Meta-analysis of Effect of Modest (≥10%) Weight Loss in Management of Overweight and Obese Patients With Atrial Fibrillation

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Obesity and atrial fibrillation (AF) are growing epidemics with significant overlap in comorbidities. Multiple smaller studies have evaluated the effects of weight loss and risk factor modification on recurrence of AF, reduction in AF burden and improvement in AF symptom severity. The objective of this study was to determine if a modest weight loss of ≥10% of initial body weight is enough to improve outcomes in overweight or obese patients with established AF. We performed an extensive literature search and systematic review of studies that compared weight loss of ≥10% versus weight loss of less than 10% or weight gain and assessed outcomes including recurrence of AF as determined through a Holter monitor, AF burden and improvement in AF symptom severity. Risk ratio 95% confidence intervals (CI) were measured for dichotomous variables and mean difference (MD) 95% CI were measured for continuous variables, where MD >0 favors the group with ≥10% weight loss. Five studies with a total of 548 patients were included. Patients who lost ≥10% of their initial body weight experienced less recurrence of AF (risk ratio 0.29; 95% CI 0.19 to 0.44) and a larger reduction in reported event frequency (MD 1.74; 95% CI 0.70 to 2.79), episode duration (MD 2.14; 95% CI 0.04 to 4.23), global episode severity (MD 1.89; 95% CI 1.34 to 2.45), and symptom severity (MD 5.36; 95% CI 3.75 to 6.97). In conclusion, weight loss is associated with less risk of recurrent AF, reduction in AF burden, and improvement in AF symptom severity. **(Am J Cardiol 2019;124:1568−1574)**

Atrial fibrillation (AF) is a growing epidemic with 15.9 million individuals projected to be affected by the arrhythmia in the United States by 2050.[1,2] This rise in incidence and prevalence is accompanied by almost a doubling in AF-related mortality over the last 2 decades.[2] Historically, the predominant management strategy in AF encompasses the 3 pillars of rate control, rhythm control, and stroke prevention. Recently, lifestyle interventions have been proposed as an important fourth pillar. The prevalence of obese individuals in the United States has tripled since the 1960s with 1/3 of the population being obese.[3] Numerous studies have demonstrated a strong and consistent association between obesity and AF.[4,5] Although there is some data to suggest benefit of weight loss in the primary prevention of AF,[6] there is already a large population of patients who suffer from this arrhythmia. The purpose of our present study was to perform a systematic review of literature and meta-analysis to compare recurrence of AF, reduction of AF burden, and improvement in AF symptom severity from baseline to follow-up between those who lost ≥10% of their body weight versus those who lost less than 10% of their body weight or gained weight.

Methods

We searched PubMed, EMBASE, clinicaltrials.gov, Medline, Google scholar and the Cochrane Central Register of Clinical Trials (Cochrane Library, Issue 09, 2017). This was assessed up to March 2019. No language restriction was applied. The reference list of all eligible studies was also reviewed. Search terms included (*Weight Loss OR Obesity) AND (Atrial Fibrillation)*.

Studies were selected by 2 independent reviewers. The PRISMA statement for reporting systemic reviews and meta-analyses was applied to the methods for this study. The studies had to fulfill the following criteria to be considered in the analysis: (1) Studies had to have evaluated outcomes between those who lost ≥10% of their body weight and those who lost less than 10% of their body weight or gained weight in patients with established AF; (2) Studies had to have reported the percentage of patients who experienced freedom from AF or AF burden scores; (3) Studies with a minimum follow-up of 12 months; (4) Study must have been published in a peer-reviewed scientific journal.

We aimed to compare the recurrence of AF, reduction in AF burden and improvement in AF symptom severity from baseline to follow-up in patients who lost who lost ≥10% of their body weight versus those who lost less than 10% of their body weight or gained weight.

Two authors (OMA and FL) independently performed literature search and extracted data from eligible studies. Outcomes were extracted from original manuscripts and

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See page 1573 for disclosure information.

