a 1:1 ratio to once-daily doses of either ezetimibe/simvastatin (10/40 mg) or simvastatin monotherapy (40 mg) and followed for 2.5 years or until at least 5250 patients experienced a primary end point event.

The primary end point of the first occurrence of CV death, nonfatal myocardial infarction (MI), rehospitalization for unstable angina (UA), coronary revascularization (occurring ≥30 days after randomization), or stroke occurred in significantly more patients in the simvastatin monotherapy arm vs combination therapy arm (34.7% vs 32.7%; HR, 0.94; 95% CI, 0.89 to 0.99; $P=.016$). The number needed to treat was 50.

The occurrence of a first event for each of the 3 prespecified secondary end points was also significantly higher with simvastatin monotherapy vs combination therapy. All-cause death/MI/UA/coronary revascularization/stroke occurred in 40.3% vs 38.7%, respectively ($P=.034$). Coronary heart disease (CHD) death/MI/urgent coronary revascularization occurred in 18.9% vs 17.5% ($P=.016$). CV death/MI/UA/any revascularization/stroke occurred in 36.2% vs 34.5% ($P=.035$). Significance was driven by fewer MIs, strokes, and urgent revascularization events.

The present analysis determined the number of first and recurrent events recorded during the mean 6-year follow-up, with the hypothesis that the number of total events would be reduced with combination therapy vs simvastatin monotherapy. There were 5314 first primary end point events and 4231 additional primary end point events, the majority of which were revascularization for both first and recurrent events. Overall, there were significantly fewer total primary end point events with combination therapy (RR, 0.91; 95% CI, 0.85 to 0.97; $P=.007$; Figure 1). These results were reflected in a reduction in additional primary end point events (RR, 0.88; 95% CI, 0.79 to 0.98; Figure 1).

Figure 1. Fewer Total (First and Recurrent) Primary End Point Events With Combination Therapy

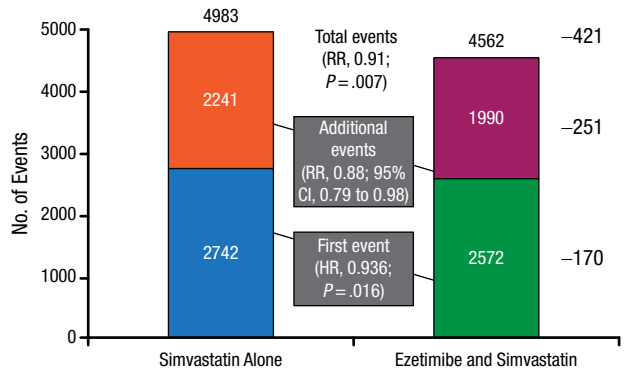

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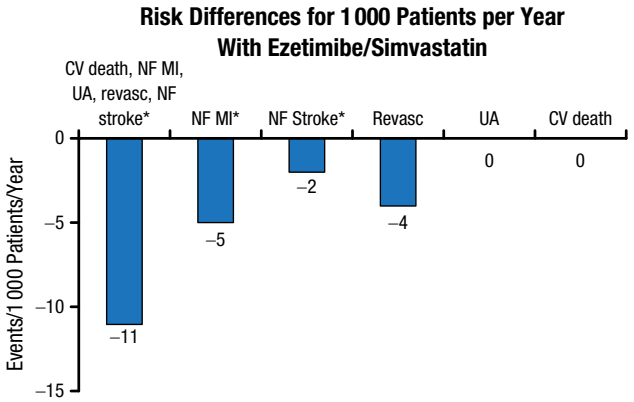
Figure 2. Risk Differences for Total Primary End Point Events



CV, cardiovascular; MI, myocardial infarction; NF, nonfatal; Revasc, revascularization; UA, unstable angina.
*$P<.05$; others not significant.
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There were fewer total secondary end point events with combination therapy as well, including fewer CHD deaths, MIs, and urgent revascularization events (RR, 0.85; 95% CI, 0.76 to 0.94; $P=.002$), fewer all-cause death/MI/UA/coronary revascularization/stroke (RR, 0.92; 95% CI, 0.87 to 0.98; $P=.009$), and fewer CV death/MI/UA/any revascularization/stroke (RR, 0.93; 95% CI, 0.87 to 0.99; $P=.02$).

Sensitivity analysis using the Wei, Lin, and Weissfeld model for the occurrence of primary end point events favored combination therapy (model average HR, 0.93; 95% CI, 0.89 to 0.99; $P=.01$). The absolute risk difference for total primary end point events, nonfatal MI, and nonfatal stroke also favored ezetimibe/simvastatin therapy ($P<.05$; Figure 2).

This is the first trial demonstrating clinical benefit when adding a nonstatin lipid-lowering agent to statin therapy. By treating patients with a daily combination of ezetimibe/simvastatin rather than simvastatin alone, more than twice the number of recurrent adverse CV events was prevented compared with first events.

