COMPARATIVE EFFICACY OF MAINTENANCE OF SINUS RHYTHM VERSUS RATE CONTROL STRATEGIES IN THE TREATMENT OF ATRIAL FIBRILLATION – SYSTEMATIC REVIEW AND META-ANALYSES

HTA Consulting

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Wojciechowski P[1], Stozek A[1], Machowska A[1], Gaweska M[1], Lis J[1], Glasek M[2], Rys P[1], Wladysiuk M[1], Plisko R[1]
1 – HTA Consulting, Krakow, Poland; 2 – Sanofi Poland, Warszawa, Poland

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www.hta.pl

Introduction

Efficacy of antiarrhythmic drugs (AAD) in atrial fibrillation (AF) has so far been appraised only with regard to the reduction of AF relapse.

The aim of our study was to compare the strategy of successful maintenance of sinus rhythm (MSR) including AAD (mainly amiodarone, sotalol, disopyramide, propafenone, dofetilide, flecainide) vs. rate control (RC) including pharmacologic agents (calcium channel blockers, beta blockers, cardiac glycosides) with regard to reduction of incidences of death and thromboembolic events in patients with atrial fibrillation (AF) or atrial flutter (AFI).

Methods

Systematic literature search was performed in order to identify RCTs fulfilling following inclusion criteria:
- Population: adult patients (>18 years) with AF or AFI.
- Comparison of treatment strategies: rate control (RC) vs. maintenance of sinus rhythm (MSR).
- Suitable clinical trials:
  - Randomised controlled trials (RCTs)
  - Endpoints (at least 1 included in the study): deaths from any causes, cardiovascular death, stroke, systemic embolism, myocardial infarction, bleedings, hospitalizations, exercise capacity, composite endpoint consisting of at least one of endpoints mentioned above, quality of life, percent of patients with at least one adverse event, prolonged QT interval.
- Studies in English, Polish, French and German were included.

Exclusion criteria included:
- previous or planned cardiovascular surgery, implantation of pacemaker, patients on short regimen prior to cardiovascular surgery, medical treatment used exclusively for cardioversion, method of data analysis excluding all patients from MSR group who were not in sinus rhythm at the end of follow up.

Databases and sources searched from 2002 up to January 2011 included:
- MEDLINE,
- EMBASE,
- The Cochrane Library,
- webpages of associations dealing with cardiovascular diseases (ACC, AHA, ESC),
- Studies published before 2002 were included on the basis of two systematic reviews issued by Cochrane Collaboration[1,2]

Two authors independently reviewed the articles at each stage of the selection.
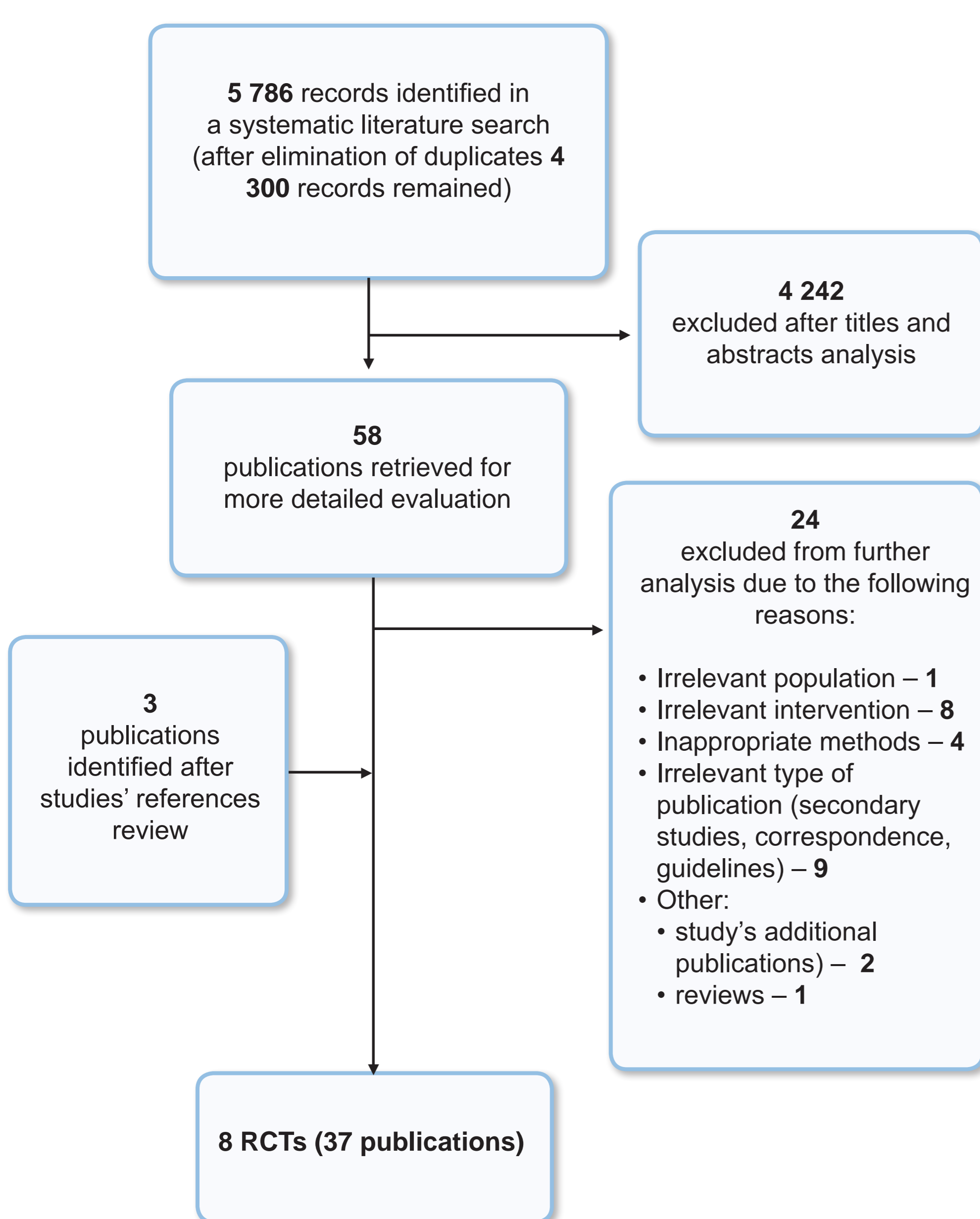
Statistical analyses