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0002-9149/
https://doi.org/10.1016/j.amjcard.2019.08.009

supplementary data. Information was gathered using standardized protocol and reporting forms. Disagreements were resolved by consensus. Two reviewers (OMA and FL) independently assessed the quality items and discrepancies were resolved by consensus or involvement of a third reviewer (JCH), if necessary.

Two authors (OMA and FL) independently assessed the risk of bias of the included trials using standard criteria defined in the Cochrane Handbook for Systematic Reviews of Interventions. Discrepancies were resolved by discussion or adjudication by a third author (JCH).

Data was summarized across treatment arms using the Mantel-Haenszel risk ratio and inverse variance mean difference (MD), where a MD >0 favored the group with ≥10% weight loss. Heterogeneity of effects was evaluated using the Higgins I-squared (I^2) statistic. Random effects models for analyses were used with high heterogeneity (defined as I^2 >25%), otherwise fixed effects models of DerSimonian and Laird were used. Funnel plot analysis was used to address publication bias. The statistical analysis was performed by the *Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.* Descriptive statistics are presented as means and standard deviations (SD) for continuous variables or number of cases (n) and percentages (%) for dichotomous and categorical variables.

Results

Initial search resulted in 1,912 abstracts. Six hundred and ten were duplicates and 1,262 were excluded based on titles and abstracts (Figure 1). We included 5 studies in our final analysis; 1 randomized control trial,[7] 3 prospective non-randomized studies,[8–10] and 1 retrospective, subgroup analysis.[11]

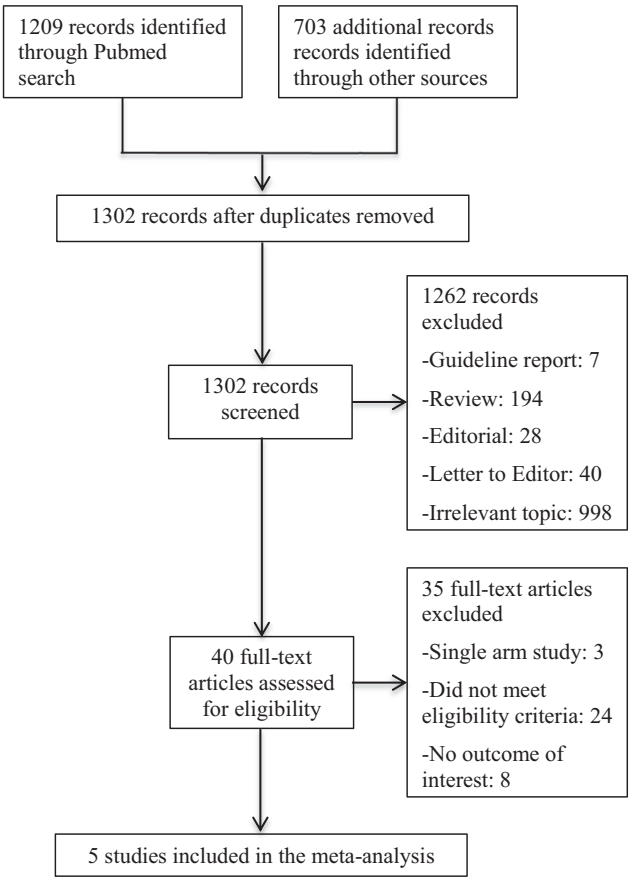

Figure 1. Selection of studies.

Baseline demographics and characteristics of the 5 studies are summarized in Tables 1 and 2. We included a total of 548 patients. In these, 232 patients (42%) had ≥10% weight loss and 316 (58%) had less than 10% weight loss or

