Drugs & Aging
https://doi.org/10.1007/s40266-019-00722-4

SYSTEMATIC REVIEW

Clinical Outcomes of Rate vs Rhythm Control for Atrial Fibrillation in Older People: A Systematic Review and Meta-Analysis

Laurence Depoorter[1] · Liza Sels[1] · Mieke Deschodt[2,3] · Bastiaan Van Grootven[4,5] · Lorenz Van der Linden[6,7] · Jos Tournoy[1,2]

Abstract

Background and Objectives Atrial fibrillation (AF) is highly prevalent in older adults and has been associated with increased morbidity and mortality. To reduce this AF-related morbidity in older adults, antiarrhythmic drugs (AADs) are regularly used for rhythm control, assuming that increasing time in sinus rhythm reduces AF-related morbidity. However, whether AADs can improve clinical outcomes in older adults remains unclear because of the increased risk for adverse drug events compared with rate control. The aim of this study was to determine the impact of rhythm control versus rate control on clinical outcomes in older adults with AF.

Design and Methods We conducted a systematic review and meta-analysis targeting patients aged ≥65 years with AF and using drugs to control rate or rhythm. Articles that met the following criteria were included: enrolled older patients (sample mean ≥75 years) with AF, compared pharmacological rate versus rhythm control, and reported all-cause mortality, cardiovascular mortality, or ischemic stroke.

Results Five observational studies were included. In total, 86,926 patients with AF with a mean age ranging from 75 to 92 years were studied. No differences were found between rhythm and rate control for all-cause mortality (odds ratio [OR] 1.11; 95% confidence interval [CI] 0.78–1.59; $I^2 = 79.6\%$; $n = 28{,}526$; four studies) and cardiovascular mortality (OR 1.09; 95% CI 0.81–1.47; $I^2 = 0\%$; $n = 2292$; two studies). Rhythm control resulted in fewer strokes (OR 0.86; 95% CI 0.80–0.93; $I^2 = 0\%$; $n = 59{,}496$), although this was mainly determined by one study.

Conclusion All collected data were observational, which precluded making strong recommendations. Furthermore, all CIs were wide, increasing the uncertainty of the observed effects. As such, evidence was insufficient to recommend rhythm or rate control as the first-line therapy for AF in older adults. As AF is particularly prevalent in older people, more randomized controlled trials are needed in this population.

1 Introduction

Atrial fibrillation (AF) is the most common rhythm disorder in older adults, and both the incidence and the prevalence of this disorder are increasing. AF currently affects 5% of all people aged ≥ 70 years and approximately 9% of those aged > 80 years [1, 2]. AF is associated with increased morbidity and mortality, especially in older patients, signified by an annual mortality rate of 8% in patients with AF aged > 75 years [3]. This is mainly because of the development of heart failure and the risk for thromboembolic complications such as stroke and transient ischemic attack (TIA) [4]. Yet, clinicians are regularly confronted by the paucity of trial data on best practice in older adults, especially in regard to managing heart rate and rhythm in older adults with AF. Rhythm control is the use of pharmacological and/or electrical means to restore (in the acute setting) and maintain (in the chronic setting) sinus rhythm. Conversely, rate control commonly pertains to the use of atrioventricular nodal blocking agents (e.g., β-blockers) that lower the ventricular response rate in AF.

European and North American clinical practice guidelines on the management of AF do not provide explicit guidance on which approach to prefer in stable outpatients

Joint first authorship: Laurence Depoorter and Liza Sels.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40266-019-00722-4) contains supplementary material, which is available to authorized users.

✉ Jos Tournoy
Jos.tournoy@uzleuven.be

Extended author information available on the last page of the article

Published online: 20 November 2019

Key Points

Our meta-analysis found no differences in all-cause mortality and cardiovascular mortality between rhythm and rate control strategies in older patients with atrial fibrillation (AF).

Rhythm control was associated with fewer strokes than was rate control in the meta-analysis. However, this result was because of the effects observed in one large observational study and remains to be confirmed by randomized controlled trials.