- Results of each trial were expressed as relative risk (RR) or relative benefit (RB) with 95% confidence intervals (CI).
- Heterogeneity between studies was assessed with Cochrane Q test with p < 0.1 considered as significant. Heterogeneity was quantitated with I[2] statistics.
- Meta-analyses were performed according to Mantel-Haenszel fixed effect model in case of homogenous data or with DerSimonian random effect model if heterogeneity was significant. Results were considered significant when p < 0.05.

Results

Study flow

The systematic literature search identified 5 786 records of which 1 486 records were eliminated as duplicated titles. After reviewing of titles and abstracts, 58 papers were screened for potential inclusion on the basis of full texts. Of these, 8 RCTs were identified in 34 publications (Figure 1).

Figure 1. Systematic literature search according to QUOROM

5 786 records identified in a systematic literature search (after elimination of duplicates 4 300 records remained)

4 242 excluded after titles and abstracts analysis

58 publications retrieved for more detailed evaluation

24 excluded from further analysis due to the following reasons:
- Irrelevant population – 1
- Irrelevant intervention – 8
- Inappropriate methods – 4
- Irrelevant type of publication (secondary studies, correspondence, guidelines) – 9
- Other:
  - study's additional publications) – 2
  - reviews – 1

3 publications identified after studies' references review

8 RCTs (37 publications)

Study characteristics

All studies included in the analysis were two-armed, comparing MSR with RC strategies in patients with AF. One study (RACE) included patients with AF or AFI. Studies differed with regard to the type of AF and concomitant diseases. Medium follow-up length ranged from 12 to 42 months. *Intention to treat* (ITT) analysis was applied in all trials except for one study (J-RHYTHM) in which *per protocol* (PP) analysis was used. Studies' credibility ranged from low (1 out of 5 points in Jadad scale) to moderate credible (3 out of 5 points in Jadad scale). Due to technical unfeasibility of double blinding all studies were carried out in accordance with open label fashion (Table 1).