Table 1
Patient demographics and characteristics

Study (ref)	Abed et al[7]		ARREST-AF[8]		LEGACY[9] REVERSE-AF[11]		CARDIO-FIT[10]	
	≥10% WL	<10% WL	≥10% WL	<10% WL	≥10% WL	<10% WL	≥10% WL	<10% WL
Patients - n	75	75	61	88	135	220	28	34
Age (years)	60 ± 10	60 ± 10	58 ± 11	57 ± 10	65 ± 11	62 ± 11	NR	NR
Men	51 (68%)	50 (67%)	34 (56%)	61 (69%)	86 (64%)	148 (67%)	NR	NR
Anthropometric values								
Waist circumference, cm	110 ± 10	112 ± 11	NR	NR	NR	NR	NR	NR
Weight (kg)	99 ± 13	101 ± 16	101 ± 18	97 ± 17	101 ± 17	99 ± 17	NR	NR
Body mass index (kg/m^2)	33 ± 4	34 ± 4	34 ± 5	32 ± 5	34 ± 5	33 ± 5	NR	NR
Body surface area (m^2)	2.1 ± 0.2	2.2 ± 0.2	NR	NR	NR	NR	NR	NR
Paroxysmal atrial fibrillation	44 (59%)	42 (56%)	49 (56%)	40 (65%)	71 (53%)	117 (53%)	NR	NR
Number of antiarrhythmic agents	1.3 ± 0.6	1.4 ± 0.5	1.1 ± 0.3	1.0 ± 0.2	1.1 ± 0.7	0.9 ± 0.8	NR	NR
Risk factors								
Hypertension	62 (83%)	65 (87%)	53 (87%)	73 (83%)	109 (81%)	165 (75%)	NR	NR
Hyperlipidemia	45 (60%)	51 (68%)	39 (64%)	47 (53%)	66 (49%)	101 (46%)	NR	NR
Diabetes mellitus	18 (24%)	21 (28%)	9 (15%)	17 (19%)	41 (30%)	62 (28%)	NR	NR
Apnea hypopnea index >30	NR	NR	32 (53%)	55 (62%)	69 (51%)	113 (51%)	NR	NR
Coronary artery disease	7 (9%)	10 (13%)	10 (16%)	10 (11%)	21 (16%)	23 (10%)	NR	NR
Valvulopathy	5 (7%)	4 (5%)	NR	NR	8 (6%)	11 (5%)	NR	NR
Alcohol (>30 g/week)	26 (35%)	26 (35%)	11 (18%)	24 (27%)	42 (31%)	69 (31%)	NR	NR
Smoker	32 (43%)	30 (40%)	20 (33%)	31 (35%)	50 (37%)	88 (40%)	NR	NR

Values are presented as ± SD or as n (%).
NR = not reported.

Table 2
Study characteristics

<table>
<tr><th>Study</th><th>Abed et al[7]</th><th>ARREST-AF[8]</th><th>LEGACY[9]</th><th>REVERSE-AF[11]</th><th>CARDIO-FIT[10]</th></tr>
<tr><td>Study design</td><td>Prospective Randomized Partially blinded</td><td>Prospective Nonrandomized</td><td>Prospective Nonrandomized</td><td>Retrospective Sub-analysis</td><td>Prospective Nonrandomized</td></tr>
<tr><td>Mean follow up (months)</td><td>15</td><td>42</td><td colspan="2">48</td><td>49</td></tr>
<tr><td>Study population</td><td>Overweight/obese patients with symptomatic AF</td><td>Initial ablation with BMI ≥27 kg/m² and ≥1 risk factor</td><td colspan="2">Symptomatic paroxysmal or persistent AF who had a BMI ≥27 kg/m²</td><td>Symptomatic paroxysmal or persistent AF who had a BMI ≥27 kg/m²</td></tr>
<tr><td>Intervention</td><td>2 phase weight management program</td><td>Attended a physician-directed risk factor management clinic</td><td colspan="2">Optional physician-led or self-managed weight loss program.</td><td>Physician-led risk factor management clinic and a tailored exercise program.</td></tr>
<tr><td>Comparator arm</td><td>Written and verbal nutrition and exercise advice</td><td>Given information on management of risk factors</td><td colspan="2">No comparator arm. Groups based on degree of weight loss.</td><td>No comparator arm. Groups based on fitness and degree of weight loss.</td></tr>
<tr><td>Primary Outcome</td><td>AF burden as determined by the AFSS</td><td>Procedural success</td><td colspan="2">AF burden as determined by the AFSS and AF freedom</td><td>AF burden as determined by the AFSS and AF freedom</td></tr>
<tr><td>AF recurrence</td><td>7-day Holter</td><td>Symptoms, ECG and Holter</td><td colspan="2">7-day Holter</td><td>7-day Holter</td></tr>
</table>