Randomized controlled trial data are lacking as to whether rate or rhythm control should be preferred in terms of the clinical outcomes of patients aged ≥ 75 years with AF.

Drug safety profiles and patient preferences should largely determine the treatment strategy used in older adults with AF.

[5, 6]. In contrast, AF guidelines do strongly recommend the use of anticoagulation because the evidence base, including in older people, is clear: oral anticoagulation reduces the relative risk of stroke by 64% compared with placebo [7, 8].

Since 2002, multiple published randomized controlled trials (RCTs) and systematic reviews have compared rhythm and rate control for the treatment of AF in the general population. Yet, data on treatment strategies for AF in patients aged >75 years remain scarce [9, 10]. We therefore conducted a systematic literature review with meta-analysis to determine whether pharmacological rhythm control was superior to rate control in older patients with AF in terms of mortality, morbidity (stroke, heart failure, hospitalization), and quality of life.

2 Methods

2.1 Search Strategy

We systematically searched the electronic databases PubMed and Embase for relevant papers using a comprehensive search string (see Appendix 1 in the Electronic Supplementary Material [ESM]). This search strategy was composed using the following three concepts (terms): age >65 years (elderly, aged, geriatric), AF (AF, auricular fibrillation), and rate- or rhythm-control drugs (amiodarone, cordarone, sotalol, dronedarone, flecainide, tambocor, apocard, encainide, β-blockers, bisoprolol, nebivolol, verapamil, isoptin, digoxin, lanoxin). The Boolean operators "AND" and "OR" were used to combine the terms and concepts. Editorials, letters, conference abstracts, comments, and case reports were excluded using the Boolean operator "NOT". The search was limited to papers published in Dutch, French, and English. The search was conducted in November 2017 without limitations to the year of publication. The search was updated in June 2019. We also hand searched the reference lists of included studies to identify additional studies.

2.2 Study Selection

Two reviewers (LD and LS) independently screened first titles, then abstracts, then the full texts of relevant papers. In case of disagreement between the two reviewers, a third reviewer (JT) was consulted to discuss eligibility. Articles were included if the following criteria were met: enrolled older patients (population minimum age 65 years and mean age of sample >75 years) with AF; compared pharmacological rate versus rhythm control; and reported all-cause mortality, cardiovascular mortality, ischemic stroke, heart failure, hospitalization, or quality of life. Only quantitative studies (randomized prospective, observational prospective and retrospective studies) were included. Systematic reviews and qualitative studies were excluded.

2.3 Methodological Quality Assessment

We assessed the methodological quality of the studies using the Methodological Index for Non-Randomized Studies (MINORS), which contains 12 items for comparative studies [11]. The maximum score per item was 2, with the total score ranging from 0 to 24 (see Appendix 2 in the ESM).

2.4 Data Extraction and Synthesis

The following data were extracted from the included studies: design, population characteristics, sample size, age, and percentage of patients receiving anticoagulation and investigational drugs (see Table 1). Data regarding the primary outcome (all-cause mortality, cardiovascular mortality, ischemic stroke, heart failure, hospitalization) were also extracted (see Table 2). Data were retrieved by one author (LS) and confirmed by a second author (LD). A narrative qualitative summary of all studies was compiled.

We performed a meta-analysis and calculated odds ratios (ORs), 95% confidence intervals (CIs), and the number needed to treat. To that end, a DerSimonian–Laird random-effects model was derived using the "metan" command in STATA. Statistical heterogeneity was explored using forest plots and the I^2 statistic. Publication bias was not assessed because of the limited number of studies included. Primary publications did not report missing data.

3 Results

A total of 8370 unique studies were identified in the database search, of which 8319 were excluded after screening the title and abstract. As a result, the full texts of 51 articles were screened, after which 46 articles were excluded. The search flow is summarized in Fig. 1. Finally, five observational studies (two prospective, three retrospective) were included in this review.

