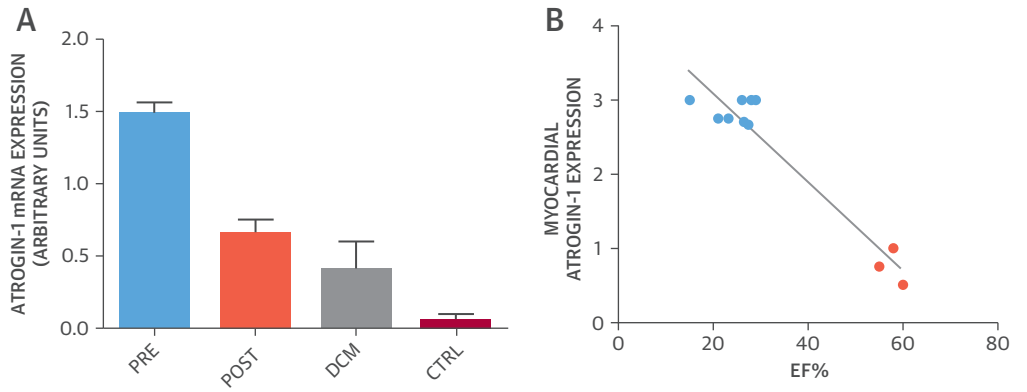
FIGURE 1 Myocardial Atrogin-1 Expression in Cushing Syndrome Cardiomyopathy



(A) Myocardial atrogin-1 messenger ribonucleic acid (mRNA) expression in Cushing syndrome cardiomyopathy before and after adrenalectomy, in idiopathic dilated cardiomyopathy (DCM) and control (CTRL) biopsy samples. **(B)** Inverse correlation between myocardial atrogin-1 and left ventricular ejection fraction (EF). **Blue circles** indicate failing state; **orange circles** indicate recovery state.

Myocardial fibrosis derives from a direct glucocorticoid stimulation of fibroblast activity, likely through Smad and the transforming growth factor beta-1 pathway, and was reduced in our CS population from 11.5% to 3.1% after adrenalectomy, confirming the data obtained by speckle tracking echocardiography (3).

Along with CS, chronic steroid administration may result in cardiac arrhythmias, remodeling, and dysfunction that reflect a direct detrimental action on cardiomyocyte structure and function. Patients on steroids who manifest with cardiomyopathy should consider drug discontinuation.

In conclusion, CS cardiomyopathy is a reversible entity induced by high levels of glucocorticoids, characterized by cell hypertrophy, myofibrillolysis, and myocardial fibrosis that revert after adrenalectomy. Atrogin-1 activation has a major pathogenetic role.

*Andrea Frustaci, MD
Claudio Letizia, MD
Romina Verardo, PhD
Claudia Grande, PhD
Camilla Calvieri, MD
Matteo Antonio Russo, MD
Cristina Chimenti, MD, PhD

*Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences
La Sapienza University
Viale del Policlinico 155
Rome 00161
Italy
E-mail: biocard@inmi.it

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Time Course of Change in Ectopic Fat Stores After Bariatric Surgery

More than body mass index (BMI), adiposity distribution in visceral area and in ectopic sites likely plays an important role in the obesity-related risk. Ectopic fat accumulation in the heart, the liver, and the pancreas, namely steatosis, could induce accumulation of toxic lipid intermediates leading ultimately to organ dysfunction. Whether ectopic fat stores are subjected to modification through intervention approaches is therefore crucial. The development of noninvasive imaging has made it possible to quantify ectopic fat stores with accuracy. Myocardial triglyceride content (MTGC), hepatic triglyceride content (HTGC), and pancreatic triglyceride content (PTGC) can be measured in humans by proton magnetic resonance spectroscopy (1). We previously demonstrated

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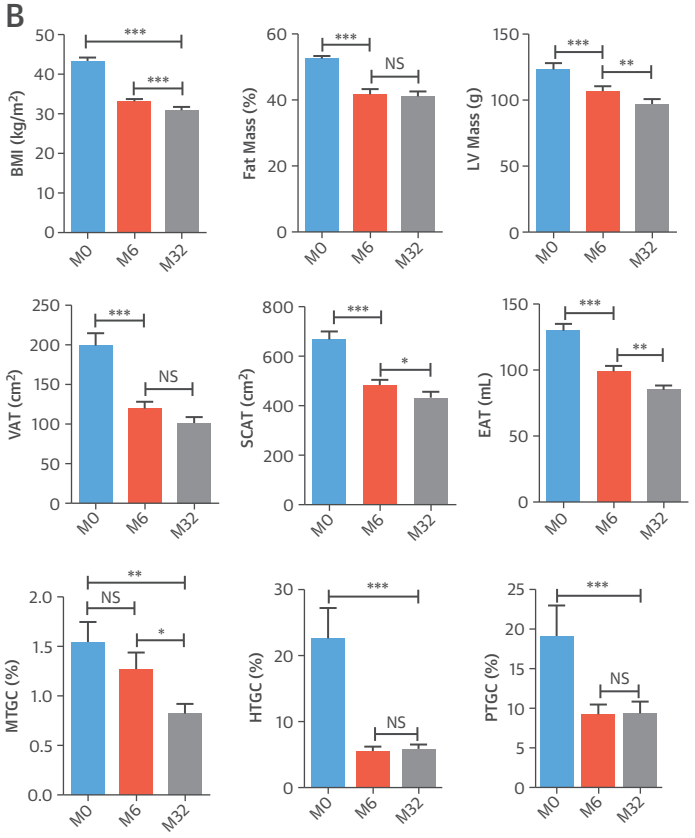
FIGURE 1 Dynamics After Bariatric Surgery