**Table 1. Characteristics of RCTs included in the analysis**

Study	Type of AF	Concomitant diseases (>10% of population)	No of patients RC	No of patients MSR	Medium follow-up [months]	Results analysis	AAD used for MSR	Jadad score
AF-CHF [1-3]	persistent	CHF	694	682	37	ITT	amiodarone, sotalol, dofetylide	3
AFFIRM [4-15]	persistent	hypertension, diabetes mellitus, CHF	2027	2033	42	ITT	amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenon, chinidine, sotalol, dofetylide	2
CAFE-II [16]	persistent	heart failure NYHA class ≥2, diabetes mellitus, ischaemic heart disease	31	30	12a	ITT	amiodarone	3
HOT-CAFÉ [17-22]	persistent	hypertension, diabetes mellitus, ischaemic heart disease	101	104	20,4	ITT	propafenon, sotalol, disopyramide, amiodarone	3
J-RHYTHM [23,24]	persistent or paroxysmal	hypertension, diabetes mellitus	404	419	19	PP	pilsicainide, cibenzoline, propafenone, disopyramide, flecainide, aprindine, pirmenol, beridil, amiodarone	1
PIAF [25-27]	symptomatic persistent	hypertension	125	127	12a	ITT	amiodarone	3
RACE [28-35]	recurrent persistent AF or AFI	hypertension, diabetes mellitus, CHF	256	266	27,6	ITT	sotalol, flecainide, propafenon, amiodarone	1
STAF [36, 37]	persistent	hypertension	100	100	RC: 19.7 MSR: 19.5	ITT	class 1 AAD, sotalol, beta-blockers, amiodarone	2

a) complete follow-up period

Deaths

All 8 RCTs that fulfilled the inclusion criteria reported total number of deaths. None of the studies demonstrated statistically significant difference with regard to the number of deaths between RC and MSR groups. Pooled data of 8 RCTs also showed no statistically significant difference between the groups with respect to risk of death regardless of the reason (RR = 1.06 [0.96; 1.17]) (Figure 2).

Figure 2. Relative risk of death for the comparison between MSR and RC groups
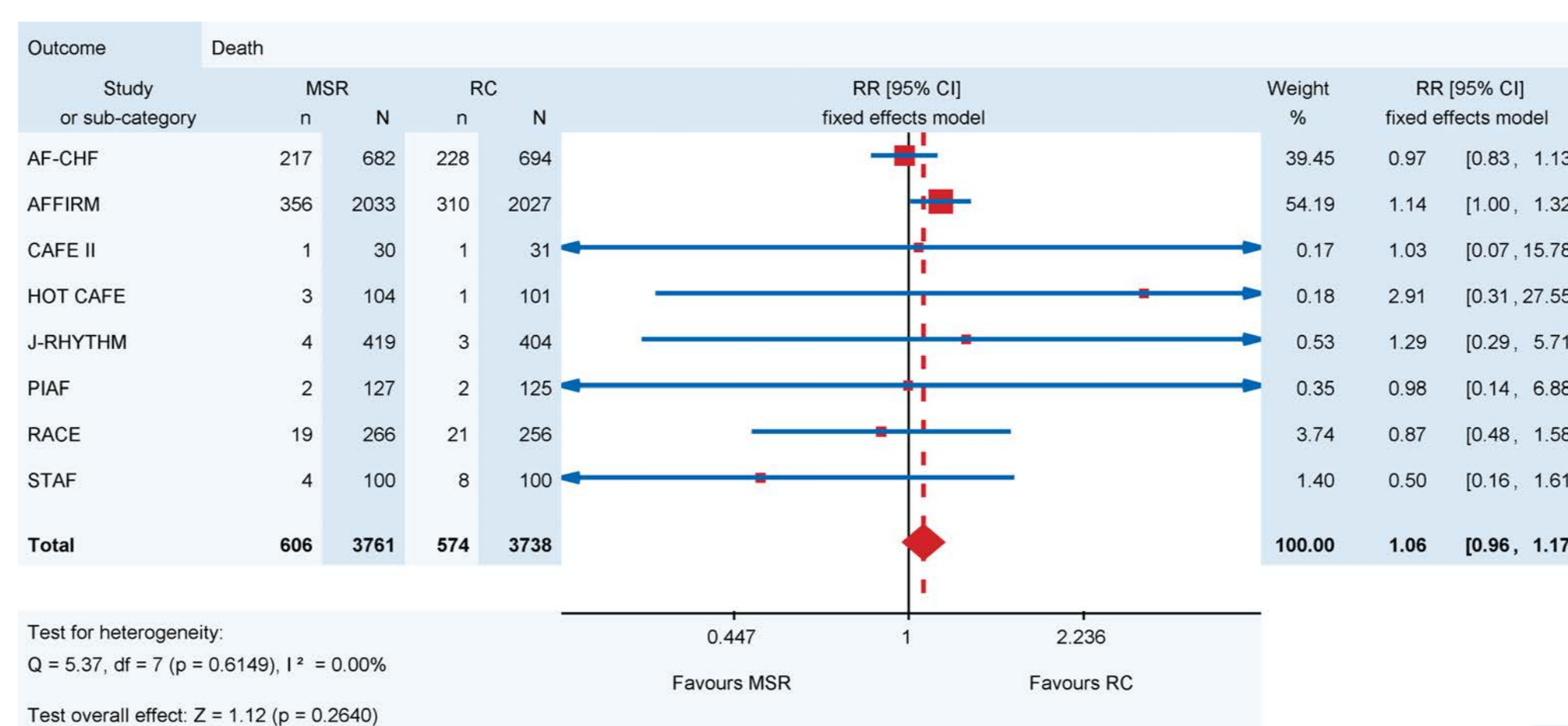
Cardiovascular deaths