AF = atrial fibrillation; AFSS = Atrial Fibrillation Symptom Severity Score; BMI = body mass index.

weight gain from baseline to follow-up. The risk of bias is summarized in Figures 2 and 3. Four studies were considered to be at "high risk" for selection bias due to the study design.[8–11] Three studies were considered to have "unclear risk" for attrition bias given the data on attrition after final cohorts were selected is unavailable.[9–11] Finally, one study was considered to have "unclear risk" of other biases, such as recall bias, as it was not mentioned how data was obtained retrospectively.[11]

Patients who lost ≥10% of their initial body weight experienced less recurrence of AF (risk ratio 0.29; 95% confidence interva [CI] 0.19 to 0.44) at final follow-up (Figure 4). Additionally, there was a statistically significant reduction in reported event frequency (MD 1.74; 95% CI 0.70 to 2.79), episode duration (MD 2.14; 95% CI 0.04 to 4.23), global episode severity (MD 1.89; 95% CI 1.34 to 2.45), and symptom severity (MD 5.36; 95% CI 3.75 to 6.97) (Figure 5).

Funnel plot analysis of the included studies showed no evidence of publication bias on recurrence of AF, AF burden or improvement in AF symptom severity (Figure 4 and Supplementary data Figure 1).

Discussion

This is the first systematic review and meta-analysis of studies comparing outcomes between symptomatic AF patients who lost ≥10% of their initial body weight compared with those who lost less than 10% of their body weight or gained weight. The results of this meta-analysis show that a reduction of 10% or more of initial body weight is associated with less recurrence of AF, as well as improvements in AF burden and AF symptom severity. Although recent guidelines have already been updated to advocate for weight loss in the management of AF,[12] these findings are significant given that they show a modest weight loss of ≥10% is associated with improved outcomes, providing physicians with a practical target to counsel their patients.

Obesity is an independent risk factor for AF, with a 4% to 5% increased risk of developing AF with each unit increase in body mass index.[4,5] Fortunately, weight loss has been shown to reduce AF recurrence in a dose dependent manner, with a greater freedom from AF with greater weight loss.[8,9] Additionally, weight loss seems to slow or reverse the progression of paroxysmal AF to persistent and permanent AF seen in sustained obesity.[11]

This strong association between obesity and AF can in part be explained by the structural and electrical remodeling of the atria seen in obesity and its association with a multitude of proarrhythmic changes including diastolic dysfunction, atrial enlargement, autonomic tone abnormalities, and a systemic proinflammatory state.[7,13,14] Furthermore, obesity has been shown to be associated with a unique atrial substrate, linking epicardial or pericardial fat with the presence, severity, and outcomes of AF.[14] This extensive remodeling is reversible with weight loss, which has been shown to reduce left atrial volumes and left ventricular hypertrophy.[9]

The benefits of weight loss extend past reversal of the remodeling seen in obesity; the greater freedom from AF was also accompanied by less antiarrhythmic drug[7–10] use

