**

**S29 Fig. Forest plot of 'worst-best case' scenario for stroke.**

**S30 Fig. Forest plot of 'best-worst case' scenario for ejection fraction.**

**S31 Fig. Forest plot of 'worst-best case' scenario for ejection fraction.**

**S32 Fig. Forest plot for serious adverse events with hospitalization (including hospitalization for non-acute electrical cardioversion and hospitalization for elective antiarrhythmic drug loading).**

**S33 Fig. Forest plot of the composite outcome for all-cause mortality and stroke.**

**S1 Table. Bias risk assessment of each included trial.**

**S2 Table. Inclusion- and exclusion criteria for each included trial.**

**S3 Table. Trial characteristics of each included, excluded, and ongoing trial.**

**S4 Table. Specific types of serious adverse events in each trial.**