Number of cardiovascular deaths was reported in 6 RCTs. None of the studies showed statistically significant difference between the groups. Meta-analysis of 6 RCTs also did not demonstrate significant difference between MSR and RCT strategies with respect to cardiovascular deaths (RR = 1.01 [0.88; 1.16]) (Figure 3).

Figure 3. Relative risk of cardiovascular death for the comparison between MSR and RC groups
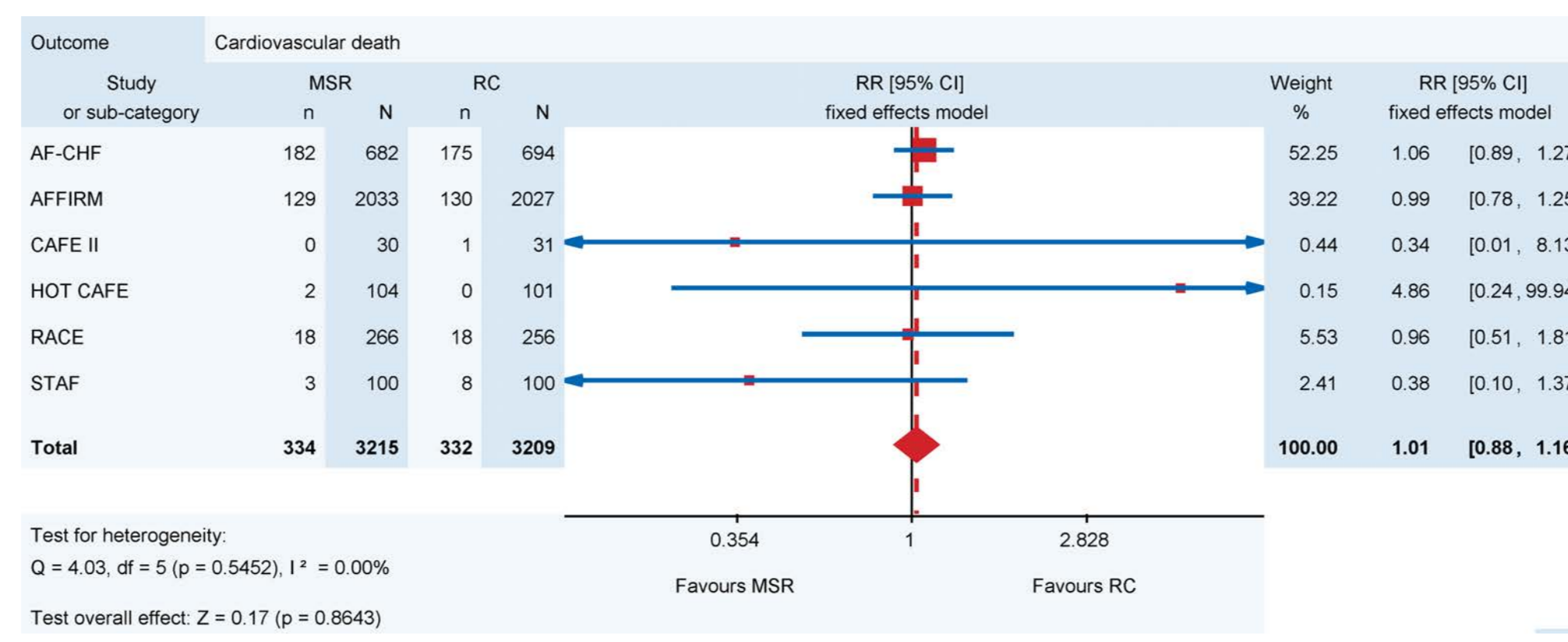
Stroke

Number of strokes was reported in 6 RCTs, however 2 of them (RACE, STAF) reported incidence of stroke as a part of a composite endpoint. Neither separate studies nor the pooled results of 6 RCTs revealed significant differences between the MSR and MSR strategies (RR = 1.02 [0.82; 1.26]) (Figure 4).