A total of 86,926 patients with AF with a mean age ranging from 75 [12] to 92 years [13] were studied. The proportion of women in the included samples ranged from 45 [12] to 73% [13]. The anticoagulation percentage ranged from 35 [13] to 84% [12]. Mean follow-up times ranged from 1 [14] to 3.4 years [12] (see Table 1). According to the MINORS criteria, high scores were obtained for four of five studies (20 or 21); only one study had a score of 14 (see Appendix 2 in the ESM).

3.1 Mortality

All-cause mortality was assessed in four studies [12–15] (see Table 2). Ionescu-Ittu et al. observed lower mortality with rhythm control; conversely, data from Shariff et al. indicated fewer deaths with rate control (see Fig. 2). The pooled analysis showed no difference between rhythm and rate control (OR 1.11; 95% CI 0.78–1.59; $I^2 = 79.6\%$; $n = 28{,}526$; median time to follow-up 25.5 months). Two studies assessed cardiovascular mortality and found no difference between rhythm and rate control, either in the individual studies or in the pooled analysis (OR 1.09; 95% CI 0.81–1.47; $I^2 = 0\%$; $n = 2292$; median time to follow-up 26.4 months) [12, 14] (see Fig. 2).

3.2 Morbidity (Ischemic Stroke, Heart Failure, and Hospitalization)

Three studies [12, 13, 16] assessed the onset of TIA or stroke (see Table 2). Tsadok et al. observed a lower incidence of stroke in the rhythm control group (see Fig. 2). The pooled analysis showed fewer strokes/TIA with rhythm control (OR 0.86; 95% CI 0.80–0.93; $I^2 = 0\%$; $n = 59{,}496$; median time to follow-up 33.6 months). This equals a number needed to treat of 107 (95% CI 74–193).

Only two studies reported the incidence of heart failure and hospitalization, so this was not included in the

Table 1 Study characteristics

Study	Country	AF population	Study design	Rate vs rhythm (*N*)	Mean age (years)	Men (%)	Anticoagulated patients: rate vs rhythm (%)	Rate intervention	Rhythm intervention
Shariff et al. [12]	USA	Recurrent AF in patients 70–80 years, risk factor for stroke or death	Retrospective, observational	1118/1130	75	55	86/83	BB, CCB, digoxin	Amiodarone, flecainide, disopyramide, moricizine, procainamide, and/or electrical cardioversion
Tsadok et al. [16]	Canada	All types of AF in patients > 65 years	Retrospective, observational	41,193/16,325	79	45	78/77	BB, CCB, digoxin	Class Ia, Ic, and III AAD
Ionescu-Ittu et al. [15]	Canada	New-onset AF during hospitalization, patients > 66 years	Retrospective, observational	19,728/6402	79	44	54/60	BB, CCB, digoxin	Amiodarone, sotalol, class I AAD
Wutzler et al. [13]	Germany	All types of AF in patients > 89 years	Prospective, observational	242/37	92	27	35	BB, CCB, digoxin	Flecainide, amiodarone, sotalol
Paciullo et al. [14]	Italy	Patients > 65 years admitted with AF in internal and geriatric wards	Prospective, observational	626/125	81	49	46	BB, CCB, digoxin	Class Ic and III AAD

AF atrial fibrillation, *AAD* antiarrhythmic drug, *BB* β-blocker, *CCB* calcium channel blocker

Table 2 Results from individual studies

Outcomes	Shariff et al. [12]			Tsadok et al. [16]			Ionescu-Ittu et al. [15]			Wutzler et al. [13]			Paciullo et al. [14]		
	Rate (*N*)	Rhythm (*N*)	*P* value	Rate (*N*)	Rhythm (*N*)	*P* value	Rate (*N*)	Rhythm (*N*)	*P* value	Rate (*N*)	Rhythm (*N*)	*P* value	Rate (*N*)	Rhythm (*N*)	*P* value
All-cause mortality	154/937	200/937	0.01				9879/19,728	3034/6402	> 0.05	12/94	3/10	0.7	55/347	10/71	0.7
Cardiovascular mortality	84/937	92/937	0.39										21/347	4/71	0.89
Ischemic stroke	41/937	44/937	0.61	2705/41,193	928/16,325	< 0.001				33/94	3/10	0.75			
Heart failure										46/94	4/10	0.59			
Hospitalization	571/937	641/937	< 0.001												

meta-analysis [12, 13]. Shariff et al. reported significantly lower hospitalization rates in the rate control group than in the rhythm control group (hazard ratio 0.76; 95% CI 0.68–0.86) (see Table 2). Wutzler et al. reported no significantly increased incidence of heart failure with rate control versus rhythm control ($p = 0.59$) (see Table 2).