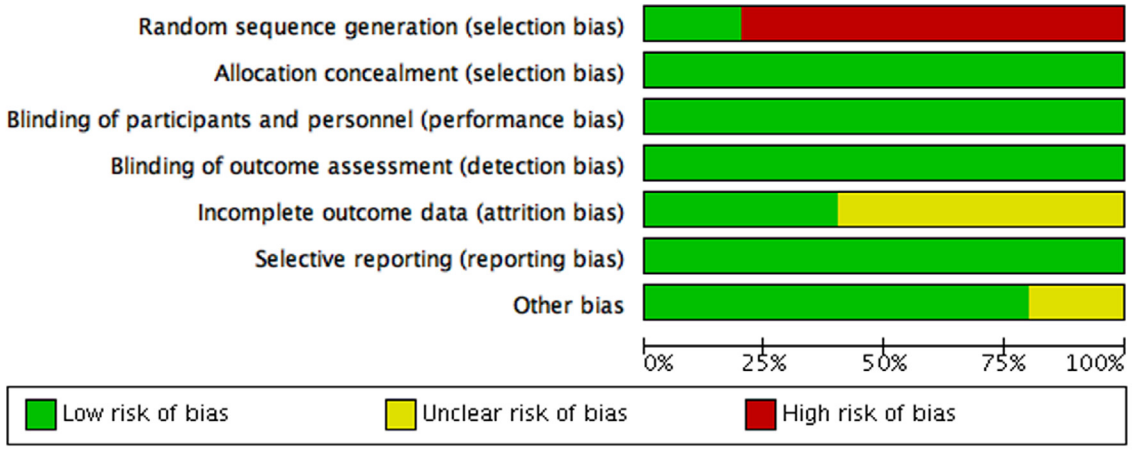

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies, according to The Cochrane Handbook for Systematic Reviews of Interventions.

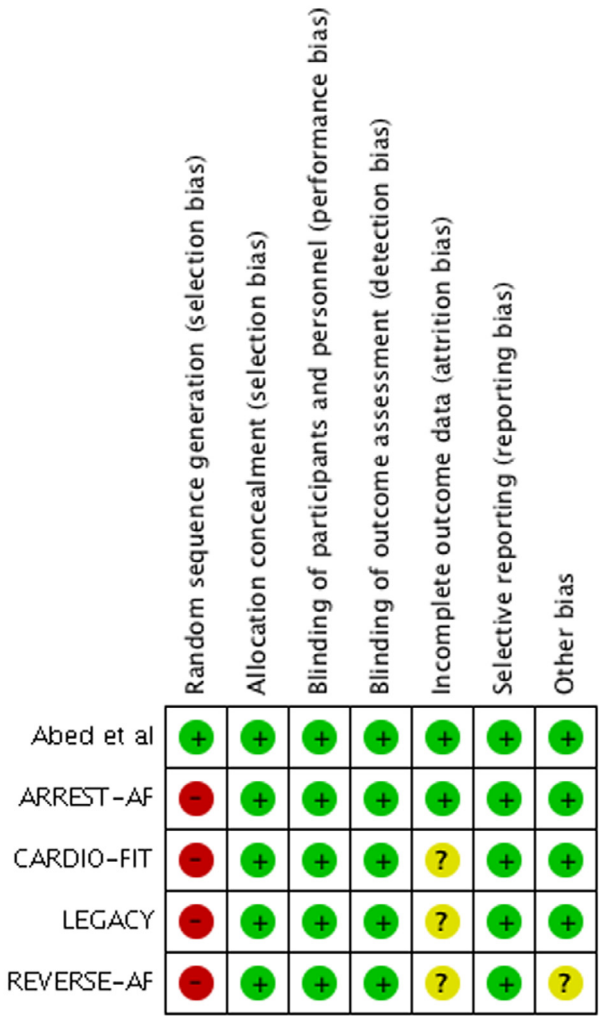

Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study, according to The Cochrane Handbook for Systematic Reviews of Interventions.

and fewer ablation[10,11] procedures in studies that recorded this information. This is important given that long-term outcomes of ablation including freedom from AF have not improved in proportion to the advances in ablative techniques and technologies.[15] Late recurrence of AF following ablation procedures was initially presumed to be secondary to persistent pulmonary vein conduction. However, this explanation would better support mechanisms for early recurrence of AF. Furthermore, progressive atrial substrate is observed even after successful ablation.[16] All of this argues in favor of the notion that an underlying substrate responsible for AF is promoted by unrecognized and undertreated risk factors such as obesity and its related co-morbidities. This is further supported by the variety of cardiac risk factors that have been found to be present more frequently in patients with late recurrence of AF following ablation.[17] This may also explain the improved outcomes postablation in patients who had lost more than 10% of their body weight.[8]

