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Lessons from the trials

The heavy LEGACY: Should weight management be part of every atrial fibrillation clinic?

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ABSTRACT

As the global burden of atrial fibrillation (AF) and its attendant economic impact on the healthcare system surges, there is increasing interest in the secondary prevention of AF with various therapies. Of the several identified risk factors for AF, obesity is an important contributor that may be managed with intensive lifestyle modification. Prior studies have demonstrated the short-term and long-term benefits of weight loss in reduction of AF symptoms. In the LEGACY study [Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study], the investigators evaluated the long-term effects of a weight management program on AF symptoms. Of the 355 patients included in this cohort, outcomes such as AF symptom burden, arrhythmia-free survival, inflammatory markers and structural cardiac changes all appear to have improved in the intense weight loss group as compared to the 2 other groups. Further, the benefits of weight loss appear to be lost when > 5% weight fluctuation (WF) occurred over the 5-year follow-up period. In this review, we discuss the design of the weight management clinic and its impact on the management of AF in the LEGACY study. Given that weight management appears to be an effective intervention that will not have the marketing and financial push that pharmaceutical and device based therapies enjoy, it behooves administrators of AF clinics to develop innovative funding strategies to incorporate weight management programs in order to improve patient-centered outcomes.

Keywords: LEGACY study, atrial fibrillation, catheter ablation for atrial fibrillation, weight reduction, cardiac risk factors, obesity

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INTRODUCTION

The burgeoning atrial fibrillation (AF) epidemic which currently affects over five million Americans is expected to reach a prevalence of nearly 16 million in the United States by 2050.^{1,2} Another established public health problem with far reaching health consequences is obesity³, which has been identified as an independent risk factor for AF. Together, these two global diseases significantly impact cardiovascular outcomes, and pose an immense economic burden. As a result, a significant amount of research has been conducted to elucidate the association between obesity and AF.^{4,5}

Three prior studies inform the design of the LEGACY study [Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study] to a large extent.⁶ In the Women's Health Study, with a follow-up duration of nearly 13 years, obesity was significantly associated with AF risk after adjusting for confounders.⁷ Additionally, the authors also found that dynamic changes in body-mass index were associated with short-term increased risk of AF.⁷ To further investigate the causal relationship between obesity and AF, authors at the Centre for Heart Rhythm Disorders (CHRD) at the University of Adelaide in Australia conducted a randomized controlled study where patients were randomized to weight management vs. general lifestyle advice and found that patients in the weight management group had significantly greater weight loss (WL) and lower AF symptom burden using the Atrial Fibrillation Severity Scale (AFSS) instrument after follow-up of approximately 15 months.⁸ The CHRD investigators further studied the impact of risk factor management, including WL, in a cohort of obese AF patients undergoing catheter ablation.⁹ The ARREST-AF study [Aggressive Risk Factor Reduction Study for Atrial Fibrillation] concluded that patients receiving risk factor management (n = 61) fared much better than patients in the control group (n = 88) in terms of WL, blood pressure control, glycemic control, lipid profile as well AF symptom burden (using the AFSS instrument).⁹

In the LEGACY study, authors from the CHRD sought to further characterize the benefit of aggressive weight management in AF patients. Specifically, they studied the impact of long-term WL and WF on rhythm control in obese patients with AF.

DESCRIPTION OF TRIAL

The LEGACY study, conducted by Pathak et al., was a prospective cohort study that consisted of obese patients (body mass index ≥ 27 kg/m²) who were consecutively referred to the CHRD with symptomatic AF (paroxysmal or persistent). Patients were excluded based on pre-defined criteria (n = 293) or if they lived out of state (n = 177), and the remaining 355 patients were included in the analysis. All patients referred to the CHRD received weight and risk factor management counseling. Additionally, everyone was given the option of participating in a physician-led dedicated weight management program. Alternatively, enrollment in a self-managed WL program was offered. Irrespective of the type of weight management strategy, the initial goal for everyone was to reduce weight by 10%. The next goal was to achieve a body mass index of ≤ 25 kg/m² with maintenance of WL. For the purposes of analyses, the authors categorized WL into 3 groups—group 1 ($\geq 10\%$ WL), group 2 (3–9% WL) and group 3 (<3% WL). It appears that the authors used a 3% cut off as WL less than 3% is not considered to be clinically meaningful by the ACC/AHA.¹⁰ Patients underwent management of AF as per treating physicians' discretion—any combination of rate control, anti-arrhythmic drugs (AAD) (sotalolol or flecainide) or catheter ablation (pulmonary vein isolation \pm roofline and/or mitral isthmus linear ablation) was allowed. The primary outcome was AF symptom burden using the AFSS instrument and freedom from AF (based on clinical data, 12-lead EKG and 7-day Holter monitor at yearly follow-ups). Secondary outcomes of left atrial volume and left ventricular thickness were assessed by echocardiography, and metabolic/ inflammatory markers were assessed by measuring high sensitivity C reactive protein (hs-CRP), lipid profile and fasting insulin at baseline and final follow up. Changes in primary and secondary outcomes from baseline to follow-up (5-years) were assessed for statistical significance. Additionally, survival analyses for freedom from AF were also estimated.