LEGACY: Sustained Weight Loss Improves Heart Rhythm Control in 5-Year Trial

Written by Francesca Coltrera

Steady, sustained weight loss can help control atrial fibrillation (AF) in overweight patients, even freeing some from the need for medications or surgical ablation. Rajeev K. Pathak, MBBS, University of Adelaide

and Royal Adelaide Hospital, Adelaide, Australia, presented findings from the 5-year LEGACY trial [Pathak RK et al. *J Am Coll Cardiol*. 2015].

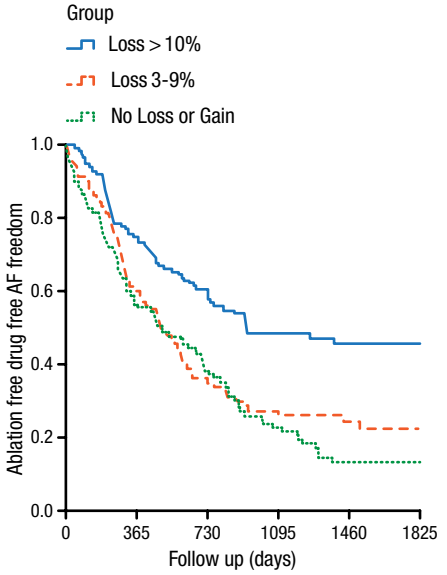
The incidence of AF is increasing in concert with the global increase in the body mass index (BMI), perhaps in part because of the influence of shared risk factors for the metabolic syndrome, as suggested by the ARIC cohort study [Chamberlain AM et al. *Am Heart J*. 2010]. In 2013, a smaller, 15-month study on short-term weight loss and metabolic risk factor management found reductions in AF symptoms and severity after a weight management intervention [Abed HS et al. *JAMA*. 2013].

LEGACY investigators enrolled 355 patients with AF and a BMI ≥27 kg/m^2 who agreed to participate in a physician-led metabolic risk factor and weight management clinic. The study sought to determine whether there was a dose-dependent relationship between long-term weight loss and freedom from AF and the impact of fluctuations in weight on AF.

The co-primary outcomes were AF symptom burden measured by a validated questionnaire and freedom from AF by 7-day Holter monitoring. Secondary outcomes were the impact of weight loss on left atrial volume and left ventricular (LV) thickness, and metabolic and inflammatory risk factors.

After participating in the clinic, patients were divided into 3 groups: group 1, ≥10% weight loss (WL; n = 135); group 2, 3% to 9% WL (n = 103); and group 3, <3% WL, or weight gain (n = 117).

Figure 1. Freedom From Antiarrhythmic Drugs, Ablation, and Atrial Fibrillation

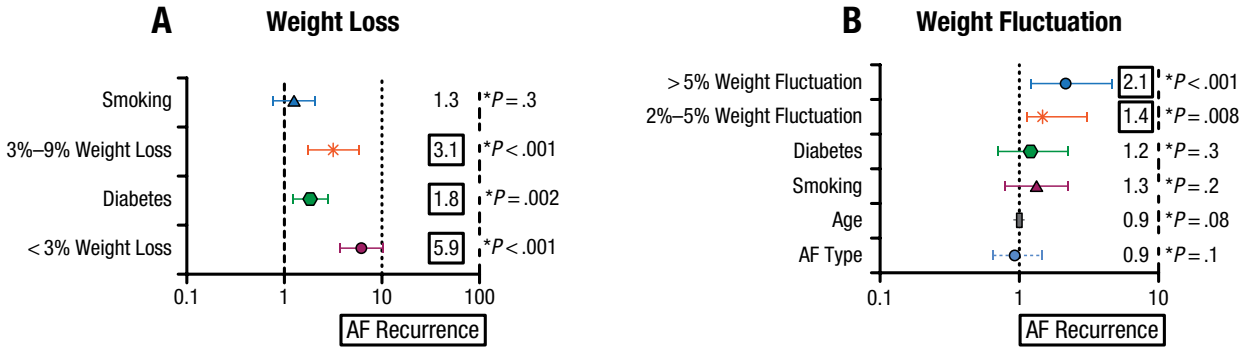


Time (Days)	0	365	730	1095	1460	1825
>10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9

AF, atrial fibrillation; WL, weight loss.

Reprinted from *J Am Coll Cardiol*, Pathak RK et al. Long-term effect of goal directed weight management in an atrial fibrillation cohort: a long-term follow-up study (LEGACY Study). Article in Press, DOI: 10.1016/j.jacc.2015.03.002. Copyright (2015), with permission from American College of Cardiology.

Figure 2. Multivariate Predictors of Atrial Fibrillation-Free Survival and Atrial Fibrillation Recurrence



AF, atrial fibrillation.