Figure 4. Relative risk of stroke for the comparison between MSR and RC groups
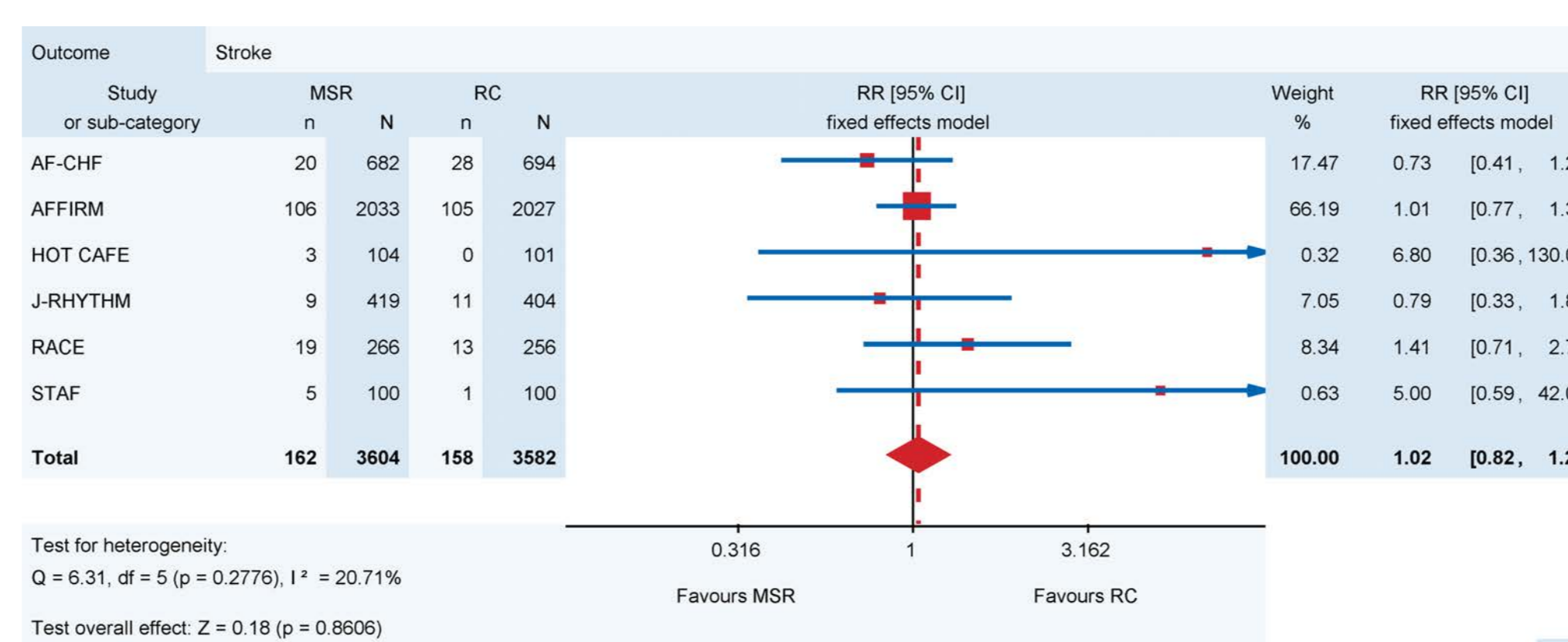
Systemic embolism

Data on risk of systemic embolism incidence was presented in 5 studies. Four RCTs (AFFIRM, J-RHYTHM, RACE, STAF) reported systemic or peripheral embolism whereas in 1 study (HOT-CAFÉ) only single case of pulmonary embolism was recorded. None of the studies showed statistically significant differences between the groups with regard to the incidence of embolism. Meta-analysis of 5 studies also did not demonstrate statistically significant difference between treatment strategies (RR = 0.78 [0.35; 1.71]) (Figure 5).