Baseline demographics, risk factor characteristics, cardiac structure and medication use appeared to be balanced among the 3 WL categories. One important baseline difference was in the degree of WL clinic attendance—84% of patients in group 1 ($\geq 10\%$ WL), 57% of patients in group 2 and 30% of patients in group 3 attended the WL clinic (p < 0.001). Among primary outcomes, AF symptom burden improved across all 3 groups, but were more pronounced in group 1 as compared to the other groups. There were improvements across every component of the AFSS instrument- AF frequency, duration, severity and global well-being scores. At final follow-up, arrhythmia-free survival rates were 86.2% in

group 1 vs. 65.5% in group 2 vs. 39.6% in group 3 ($p < 0.001$); this was despite decreased AAD use in group 1 as compared to groups 2 & 3 ($p < 0.001$). However, there were no differences in mean ablation procedures across groups. In order to show that the superior rhythm control in group 1 was independent of differential ablation or AAD use among the groups, the authors also presented data regarding “ablation and drug-free” rhythm control. Over 5 years, it was estimated that 45.5% of group 1 as compared to 13.4% of group 3 ($p < 0.001$) maintained AF freedom without ablation or AAD use. This demonstrated a direct association between WL and rhythm control. Further, there were “dose-dependent” improvements in all risk factors and secondary outcomes—patients in group 1 had better blood pressure and diabetes control, required less anti-hypertensive therapy, less lipid therapy, had lower hs-CRP and fasting insulin levels, as well as healthier lipid profiles as compared to group 2 and group 3 patients. Interestingly, over the follow-up period of 5 years, group 1 & 2 patients also were noted to have reduced left atrial volumes, left ventricular thickness and better diastolic function as compared to group 3.

The authors further hypothesized that significant WF would have an adverse impact on rhythm control in obese patients. Weight trends were defined as follows; linear WL (no interim weight gain $\geq 1\%$), linear weight gain (no interim WL $\geq 1\%$), and WF ($\geq 1\%$ WL or gain). WFs were further categorized as wide ($>5\%$), average ($2 - 5\%$) or stable ($<2\%$), in order to assess characterize the association between the magnitude of WF and rhythm control. Of the 355 patients in the analysis, 179 patients (50%) were noted to have WF. Patients with linear WL had better rhythm control as compared to patients with WF (76% vs. 59%, $p < 0.001$). As expected, patients with weight gain had even worse AF-free survival (38%). When AF-free survival curves were estimated for the groups of patients with WF, it was found that only 44.2% of patients with $>5\%$ WF maintained rhythm control, which was much lower than the percentage of patients maintaining rhythm control in the 2-5% WF (59%) and those with $< 2\%$ WF (85.2%). From these data, it appears that rhythm control in patients with $> 5\%$ WF is poor and on par with those who gained weight (44.2% and 38% respectively).

CRITIQUE & DISCUSSION OF TRIAL

This observational study is an important contribution to the growing body of literature on the influence of WL on AF burden and rhythm control in obese patients. The strengths of the study include its meticulous design and standardized data collection over a five-year period. However, it is important to note that despite the detailed study design, it is still a small, observational study consisting of 355 patients which limits generalizability. Additionally, the study findings need to be interpreted in the context of the known biases and confounding which limit all observational data.

