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# **Risk-benefit Profile of Warfarin vs. Aspirin in Patients with Heart Failure and Sinus Rhythm: A Meta-Analysis**

Lee et al: Warfarin in Heart Failure with Sinus Rhythm

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## Abstract

**Background**—The risk-benefit profile of warfarin versus aspirin for patients with heart failure in normal sinus rhythm has not been definitively established. Our objective was to evaluate the overall comparative effects of warfarin and aspirin in patients with heart failure and normal sinus rhythm.

**Methods and Results**—Pubmed, EMBASE, Cochrane Central Register of Controlled Trials, and Clinicaltrials.gov from 1966 to June 2012 were searched to identify relevant studies. We included randomized controlled trials that included comparison of warfarin vs. aspirin, and composite endpoint of death or stroke separately for active treatment and control groups. Summary incidence rates, relative risks (RRs), and 95% confidence intervals (CIs) were calculated using random-effects models. The search identified 4 randomized controlled trials of warfarin vs. aspirin therapy, enrolling 3663 patients. There was no significant difference between the two treatments for the primary endpoint (warfarin vs. aspirin: RR 0.94, 95% CI: 0.84 to 1.06,  $p=0.31$ ). Warfarin (vs. aspirin) was associated with lower risk of any stroke (RR 0.56, 95% CI: 0.38 to 0.82,  $p=0.003$ ) and ischemic stroke (RR 0.45, 95% CI: 0.24 to 0.86,  $p=0.02$ ) but had a neutral effect on death (RR 1.01, 95% CI: 0.89-1.14,  $p=0.89$ ) and a higher risk of major bleeding (RR 1.95, 95% CI 1.37 to 2.76,  $p=0.0002$ ).

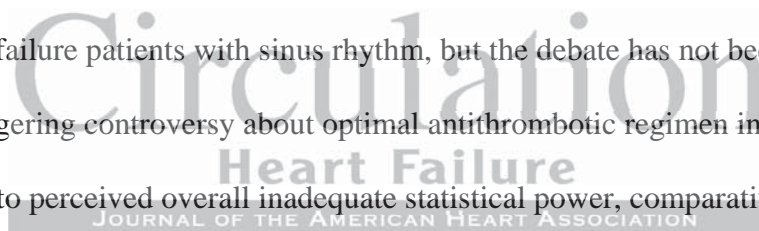
**Conclusions**—Compared to aspirin, warfarin does not provide benefit in the prevention of stroke and death among patients with heart failure in sinus rhythm, but raises the risk of major bleeding; and therefore its use in these patients is not justified.

**Key Words:** heart failure, warfarin, aspirin, death or stroke, randomized controlled trial

The best antithrombotic therapy for use in patients with heart failure and sinus rhythm has been the subject of debate for more than 50 years. Heart failure, even when not accompanied by atrial fibrillation, is associated with a hypercoagulable state, formation of left ventricular thrombus, and cerebral embolism.<sup>1,2</sup> Indeed, it is believed that thrombi that develop in the chambers of heart are rich in fibrin and trapped erythrocytes, i.e. red thrombi, and are thus more likely to be responsive to oral anticoagulation than antiplatelet agents. However, while early clinical trials showed that anticoagulation reduced the rates of embolic events and death in heart failure patients, many patients in these trials had atrial fibrillation, making it difficult to generalize the results to heart failure patients in sinus rhythm.<sup>3-5</sup>

Since then several randomized trials, comparing warfarin and aspirin, have been conducted in heart failure patients with sinus rhythm, but the debate has not been definitively resolved.<sup>6-8</sup> The lingering controversy about optimal antithrombotic regimen in these patients may in part be due to perceived overall inadequate statistical power, comparatively short follow-up periods, varied risk-benefit assessments, and small numbers of important sub-groups (e.g. those with very low cardiac ejection fraction) in single randomized trials to date. Furthermore, recommendations based on the results of individual trials can be misleading (especially if these trials are not large enough) owing to the risk of both false-positive and false-negative results.<sup>9</sup>

To achieve the most robust up-to-date estimate of the treatment effect of oral anticoagulant treatment vs. antiplatelet therapy in heart failure patients with sinus rhythm, we conducted a systematic review and meta-analysis of published randomized controlled trials that specifically compared warfarin to aspirin in these patients.