Although obesity is a crucial modifiable risk factor in the management of AF, it is by no means the only one. Hypertension, diabetes mellitus, dyslipidemia, sleep apnea, and elevated levels of c-reactive protein have all been shown to be associated with AF, with improved outcomes when these cardiac risk factors are treated.[18–24] Even though it is out of the scope of this study to determine the relative contribution of each of these risk factors, it is well established that weight loss in obese patients reduces all of these co-morbid conditions.[25–29]

However, the sustainability of weight loss remains a controversial topic. This is especially pertinent given that fluctuations in weight have been shown to attenuate the benefits of weight loss, which is expected given weight fluctuation has been shown to increase the risk of various cardiometabolic risk factors.[25–29] Still, participation in dedicated, physician-led weight loss and risk factor modification clinics has shown promising results.[9] Additionally, incorporation of tailored exercise programs to improve cardiorespiratory fitness has been shown to augment the effects of weight loss.[10] Similarly, other elements of AF care that may be associated with weight loss such as medication

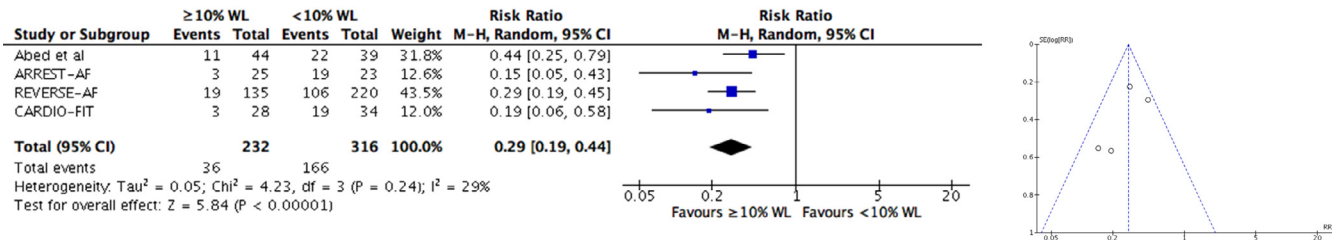

Figure 4. Forrest plots and funnel plots for the comparative analysis of risk of recurrent atrial fibrillation in those who lost 10% or more of their body weight compared to those who lost less than 10% of their body weight or gained weight from baseline to follow-up.