Despite the fact that the 3 groups appeared to have similar baseline characteristics, confounding remains an issue in this study. It is important to note that the WL goals for all people attending the CHRd was $>10\%$ reduction in body weight, followed by the next target of achieving a body mass index ≤ 25 kg/m², irrespective of enrollment in the weight management clinic. Therefore, the 3 WL groups ($\geq 10\%$ WL, 3–9% WL and $<3\%$ WL) were “observed” and not “intended”. This introduces confounding-by-indication as well as the issue of residual confounding among the 3 WL groups. For example, individuals who managed to achieve $\geq 10\%$ WL were perhaps also motivated to improve their risk factor profile through greater medication and dietary compliance. The effect of these behavioral differences among patients who were “categorized” into different WL groups cannot be estimated in this study. This confounding-by-indication is independent of the clustering effect of obesity and WL on other risk factors, which in turn confound our understanding of the relationship between long-term WL and AF free survival. Further, we have to be cautious with the generalizability of these data. For example, over 50% of patients in each WL group in this study have apnea-hypopnea indices that would be categorized as severe obstructive sleep apnea (OSA) by the American Academy of Sleep Medicine.¹¹ This is very different from the prevalence of OSA in other AF cohorts. In the ORBIT-AF cohort [Outcomes Registry for Better Informed Treatment of Atrial Fibrillation], which was a large ($n = 10,132$) US based registry of outpatient AF patients, only 18% had any form of OSA.¹² Since WL is a major component of the management of OSA, it is possible that the dramatic differences seen in the outcomes between the groups in the LEGACY study were mostly due to WL-related improvement in OSA, which in turn affected AF outcomes. Therefore, it is plausible that the magnitude of association between WL and freedom from AF seen in this study may not be replicated in other populations.

Another important consideration while interpreting data from the LEGACY study is to identify the true exposure variable—is it purely the degree of WL that is relevant, or is enrollment in the weight

management clinic more important? Obviously, the two are interrelated but the key “exposure variable” of this study appears to be enrollment in the weight management clinic. The degree of WL was an outcome that was observed over a 5-year period. Therefore, to be able to replicate the encouraging findings of this study, it is vital that we understand how the weight management clinic was designed. This clinic was run by a dedicated physician and research assistant who performed face-to-face motivational and goal-directed counseling at 3-month intervals. Initially, participants received a meal plan (high protein, low glycemic index, calorie-controlled) and if they did not lose adequate weight ($> 3\%$), then they received very-low-calorie meal replacement sachets (1–2 times/day). Participants were also asked to exercise (starting with low intensity exercise for 20 minutes three times a day which was increased to moderate intensity exercise 200 minutes weekly). In addition, all participants were also asked to maintain a journal to record daily food intake, exercise duration, weight and blood pressure. For patients attending the WL clinic, all other risk factors such as hypertension, diabetes, dyslipidemia, sleep-disordered breathing, tobacco and alcohol use were managed according to ACC/AHA guidelines every 3 months.

In reality, global risk factor management may have been the element of the weight management clinic that truly impacted AF-related primary and secondary outcomes. The weight management clinic is the real success behind the stunning findings from the LEGACY study. It is easy to envision the heightened level of care that patients attending the WL clinic received, which is much more attention than real world patients receive. Not only did they receive motivation and guidance for WL, they also received counseling regarding most other risk factors for AF, which ultimately translated to better clinical outcomes in the long-term. This is akin to the dramatic benefits of a cardiac rehabilitation program in post-myocardial infarction patients. Benefits accrue from the exercise programs as well the ancillary support such as pharmacy counseling, lifestyle counseling, nutritional counseling, emotional support etc. Therefore, the weight management clinic offers a holistic approach to disease management, rather than isolated WL.

WHAT HAVE WE LEARNED?

The take-home point of the LEGACY study is that a concerted effort at risk factor management (including obesity management) is vital for achieving better outcomes with AF. While there is a strong signal that suggests that WL itself may be independently associated with prolonged rhythm control, it is nearly impossible to estimate the relative importance of WL as compared to co-management of other contributory risk factors. The more recently published CARDIO-FIT study [Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals with Atrial Fibrillation: The CARDIO-FIT Study], conducted in the same Australian cohort, by the same group of investigators highlights this point.¹³ In this study, the authors provide further details of the graded exercise program in the weight management clinic. Using exercise treadmill tests to assess gender-specific metabolic equivalents (METs) at baseline and study conclusion, the authors reported that AF burden and symptom severity decreased significantly in the group with cardiorespiratory fitness gain ≥ 2 METs over the study period as compared to < 2 METs.¹³ This raises the question of how much of the benefits in AF symptom improvement accrue from graded exercise and improved oxygenation and how much is the result of the ensuing WL?

In conclusion, it is important to understand that AF burden has multifactorial inputs and the overall process of risk factor management is the key for AF management, just like any other cardiovascular disease. The editorial accompanying the LEGACY study points out that the “the 3 pillars for treatment of AF include anticoagulation, rhythm control, and rate control”.¹⁴ In addition to these classic tenets that we address in all AF patients, based on the LEGACY study findings, we ought to consider multi-faceted obesity/cardiovascular risk factor management as the fourth pillar of AF management.

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