## Methods

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis: The PRISMA Statement.<sup>10</sup>

### *Search Strategy*

We systematically searched Pubmed (1966 to June 2012), EMBASE (1966 to June 2012), the Cochrane Central Register of Controlled Trials (CENTRAL), and the clinical trial registry maintained at clinicaltrials.gov with the terms “heart failure” or “congestive heart failure” or “left ventricular ejection fraction” AND “warfarin” or “coumadin” or “anticoagulant” or “vitamin K antagonist”. We restricted our search to human beings and clinical trials. There were no language restrictions. We also reviewed the Introduction and Discussion sections of retrieved trials and relevant review articles to identify additional trials.

### *Study Selection and Data Abstraction*

Studies were selected when they met the following entry criteria: (1) the study design was a randomized controlled trial; (2) participants with heart failure and sinus rhythm; (3) comparison of warfarin and aspirin; (4) the treatment duration was at least 6 months; (5) reported end points included composite of death or stroke; (6) total number of patients and events were reported separately for warfarin and aspirin groups. Participants of any age or of either sex were included. Studies were excluded when (1) atrial fibrillation was noted in a non-negligible portion of participants (> 10%); (2) either the control or the active therapy group received an additional treatment that the other group did not receive. All data from eligible studies were abstracted by 2 independent investigators (ML and KSH) according to a standard protocol. Discrepancies were resolved by discussion with a third investigator (BO) and by referencing the original report. Relevant data included the trial's name, first author's name, year of publication, country of

origin, population of participants, age of participants, trial duration, percentage of stroke history at trial entry, percentage of atrial fibrillation at trial entry, mean left ventricular ejection fraction, number of participants in warfarin and aspirin groups, number of composite endpoint of death or stroke, any stroke, ischemic stroke, intracranial hemorrhage, death from any cause, myocardial infarction, hospitalization for heart failure and major bleeding, in warfarin and aspirin groups.

### ***Study Quality Assessment***

Since all included studies were randomized controlled trials, the Jadad score was used to assess study quality.<sup>11</sup> This 5-point scoring system evaluates the randomization process (two questions), blinding (two questions), and the description of withdrawals and dropouts (one question).

### ***Statistical Analysis***

The primary outcome was the composite of first stroke or death from any cause. Secondary outcomes were any stroke, ischemic stroke, intracranial hemorrhage, death from any cause, myocardial infarction, hospitalization for heart failure, and major bleeding.

Data were analyzed according to the intention-to-treat principle. Relative risk (RR) with 95% confidence interval (CI) was used as a measure of the association between warfarin vs. aspirin and outcomes. Heterogeneity was assessed by p value of chi-square statistics and  $I^2$ , which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than chance.<sup>12, 13</sup> Heterogeneity was considered significant if the p value of chi-square statistics was  $<0.05$ . We regarded  $I^2$  of  $<40\%$  as minimal and  $>74\%$  as considerable based on the suggestion of the Cochrane Handbook for Systematic Reviews of Interventions.<sup>14</sup> We pooled data across trials using the random-effects model based on Mantel-Haenszel methods and compared the results with those obtained from a fixed-effects model.<sup>15</sup> The random-effects

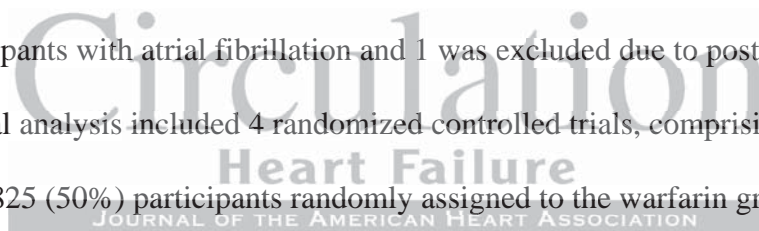
method adjusts the study weight according to the extent of variation, or heterogeneity, among the varying intervention effects and estimates the amount of between-study variation by comparing each study's result with a Mantel-Haenszel fixed-effect meta-analysis result.<sup>14</sup> Publication bias was visually assessed by funnel plots displaying standard error as the measure of sample size and RR as the measure of treatment effect.<sup>16</sup> For all analyses,  $p < 0.05$  was considered statistically significant. The Cochrane Collaboration's Review Manager Software Package (RevMan 5) was used for this meta-analysis.