A

	M0	M6	M32
Hypertension	6 (29%)	4 (19%)	4 (19%)
T2D	8 (38%)	2 (10%)*	2 (10%)*
Dyslipidemia	7 (33%)	6 (29%)	4 (19%)
Fasting plasma glucose, mmol/L	5.6 ± 0.3	4.6 ± 0.1*	4.8 ± 0.2*
Fasting plasma insulin, mUI/L	18.9 ± 2.6	7.1 ± 1.2*	11.6 ± 2.9*
HDL-CT/TG	1.16 ± 0.13	1.32 ± 0.11	2.4 ± 0.33*†
HbA1c, %	6.2 ± 0.2	5.5 ± 0.1*	5.4 ± 0.1*
PAI-1, UI/mL	25.8 ± 4.2	8.8 ± 1.6*	6.4 ± 1.0*
Adiponectin, μg/mL	4.4 ± 0.6	7.0 ± 0.9*	9.0 ± 1.2*†
Leptin, ng/mL	119.3 ± 13.6	44.9 ± 4.7*	23.2 ± 3.7*†
Uric acid, μmol/L	325.8 ± 21.8	288.1 ± 16.7*	285.4 ± 15.0*

*p<0.05 vs M0, † p<0.05 vs M6

B



(A) Comparison of clinical and biological parameters at baseline, 6 months, and 32 months. **(B)** Dynamics of ectopic fat depots after bariatric surgery. *p < 0.05. BMI = body mass index; EAT = epicardial adipose tissue; HTGC = hepatic triglyceride content; LV mass = left ventricular mass; MTGC = myocardial triglyceride content; PTGC = pancreatic triglyceride; SCAT = subcutaneous abdominal fat; VAT = visceral abdominal fat.

that after 6 months, bariatric surgery (BS) significantly decreased visceral fat (VAT), HTGC, PTGC, and to a lesser extent, epicardial adipose tissue (EAT) (1). However, we found no significant change in myocardial fat, although it was increased at baseline (1). Whether more sustained weight loss is able to modulate cardiac fat depots is the question we addressed here.

We obtained the ethics committee's approval to re-evaluate ectopic fat deposits 2 or 3 years after surgery (mean 32 months) in a group of 23 severe obese patients who already underwent cardiac magnetic resonance imaging and proton magnetic resonance spectroscopy. EAT, MTGC, HTGC, and PTGC could be evaluated in 21 patients. The majority of patients were female (81%). Mean age was 42 ± 2 years, and mean BMI was 43.2 ± 1.1 kg/m². Changes in ectopic fat levels were tested with the paired Student *t* test or Wilcoxon test. The associations between relative changes in each variable were tested with Spearman correlation. A p value <0.05 was considered statistically significant.

At 32 months, weight significantly decreased from 118 ± 15 kg to 84 ± 18 kg and BMI from 43.2 ± 4.3 kg/m² to 30.7 ± 4.9 kg/m² (both, $p < 0.0001$). The mean percentage of excess weight loss and fat mass loss at 32 months was 67 ± 27% and 21 ± 14%, respectively. All patients lost weight between 6 and 32 months, except for 5 patients who regained weight (+10 ± 9 kg) and 1 patient who remained stable. We observed complete remission of obstructive apnea syndrome for 8 of 8 patients and diabetes remission for 6 of 8 patients. After BS, we observed an important decrease in visceral fat (VAT −46 ± 27%; $p < 0.0001$), hepatic (HTGC −31 ± 36%; $p = 0.0001$) and pancreatic fat (PTGC −44 ± 20%; $p = 0.0010$) compared with baseline, but no more reduction was found at 32 months compared with 6 months (Figure 1B). EAT (−33 ± 16%) and subcutaneous abdominal fat (−33 ± 26%) continued to decrease to a significant extent compared with their 6-month values ($p = 0.008$ and $p = 0.03$, respectively). Importantly, MTGC significantly decreased at 32 months compared with baseline (−40 ± 7%; $p = 0.001$), and left ventricular mass decreased at 6 months and continued to decrease between 6 and 32 months (−9 ± 10%; $p = 0.001$). The high-density lipoprotein/triglycerides ratio significantly increased at 32 months (Figure 1A) and was significantly associated with VAT, but not with MTGC ($r = 0.56$, $p = 0.02$; $r = 0.05$, $p = NS$, respectively).