Figure 5. Relative risk of systemic embolism for the comparison between MSR and RC groups
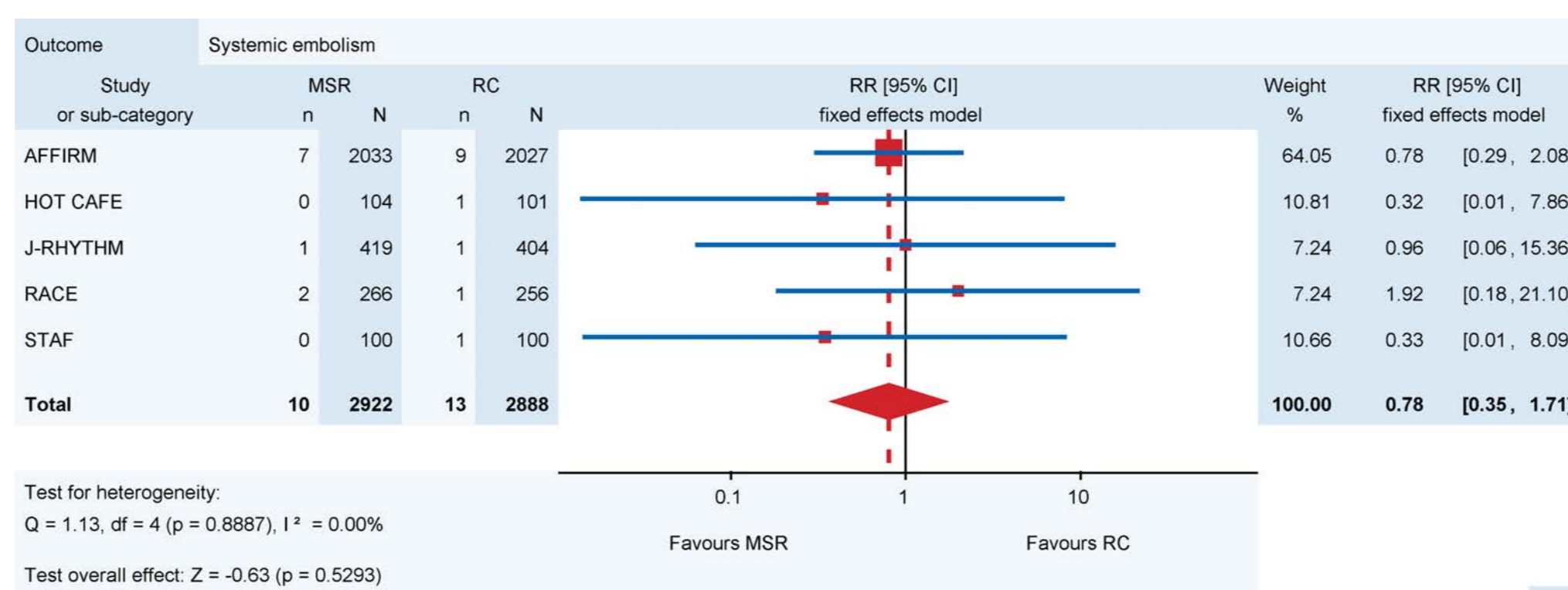
Heart failure

Incidence of heart failure was reported in 4 RCTs, however one of the studies (AFFIRM) reported only percentage of patients who discontinued therapy due to heart failure. None of the RCTs presented statistically significant differences between MSR and RC groups with regard to the incidence of heart failure. Pooled data of 4 RCTs did not show statistically significant differences between strategies (RR = 0.94 [0.80; 1.09]) (Figure 6).

Figure 6. Relative risk of heart failure for the comparison between MSR and RC groups
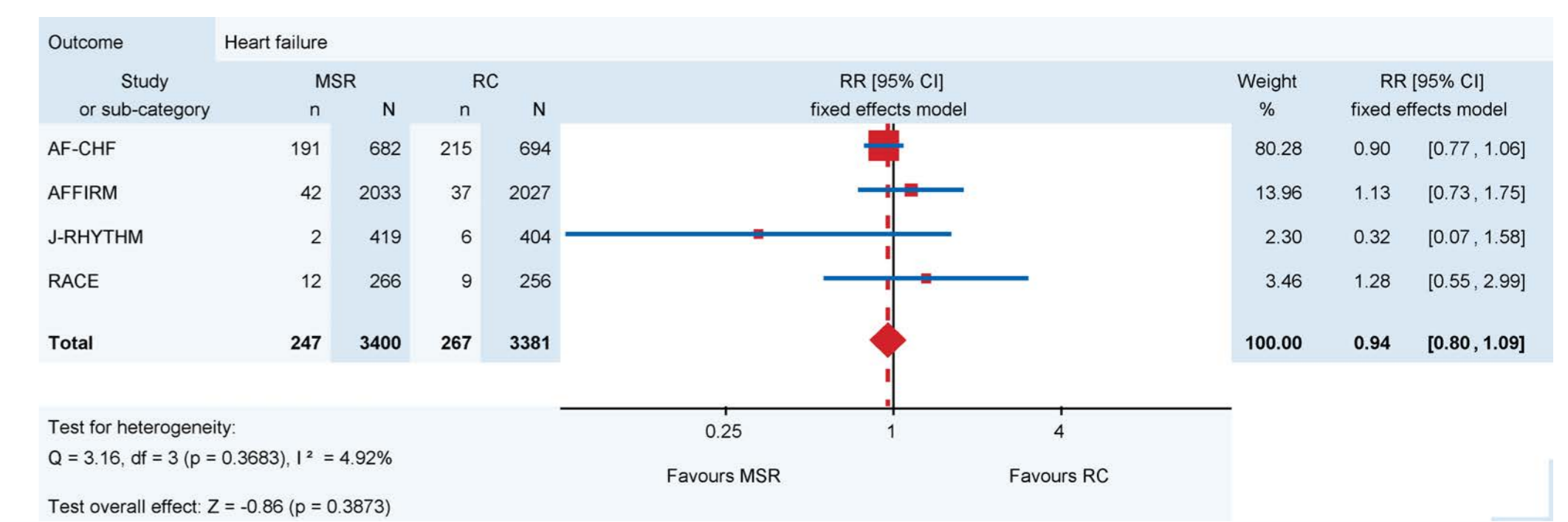
Bleeding