## Results

The literature review identified 8 articles for detailed assessment, among which 3 were excluded for participants with atrial fibrillation and 1 was excluded due to post-hoc analysis (Figure 1). Our final analysis included 4 randomized controlled trials, comprising 3663 individuals, with 1825 (50%) participants randomly assigned to the warfarin group and 1838 (50%) to the aspirin group.<sup>6-8, 17</sup> The study design, quality, and baseline characteristics of these randomized controlled trials are shown in Table 1. All trials were conducted in western countries. Three trials showed good to excellent scores ( $\geq 3$ ), and 1 trial showed a lower score<sup>17</sup> on study quality assessment. The number of participants ranged from 115 to 2305 and the trial duration ranged from 1.5 to 3.5 years.

### ***Primary outcome: Death or stroke***

Pooling the results from the random-effects model showed that there was no significant difference between the two treatments for the primary endpoint (warfarin vs. aspirin: RR 0.94, 95% CI 0.84 to 1.06,  $p=0.31$ ) and there was no heterogeneity across all trials ( $p=0.66$ ,  $I^2=0\%$ )



(Figure 2). The estimates from the fixed-effects model were the same as those of the random-effects model. There was no obvious asymmetry in a funnel plot (Supplemental Figure 1).

### ***Secondary outcomes***

Secondary outcomes of stroke, ischemic stroke, intracranial hemorrhage, death from any cause, myocardial infarction, hospitalization for heart failure, and major bleeding were reported in Table 2.

#### **Any stroke**

All 4 trials reported data on stroke. Pooling the results with the random-effects model showed that treatment with warfarin was associated with lower stroke risk (RR 0.56, 95% CI 0.38 to 0.82,  $P=0.003$ ; number needed to treat = 57 [40 to 139]). There was no heterogeneity among trials ( $P=0.42$ ,  $I^2=0\%$ ).

#### **Ischemic stroke**

Two trials reported data on ischemic stroke.<sup>7,8</sup> Pooling the results with the random-effects model showed that treatment with warfarin was associated with lower ischemic stroke risk (RR 0.45, 95% CI 0.24 to 0.86,  $P=0.02$ ; number needed to treat = 45 [33 to 179]). There was no obvious heterogeneity among trials ( $P=0.24$ ,  $I^2=27\%$ ).

#### **Intracranial hemorrhage**

Two trials reported data on intracranial hemorrhage.<sup>7,8</sup> Pooling the results with the random-effects model showed that there was no significant difference between the two treatments for intracranial hemorrhage (RR 1.10, 95% CI 0.43 to 2.83,  $P=0.85$ ). There was no obvious heterogeneity among trials ( $P=0.28$ ,  $I^2=13\%$ ).



### **Death from any cause**

All 4 trials reported data on death from any cause. Pooling the results with the random-effects model showed that there was no significant difference between the two treatments for death from any cause (RR 1.01, 95% CI 0.89 to 1.14,  $P=0.89$ ). There was no heterogeneity among trials ( $P=0.67$ ,  $I^2=0\%$ ).

### **Myocardial infarction**

All 4 trials reported data on myocardial infarction. Pooling the results with the random-effects model showed that there was no significant difference between the two treatments for myocardial infarction (RR 1.00, 95% CI 0.61 to 1.64,  $P=0.99$ ). There was no obvious heterogeneity among trials ( $P=0.26$ ,  $I^2=25\%$ ).

### **Hospitalization for heart failure**

Three trials reported data on hospitalization for heart failure.<sup>7, 8, 17</sup> Pooling the results with the random-effects model showed that there was no significant difference between the two treatments for hospitalization for heart failure (RR 0.84, 95% CI 0.55 to 1.28,  $P=0.42$ ). There was substantial heterogeneity among trials ( $P=0.0009$ ,  $I^2=89\%$ ).

### **Major bleeding**

All 4 trials reported data on major bleeding. Pooling the results with the random-effects model showed that treatment with warfarin was associated with higher risk of major bleeding (RR 1.95, 95% CI 1.37 to 2.76,  $P=0.0002$ ; number needed to harm = 38 [20 to 97]). There was no obvious heterogeneity among trials ( $P=0.37$ ,  $I^2=4\%$ ).