3.3 Antiarrhythmic-Related Adverse Events, Quality of Life

None of the five included studies reported antiarrhythmic-related adverse events or compared quality of life in rate versus rhythm control strategies.

4 Discussion

We conducted this systematic review and meta-analysis to compare the benefits of a rhythm-control versus a rate-control strategy in older patients with AF. To the best of our knowledge, our meta-analysis and systematic review is the first report dedicated to the use of antiarrhythmic drugs (AADs) in adults aged ≥75 years. Our literature search resulted in only five observational studies, and no RCT data were found. This is surprising as AF is a disease predominantly found in older adults, with a prevalence of up to 46% of patients admitted to acute geriatric wards [17]. In sum, we found no convincing evidence in favor of rhythm control. As such, given the importance of "first do no harm" [5, 6], drug safety profiles and patient preferences should dictate the preferred strategy in older patients with AF.

We could draw no robust conclusions in support of one specific strategy in terms of mortality, given the CI of the OR inferred in our meta-analysis included the value of 1.00. This falls well within the current body of literature. Since 2002, multiple RCTs have found rhythm control to be unlikely to improve all-cause and cardiovascular mortality in the overall population compared with rate control [18–21]. Nonetheless, the observational study by Ionescu-Ittu et al. [15] did report lower mortality in favor of rhythm control. However, this seemingly contradictory result might be explained by patient selection, as patients in the rate control group might have had more comorbidities or more severe disease. For the same reason, a subgroup analysis of another large observational study ($n = 5604$), the RECORD-AF, suggested that worse outcomes mostly depended more on the presence of comorbidities (congestive heart failure, chronic kidney disease, coronary artery disease, history of stroke) and age than on the choice of rate versus rhythm control [22]. Importantly, a more recent large observational trial ($n = 6988$) supported the findings of the first RCTs in 2002 (AFFIRM, RACE) and found no survival benefit for rhythm control compared with rate control [23]. Given the pathophysiology of AF, it