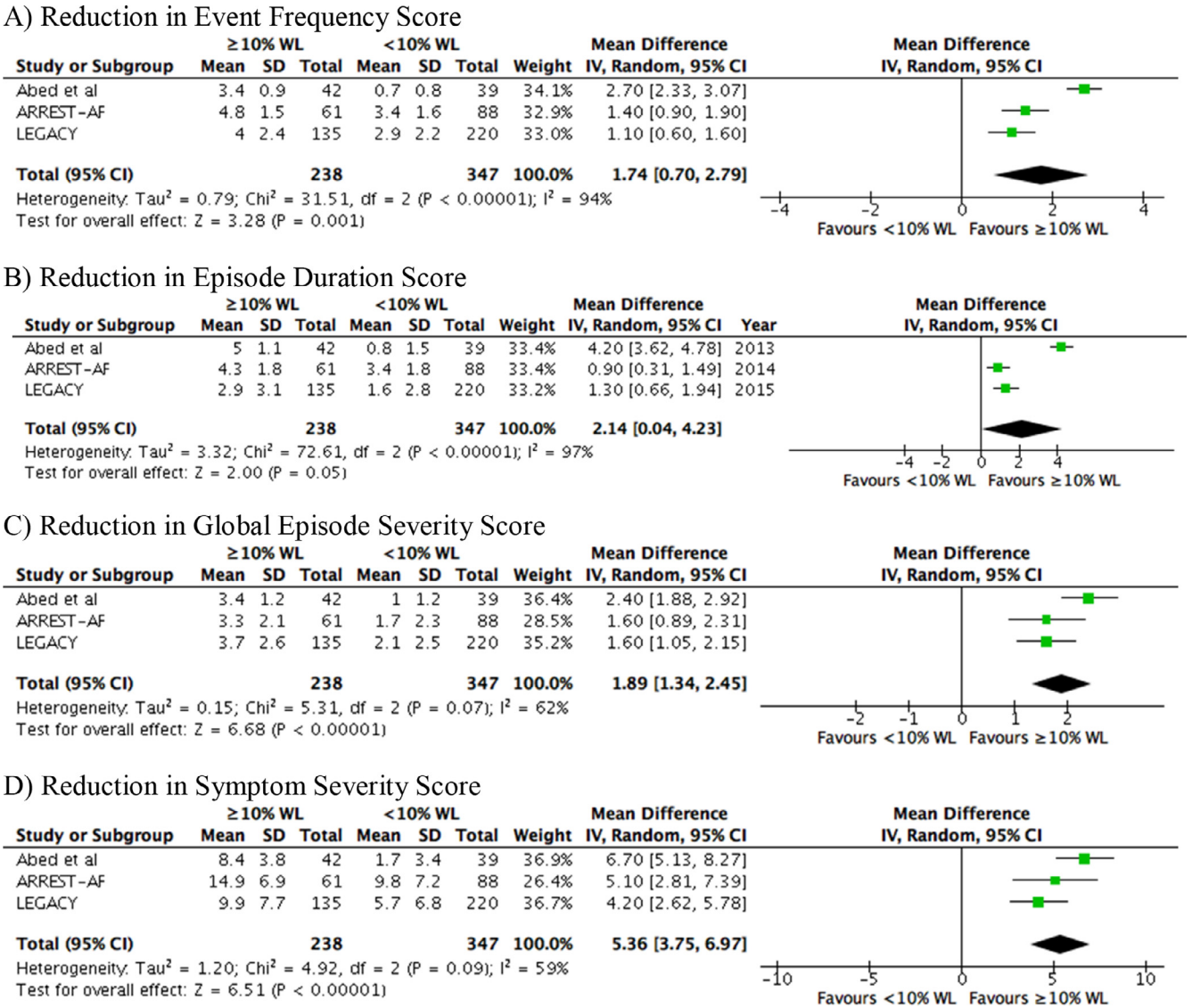

Figure 5. Forrest plots for the comparative analysis of the reduction in the various components of the Atrial Fibrillation Severity Scale scores in those who lost 10% or more of their body weight compared with those who lost less than 10% of their body weight or gained weight from baseline to follow-up. (*A*) Event frequency, (*B*) episode duration, (*C*) global episode severity, (*D*) symptom severity.

compliance, management of comorbidities, and other lifestyle changes have been associated with better outcomes.[30] All of this stresses the importance of a holistic approach to AF management. Targeting obesity and other cardiac risk factors and co-morbidities should be considered in secondary and tertiary prevention of AF.

The current systematic review and meta-analysis has several important limitations that should be acknowledged. First, the studies included were comprised of patients from a single center, which significantly restricts the generalizability of the results and contain one study using a retrospective study design in which patient overlap cannot be

ruled out. Second, there was different study protocols, with both randomized and nonrandomized trials included. Third, the Atrial Fibrillation Symptom Severity Score scores used to assess AF burden has the potential to underestimate arrhythmia burden. Similarly, the extended 7-day Holter used in all of the included studies may have potentially missed episodes of AF. However, both the Atrial Fibrillation Symptom Severity Score and extended Holter monitors were used in both groups and were thus a limitation for all groups and would be expected to be nondifferential to the outcomes studied.

In conclusion, in patients with symptomatic AF, weight loss of ≥10% is associated with less recurrence of AF, larger reduction in AF burden and improvement in AF symptom severity relative to patients who lost less weight or gained weight.

Disclosures

Dr. Hsu reports receiving honoraria from Medtronic, Abbott, Boston Scientific, Biotronik, Janssen Pharmaceuticals, and Bristol-Myers Squibb, and research grants from Biotronik and Biosense-Webster.

Dr. Ho reports receiving a research grant from Abbott, equity in Vektor Medical and fellowship support from Medtronic, Abbott, Boston Scientific, and Biotronik.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.08.009.

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