No association was observed between percentage of ectopic fat losses and body weight changes ($p = NS$). Neither EAT and VAT loss nor HTGC and MTGC loss were correlated, suggesting discrepancies in adiposity reduction.

Our findings suggest that cardiac fat has a more delayed response to BS than that seen in visceral fat, or other steatoses. Significance of triglyceride accumulation in the heart is still debated (2). The contracting heart has much higher metabolic demand than other organs. Whether the presence of lipid droplets in cardiomyocytes is detrimental or a

beneficial compensatory response to altered systemic metabolic changes in obesity needs further evaluation. Our results also confirm those obtained for skeletal muscle, with reversal of systemic and muscle metabolic derangements only 9 months after BS (3). The improvement in life-style habits may have also contributed to the late reduction in cardiac steatosis. Compared with usual care, BS is the most effective treatment for severe obesity, and the long-term results regarding reduction of cardiovascular mortality have been well established. To the best of our knowledge, this study is the first to show a significant improvement in all types of ectopic fat depots, even cardiac steatosis, long-term after BS. Whether these improvements participate in the reduction of cardiovascular risk and mortality in obese patients needs to be confirmed.

Ines Abdesselam
Anne Dutour, MD, PhD
Frank Kober, PhD
Patricia Ancel, MS
Thierry Bege, MD, PhD
Patrice Darmon, PhD
Nathalie Lesavre, MD
Monique Bernard, PhD
***Bénédicte Gaborit, MD, PhD**

*Inserm U1062, Inra U1260
Aix Marseille Université, Faculté de Médecine
27 Boulevard Jean Moulin
13385 Marseille Cedex 05
France
E-mail: benedicte.gaborit@ap-hm.fr

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Getting What the Guidelines Stated Matters

We read with interest the recently published report of the multicenter randomized controlled trial (RCT) known as PRECISE-IVUS (plaque regression with cholesterol absorption inhibitor or synthesis inhibitor evaluated by intravascular ultrasound) (1). While we noted that coronary angiographic outcomes in those assigned to combination statin plus ezetemibe therapy compared favorably to those assigned statin monotherapy, we were concerned that the authors did not refer to the 2013 ACC/AHA guidelines in an accurate fashion. Our evidence-based guidelines were not "fire and forget" as the authors write in their discussion. Moreover, they express a serious misconception about what the guidelines actually said about nonstatins.

In both the guideline recommendations tables, key figures (Figure 3 entitled Initiating Statin Therapy in Individuals with Clinical ASCVD, and Figure 5 entitled Statin Therapy: Monitoring Therapeutic Response and Adherence), and in the text, we indicate clearly what the recommendations and workflow are for secondary prevention patients (2).

We think it is crucial that readers understand what the guidelines recommended. Figure 3 shows that in secondary prevention patients, the clinician initiates high-intensity statin therapy if age ≤75 years and **without** contraindications, conditions, or drug-drug interactions influencing statin safety or a history of statin intolerance. In addition to statin therapy, lifestyle counseling was also recommended. In Figure 5 whose title alone indicates that the phrase "Fire and Forget It" does not refer to the 2013 ACC-AHA guidelines, it clearly shows that the guidelines recommend a follow-up lipid panel 4 to 12 weeks after initiation of statin therapy to assess both response to therapy (the anticipated response to high-intensity statin therapy was given as a ≥50% reduction in low-density lipoprotein cholesterol [LDL-C]) and as a baseline for adherence.

If the ACC/AHA cholesterol guidelines were followed in the participants in this trial, the anticipated LDL-C would have been approximately in the mid-50 mg/dl range since baseline LDL-C in both the LZ and L group were 109.8 and 108.3 mg/dl, respectively. Mindful that not everyone tolerates high-intensity statins, the guidelines addressed the situation where statin intolerance would occur. It specifically noted: "Clinicians treating high-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant, may consider the addition of a nonstatin cholesterol-lowering therapy. High-risk individuals include those with ASCVD, those with LDL-C ≥190 mg/dl, and those with diabetes 40 to 75 years of age. In this situation, this guideline recommends clinicians preferentially prescribe drugs that have been shown in RCTs to provide ASCVD