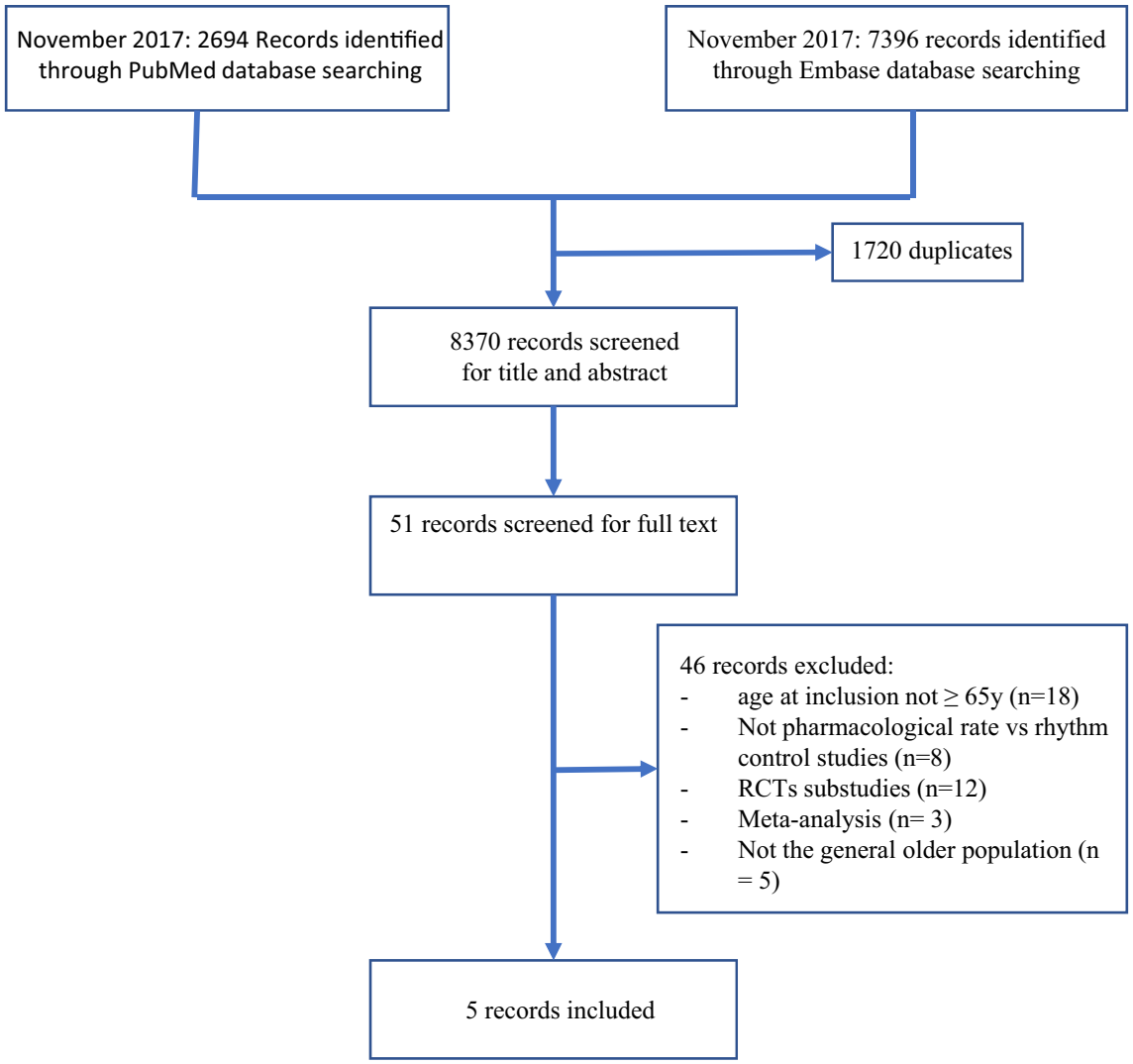

Fig. 1 Flowchart of study selection. The search was updated for the final time in June 2019, which resulted in 216 extra records in PubMed and 894 extra records in Embase compared with the search in November 2017. The extra records were screened for title and abstract, resulting in the full text of three records being screened. All three records were excluded because the age at inclusion was not >65 years

stands to reason that rhythm control should be able to reduce AF-related morbidity (e.g., strokes) to a larger degree than rate control. At first glance, this seems to be the case in our meta-analysis, which showed significantly fewer strokes in the rhythm control group. However, this effect was completely determined by the one observational study by Tsadok et al. [16] and is in contrast with other studies, which found no difference in the number of ischemic strokes or heart failure events [12, 13, 18–20, 23]. However, this study by Tsadok et al. [16] has methodological issues that raise concerns about its validity. For example, it is difficult to fully correct for selection bias. Patients in the rate control group were more multimorbid than those in the rhythm control group and might have had a higher risk of stroke. Tsadok et al. [16] also equated anticoagulation with antiplatelet therapy, an inferior protection for stroke, which might have further confounded their findings. Finally, they did not verify medication intake. Therefore, we cannot conclude from our meta-analysis whether rhythm control reduces stroke incidence. Only one study measured a hospitalization outcome, and those study findings seemed to favor rate control, which was also confirmed by other data [12, 21, 23]. This is largely because the adverse drug event (ADE) rate was lower in the rate-control group than in the rhythm-control group [18, 22, 24]. Of course, this is especially relevant in older patients, who are more susceptible to ADEs because of age-related alterations in the pharmacokinetics/pharmacodynamics of many medications [25].