## Discussion

The current meta-analysis, which pooled data from all relevant trials, showed no significant overall difference between warfarin and aspirin therapies in preventing the primary composite outcome of death or any stroke, in heart failure patients with sinus rhythm. However, there was a substantial benefit of warfarin as compared with aspirin with respect to the prevention of stroke and ischemic stroke; and a significant increase in the incidence of major bleeding. Risks of intracranial hemorrhage, myocardial infarction, and hospitalization for heart failure were not significantly different between warfarin and aspirin therapies.

In this meta-analysis, the endpoint of death happened 7 times more than the stroke endpoint, thereby justifying its inclusion along with stroke in the studied randomized trials (and this meta-analysis), as the primary outcome among these patients. In comparison, in a warfarin vs. aspirin trial among patients with atrial fibrillation,<sup>18</sup> death happened only 2.3 times more than the stroke endpoint, perhaps justifying the inclusion of only stroke as the primary outcome for trials in this patient population. Since warfarin, compared with aspirin, has a neutral effect on the endpoint of death in patients with heart failure and sinus rhythm (as well as in patients with atrial fibrillation), incorporating the endpoint of death into the primary outcome for patients with heart failure and sinus rhythm may dilute any stroke-preventative effect of warfarin therapy, especially since it appears that death dominates the primary outcome in these patients.

Two large randomized trials included in this meta-analysis showed that the international normalized ratio (INR) was in therapeutic range (2.0 to 3.5) for 63% to 70% of the total treatment time.<sup>7, 8</sup> Typically, patients enrolled in a randomized trial have better drug adherence than patients in the real world. One prospective cohort study showed that patients have difficulty maintaining adequate adherence to warfarin therapy, and this poor adherence has a significant

effect on the degree and duration of proper anticoagulation.<sup>19</sup> While novel anticoagulants like Dabigatran and Apixaban, when compared with warfarin, have been associated with a lower risk of stroke, but similar major bleeding risks in patients with atrial fibrillation, the efficacy of these agents vs. aspirin or warfarin, in patients with heart failure and sinus rhythm has not been evaluated.<sup>20, 21</sup> Of note, both dabigatran 150 mg daily and apixaban 10 mg daily (vs. warfarin) showed borderline (hazard ratio, 0.88; 95% CI, 0.77 to 1.00),<sup>20</sup> and mildly significant (hazard ratio, 0.89; 95% CI, 0.80 to 0.99)<sup>21</sup> reductions in the risk of death from any cause. Since death, not stroke, is the main outcome of patients with heart failure and sinus rhythm, finding a therapy that lowers all-cause mortality should be a major consideration when conducting future clinical trials of antithrombotic agents among these patients.



Approximately 5.7 million individuals in the United States have heart failure and most of them are in sinus rhythm.<sup>22, 23</sup> The results of this meta-analysis showing no therapeutic advantage of warfarin over aspirin, will probably lead the majority of clinicians to prescribe the more conservative treatment (i.e. use of aspirin) for these patients. However, given that the incidence of atrial fibrillation among patients with heart failure people is 54 per 1000 person-years,<sup>24</sup> it will be important for providers taking care of patients with heart failure who are in sinus rhythm to regularly screen for new-onset atrial fibrillation, and if atrial fibrillation is identified, promptly switch to treatment with an anticoagulant.

There was substantial heterogeneity among trials with regard to the endpoint of hospitalization for heart failure. It has been argued that aspirin may interfere with prostaglandin synthesis, leading to lower effectiveness of angiotensin-converting-enzyme inhibitor agents, which are commonly prescribed for patients with heart failure.<sup>25, 26</sup> Although WASH and WATCH supported the hypothesis that warfarin, as compared to aspirin, may reduce

hospitalization for heart failure, the results from WARCEF did not reveal this benefit. This issue will need to be studied in greater detail in the future.