(A) ≥10% weight loss was associated with AF-free survival (HR, 5.7; 95% CI, 3.3 to 10.1; *P* < .001).

(B) >5% weight fluctuation was associated with AF recurrence (HR, 2.2; 95% CI, 1.1 to 4.2; *P* < .001).

Reproduced with permission from RK Pathak, MBBS.

Source: Pathak RK et al. *J Am Coll Cardiol*. 2015.

Baseline characteristics, including age, BMI range, metabolic syndrome risk factors, coronary artery disease, and sleep apnea incidence, were similar across the groups. Annual follow-up determined changes in weight.

A dose-dependent relationship between weight loss and risk factors for the metabolic syndrome was found. Stepwise reductions in AF frequency, severity, and duration were found, along with stepwise increases in global well-being scores. This was most marked in group 1, in which nearly half of patients had freedom from AF without medications or ablation (Figure 1). Total arrhythmia-free survival was 86% in group 1, 66% in group 2, and 40% in group 3 ($P < .001$).

According to the multivariate analysis, a greater weight loss was associated with greater AF-free survival, while greater fluctuations in weight were associated with AF recurrence (Figure 2).

In regard to structural remodeling, there were greater reductions in left atrial volume and LV thickness as compared with baseline with more weight loss.

The LEGACY trial showed that sustained weight loss in obese patients appeared to improve AF burden and heart rhythm control, although weight fluctuations of >5% reduced this benefit. The study also showed that a dedicated weight loss clinic improved patient engagement, promoted treatment adherence, and prevented regaining weight and weight fluctuations.

After Eighty Study: Invasive Intervention Superior to Conservative Management

Written by Eleanor Mayfield

Early invasive intervention after medical stabilization following NSTEMI or unstable angina pectoris (UAP) was superior to conservative management in participants aged ≥80 years in the After Eighty Study [NCT01255540]. The results were reported by Nicolai Tegn, MD, Rikshospitalet Oslo University Hospital, Oslo, Norway.

Patients aged ≥75 years represent approximately a third of all patients with NSTEMI and UAP [Jokhadar M, Wenger NK. *Clin Interv Aging.* 2009]. However, this population is underrepresented in clinical trials; only 1 previous randomized trial, the Italian Elderly ACS Study [Savonitto S et al. *JACC Cardiovasc Interv.* 2012], has been conducted exclusively in this age group. The role of invasive management in patients aged ≥80 years following NSTEMI or UAP is a matter of debate, Prof Tegn said.

Of 4187 patients who were screened, 457 patients (mean age 85 years), who were medically stabilized after presenting with a syndrome consistent with NSTEMI/UAP, were enrolled in the After Eighty Study, an open-label randomized trial, conducted at 17 centers in Norway between 2010 and 2014. The primary reasons for the exclusion from the study were short life expectancy (<1 year), inability to comply with study protocol, refusal to participate, and clinical instability. Participants in the invasively treated group (n=229) were 45% women; in the conservatively treated group (n=228), 56% of participants were women.

Baseline medical history and risk factors were similar between the 2 groups. In both groups, >90% of participants had troponin elevation, 97% were receiving aspirin 75 mg, and >80% were receiving platelet inhibitors, β-blockers, and statins. The study's primary end point was a composite of myocardial infarction (MI), need for urgent revascularization, stroke, and death.

Among participants in the invasively treated group, angiography revealed stenosis in ≥1 vessel in 74% (n=165); 49% (n=107) underwent percutaneous coronary intervention and 3% (n=6) underwent coronary artery bypass grafting. In 90% (n=198) of participants who underwent revascularization, radial access was used. Participants in both groups received optimal medical treatment.

After a median follow-up of 1.5 years, 41% (n=93) of invasively treated participants met the composite primary end point, compared with 61% (n=140) of those treated conservatively (rate ratio [RR], 0.48; 95% CI, 0.37 to 0.63; $P < .00001$).

MI occurred in 17% of invasively treated participants (n=39) vs 30% (n=69) of those treated conservatively (RR, 0.5; $P < .0003$). Urgent revascularization was required in 2% (n=5) of invasively treated participants vs 11% (n=24) of those treated conservatively (RR, 0.19; $P = .0001$). The composite of death plus MI occurred in 35% (n=81) of invasively treated participants vs 48% (n=109) of those treated conservatively (RR, 0.54; $P < .0001$). The 2 groups did not differ significantly in rates of stroke ($P = .26$), death from any cause ($P = .53$), or bleeding complications (no P values reported).

In summary, in a highly selected randomized cohort with a mean age of 85 years, an early invasive treatment strategy after medical stabilization following NSTEMI or UAP had statistically significantly superior results compared with a conservative management strategy, with no increase in bleeding complications. The radial approach was used in 90% of the study patients.