Total number of bleedings was reported in 3 RCTs. None of the studies demonstrated statistically significant difference with regard to number of bleedings occurring in both groups. Meta-analysis of all RCTs did not reveal statistically significant difference between strategies (RR = 1.10 [0.65; 1.84]) (Figure 7).

Figure 7. Relative risk of bleedings for the comparison between MSR and RC groups
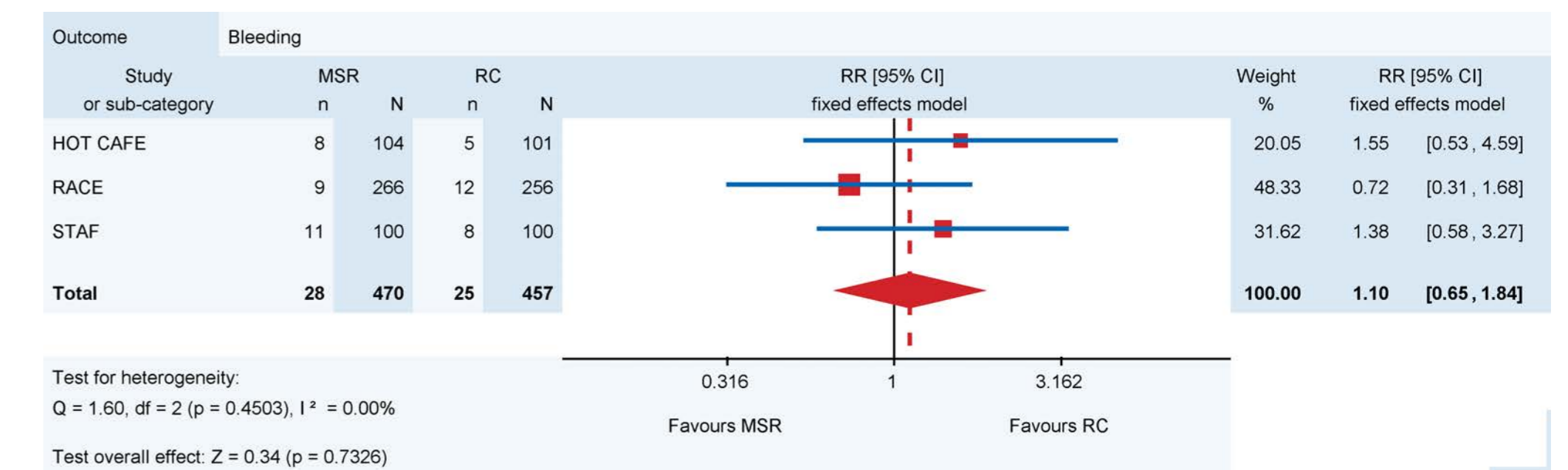
Maintenance of sinus rhythm

Maintenance of sinus rhythm was reported in 7 RCTs. All of the studies demonstrated statistically significant superiority of MSR group with respect to the maintenance of sinus rhythm. Meta-analysis of 7 studies showed that the probability of maintenance of sinus rhythm was significantly greater in patients from MSR group (RB = 4.49 [2.49; 8.09]). Number needed to treat with MSR strategy in order to maintain one additional patient with sinus rhythm after the follow up period of 12 to 37 months was 3 (NNT$_{13-37months}$ = 3 [2-4]). High level of heterogeneity was revealed (I[2] = 94.23). It can be assumed that the heterogeneity was caused by differences between studies in following fields: severity of AF, medication used in either group, follow-up lengths (Figure 8).