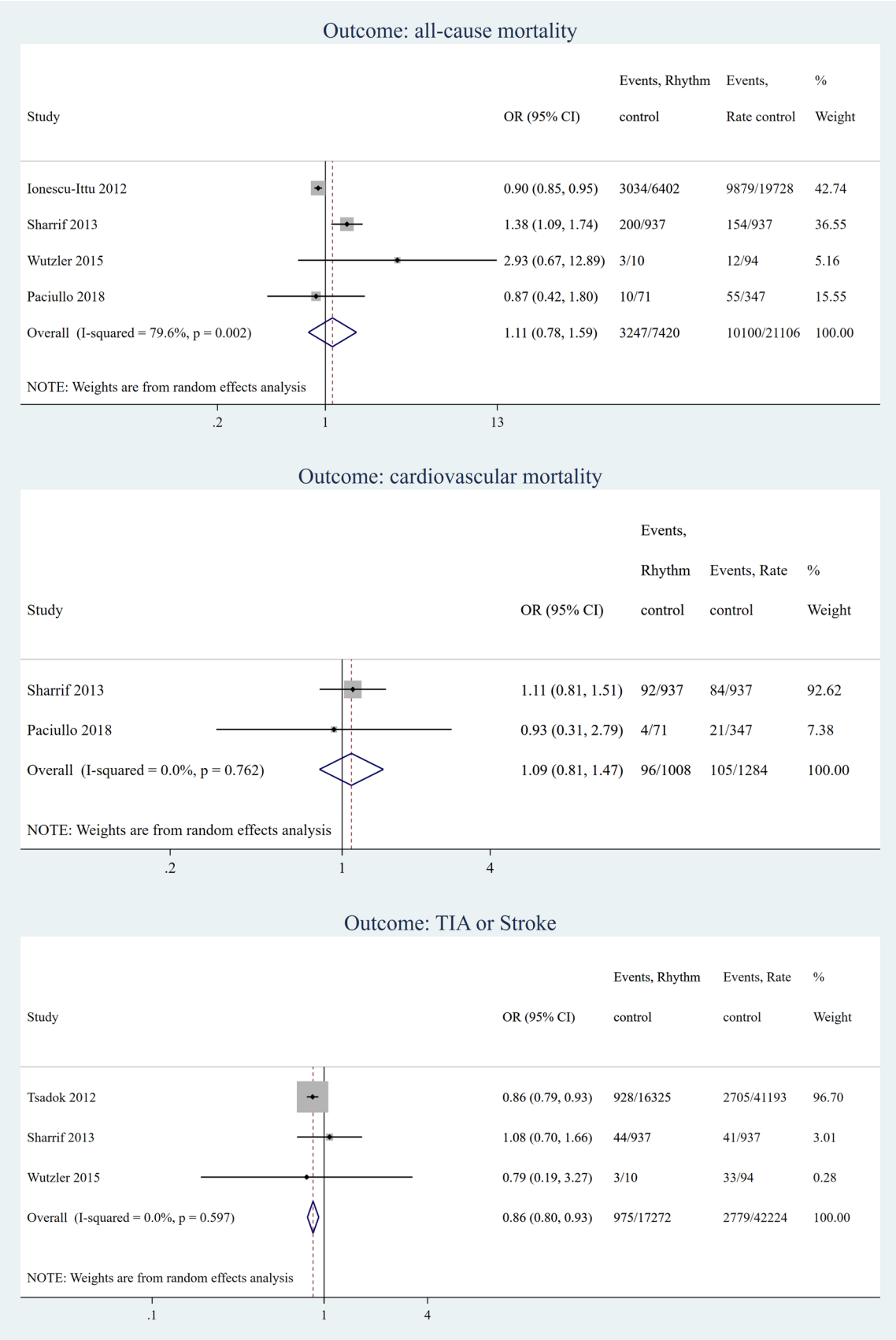

Fig. 2 Meta-analysis (note: OR < 1 favors rhythm control). *CI* confidence interval, *OR* odds ratio, *TIA* transient ischemic attack