Our study has several limitations. First, meta-analysis may be biased when the literature search fails to identify all relevant trials or the selection criteria for including a trial are applied in a subjective manner. To minimize these risks, we performed thorough searches across multiple literatures and trial databases and used explicit criteria for study selection, data abstraction, and data analysis. Second, there were only 4 relevant randomized controlled trials and the results of this meta-analysis were dominated by WARCEF.<sup>8</sup> However, our meta-analysis provides the most comprehensive evidence on this issue to date. Third, heterogeneity exists amongst heart failure patient populations and it would be helpful to conduct subgroup analyses that may demonstrate possible benefit or harm from warfarin vs. aspirin in select groups. Indeed, even the largest trial, WARCEF, did not provide information about whether the warfarin or aspirin might provide additional benefits in certain subgroups, e.g. those patients with severe heart failure.<sup>8</sup> Since our study is a study-level meta-analysis, further subgroup analysis could not be conducted. Individual-level pooled analyses of relevant trials are warranted and may provide additional insights.

In summary, this meta-analysis showed no significant overall difference between warfarin and aspirin with respect to the primary outcome of death or stroke in patients with heart failure and sinus rhythm. Although, warfarin was associated with a reduction in the risk of any stroke, strokes were comparatively much fewer than deaths, the latter endpoint of which warfarin had a neutral effect. Warfarin was also linked to a significantly higher major bleeding risk. As such, there is no compelling reason to use warfarin rather than aspirin in patients with heart failure

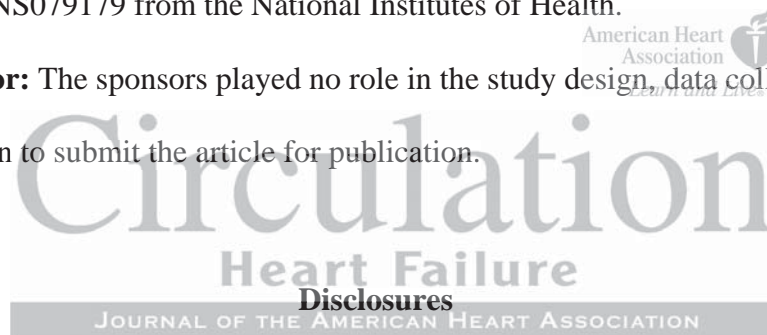
who are in sinus rhythm. Future research work will need to identify and test therapies that will specifically have an impact on the most frequent clinical outcome among these patients, death.

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None.

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Table 1. Characteristics of included trials

Variable	HELAS, 2006 <sup>6</sup>	WARCEF, 2012 <sup>8</sup>	WASH, 2004 <sup>17</sup>	WATCH, 2009 <sup>7</sup>
Countries	European countries	Multiple countries	UK and USA	USA, Canada, and UK
No. of participants	115	2305	180	1063
Mean age, year	61.6	61	63.5	63
Men, %	89	80	76	85
Inclusion criteria of Echocardiography	LVEF < 35%	LVEF ≤ 35%	LVEF ≤ 35%	LVEF ≤ 35%
Mean LVEF, %	29	25	NA	25
Study duration, year	1.5	3.5	2.3	1.9
Patient-years	173	8068	414	2020
Prior stroke or TIA, %	NA	12.8	NA	5
History of atrial fibrillation, %	0	3.7	7	0
% of patients in warfarin group had INR 2.0 to 3.5	NA	62.6% (mean 2.5; 27.1% below 2 and 10.3% above 3.5)	NA (mean 2.3)	70.4% (median 2.5; 20.3% below 2 and 9.3% above 3.5)
Use of ACE inhibitor or ARB, %	58	98	89	97
Design	Double-blinded	Double-blinded	Open-label blinded end point	Open-label blinded end point
Study quality (Jadad)	5	5	2	3



score), 5- point maximum				
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ACE: angiotensin-converting-enzyme, ARB: angiotensin II receptor blocker, INR: international normalized ratio,

LVEF: left ventricular ejection fraction, NA: not available, TIA: transient ischemic attack



Table 2. Warfarin vs. aspirin on primary and secondary endpoints in patients with heart failure and sinus rhythm

Endpoints	Warfarin, n/N (%)	Aspirin, n/N (%)	RR (95% CI)	P value	NNT or NNH (95% CI)
Stroke or death	430/1825 (23.6)	461/1838 (25.1)	0.94 (0.84-1.06)	0.31	-
Stroke	39/1825 (2.1)	73/1838 (4.0)	0.56 (0.38-0.82)	0.003	57 (40-139)
Ischemic stroke	32/1682 (1.9)	67/1686 (4.0)	0.45 (0.24-0.86)	0.02	45 (33-179)
Intracranial hemorrhage	11/1682 (0.7)	10/1686 (0.6)	1.10 (0.43-2.83)	0.85	-
Death from any cause	393/1825 (21.5)	393/1838 (21.4)	1.01 (0.89-1.14)	0.89	-
Myocardial infarction	53/1825 (2.9)	53/1838 (2.9)	1.00 (0.61-1.64)	0.99	-
Hospitalization for heart failure	346/1771 (19.5)	350/1777 (19.7)	0.84 (0.55-1.28)	0.42	-
Major bleeding	102/1825 (5.6)	51/1838 (2.8)	1.95 (1.37-2.76)	0.0002	38 (20-97)

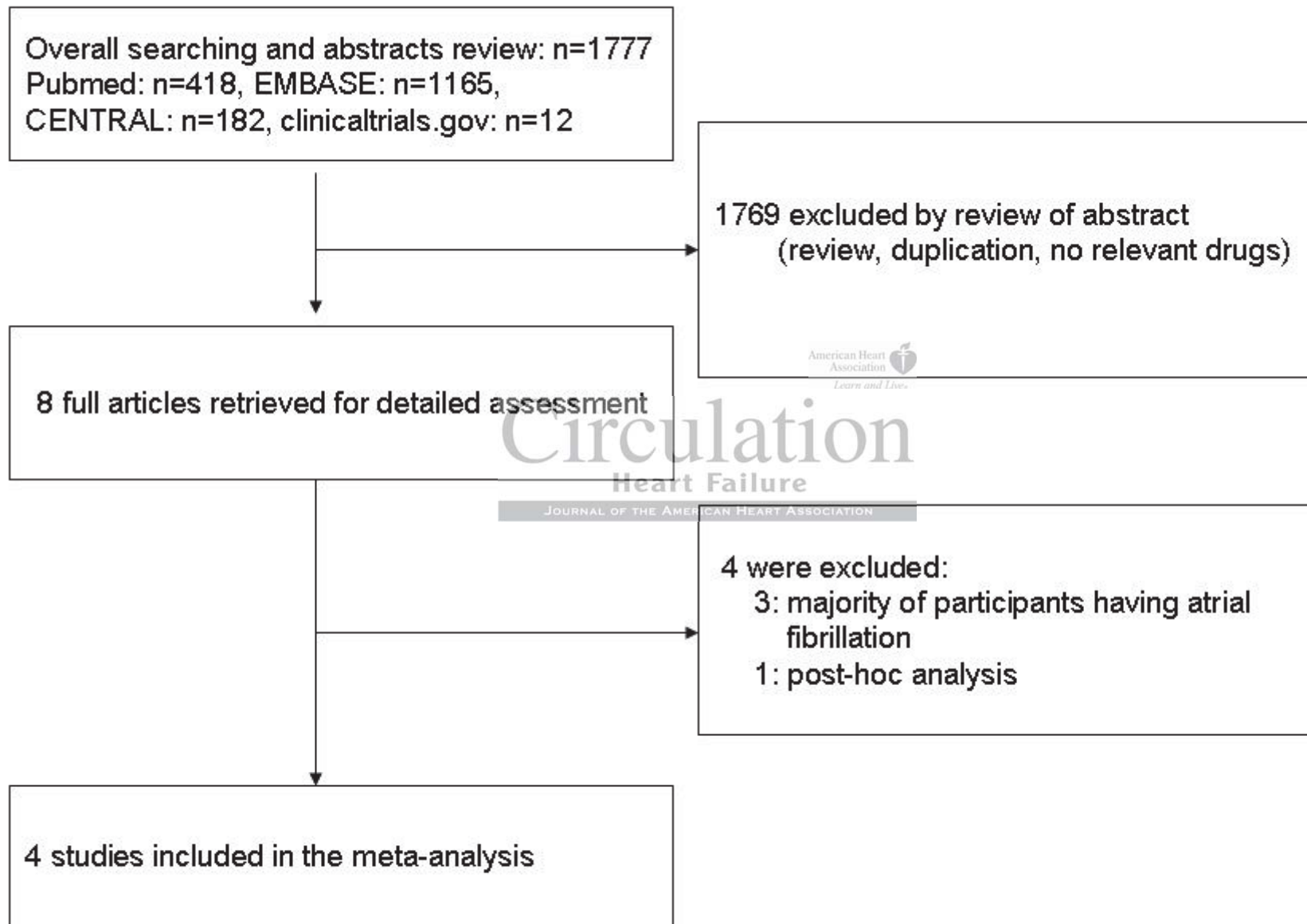
N: number of participants, n: number of death or first stroke, NNT: number needed to treat, NNH: number needed to harm, RR: relative risk, CI: confidence interval

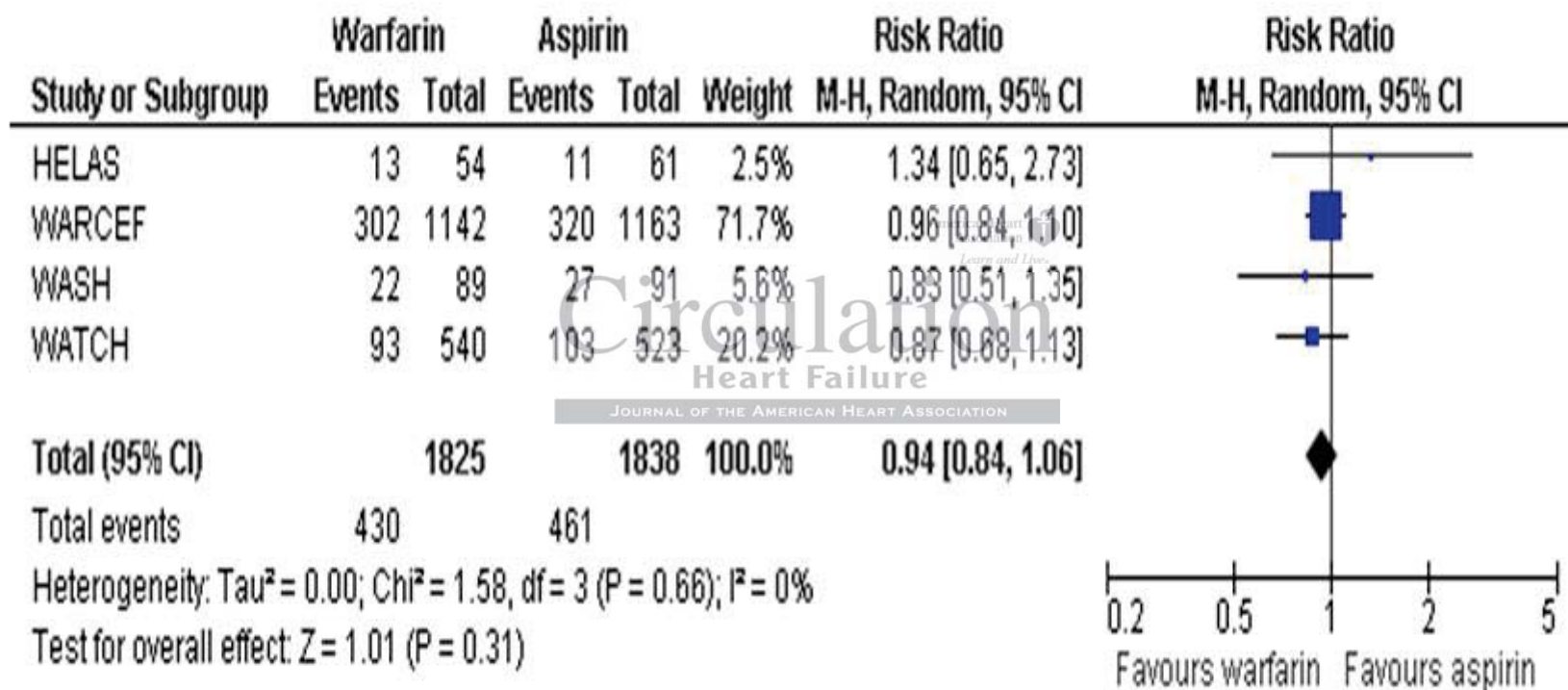
## Figure Legends

**Figure 1.** Flow of study selection

**Figure 2.** Relative risk with 95% confidence interval of death or stroke (warfarin vs. aspirin), by trials and pooled







Supplemental Figure 1 Funnel plot of included trials