Figure 8. Relative benefit of maintaining of sinus rhythm for the comparison between MSR and RC groups
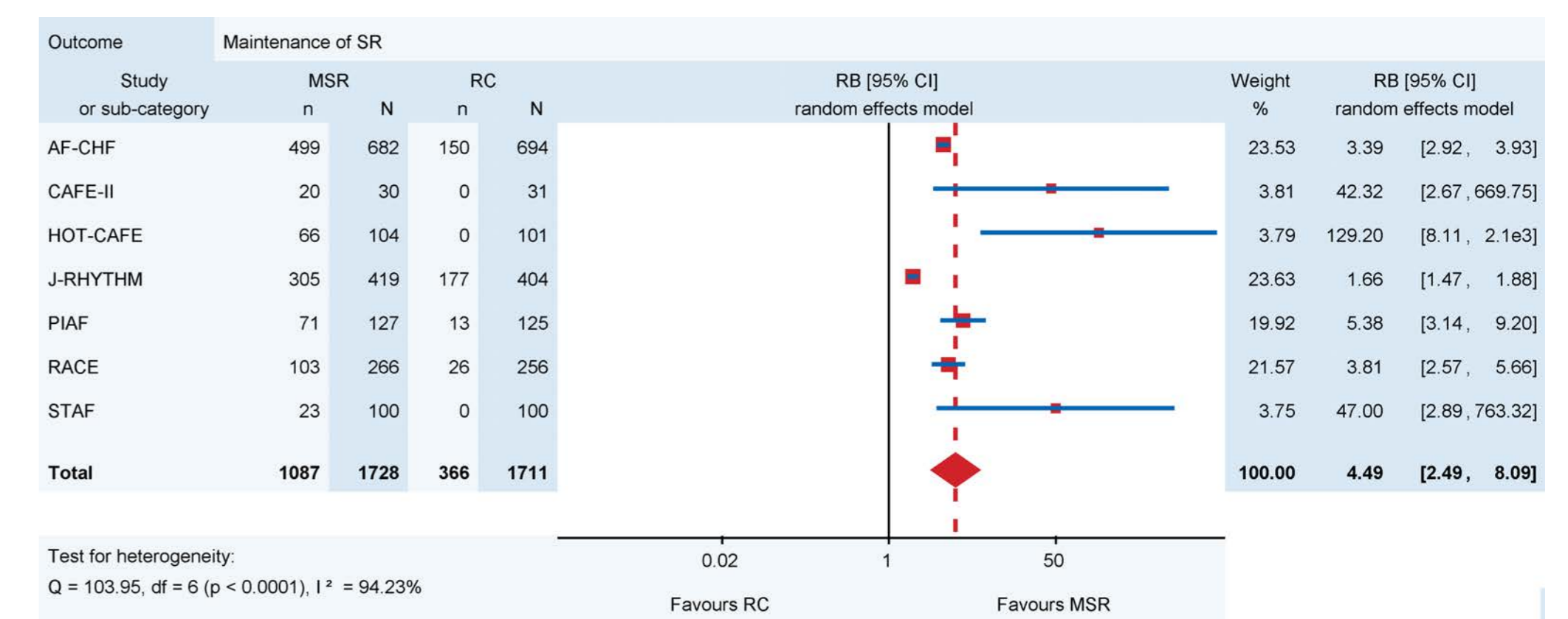
Conclusions

There is no evidence for additional benefit of maintaining sinus rhythm with the use of antiarrhythmic drugs over RC strategy with respect to clinically meaningful endpoints like overall and cardiovascular mortality, stroke, systemic embolism, heart failure or bleeding. Therefore maintenance of sinus rhythm should not be considered as a surrogate for clinically relevant endpoints.

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Abbreviations

AAD	Antiarrhythmic drugs	MSR	Maintenance of SR	RC	Rate Control
AF	Atrial Fibrillation	NNT	Number Needed to Treat	RCT	Randomized Clinical Trial
AFI	Atrial Flutter	PP	Per Protocol	RR	Relative Risk
ITT	Intention to Treat	RB	Relative Benefit	SR	Sinus Rhythm

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