One reason to prefer the use of AADs might be a greater benefit in terms of symptom relief, which could improve quality of life. Surprisingly, we found no analyses comparing quality of life with rate versus rhythm control in adults aged ≥65 years. Data in younger patients with AF also remain unconvincing; one small RCT by Shelton et al. ($n = 61$) and the observational study RECORD-AF ($n = 2439$) showed only a minimal improvement in quality of life in the rhythm-control arm [26, 27]. Furthermore, this improvement was not confirmed in the two largest RCTs ($n = 716$ in the AFFIRM substudy; $n = 352$ in the RACE substudy), which found no significant differences between rate and rhythm control strategies [28, 29]. This could be because the available AADs were only moderately effective in maintaining sinus rhythm, especially in older patients with structural heart disease, and because any benefit might be offset by increased ADE rates (e.g., atrioventricular block or anticholinergic side effects) [30].

We believe the results of our review and analysis are valid because of the clear inclusion and exclusion criteria. This approach led to a well-defined patient population of interest. Our analysis is also clinically relevant as AADs continue to be used in the daily medical care of older patients. In addition, the risk of AAD-related ADEs is a concern as these patients frequently have multiple chronic diseases and so are at higher risk of polypharmacy and drug–drug interactions [31].

The following limitations should be taken into account regarding our findings. First, we acknowledge the limited number of studies included. However, this is a striking result when considering the high prevalence of AF in the studied population. It is possible that more studies might have been included by searching additional databases and languages. Second, the included studies had high heterogeneity. Third, our meta-analysis used only data from observational studies. Fourth, our results indicated conflicting study data, especially regarding stroke risk. This made it very difficult to estimate the overall effect size and precludes making generalized conclusions of our findings. Fifth, we developed a review protocol before the review process, but it was not registered in PROSPERO or a similar public platform.

Thus, more data on rate versus rhythm control therapy in older populations are urgently needed. The available RCTs on this subject clearly lack data from older patients and are insufficiently representative of the real-world AF population. Surprisingly, in the era of direct oral anticoagulants, no recent study has been conducted on this topic. Future trials in older patients with AF should primarily be conducted with direct oral anticoagulants as the first-choice treatment and should also aim for maximum anticoagulation compliance. Improving the appropriate prescribing of oral anticoagulants in older and frail populations will also be a challenge [32], but this would allow the safety and efficacy of AADs versus rate control to be assessed on a background of a reduced baseline risk for thromboembolic events.

5 Conclusion

Evidence was insufficient to support the use of either rhythm or rate control as first-line therapy for AF in older adults. Further research on this topic is necessary. Until then, drug safety profiles and patient preferences should largely determine the treatment strategy used in older adults with AF.

Compliance with Ethical Standards

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest L. Depoorter, L. Sels, M. Deschodt, and B. Van Grootven have no potential conflicts of interest that might be relevant to the contents of this manuscript. L. Van der Linden and J. Tournoy have received lecture or consulting fees from Pfizer, Bristol-Meyers Squibb, Bayer, and Daichii Sankyo.

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Affiliations

Laurence Depoorter[1] · Liza Sels[1] · Mieke Deschodt[2,3] · Bastiaan Van Grootven[4,5] · Lorenz Van der Linden[6,7] · Jos Tournoy[1,2]

1 Geriatric Department, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium

2 Gerontology and Geriatrics, Department of Chronic Diseases, Metabolism and Ageing, KU Leuven-University of Leuven, Herestraat 49, 3000 Leuven, Belgium

3 Nursing Science, Department of Public Health, University of Basel, Bernoullistrasse 28, 4056 Basel, Switzerland

4 Research Foundation Flanders, Brussels, Belgium

5 Department of Public Health and Primary Care, KU Leuven-University of Leuven, Leuven, Belgium

6 Pharmacy Department, University Hospitals Leuven, Leuven, Belgium

7 Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium