Impact of Macroprolactinemia on Cardiometabolic Effects of Atorvastatin in Women With Hypercholesterolemia

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Premenopausal women with macroprolactinemia are characterized by increased cardiometabolic risk. No previous study has investigated the impact of any lipid-lowering agent on circulating levels of cardiometabolic risk factors in patients with elevated macroprolactin content. We studied 2 groups of women matched for age, body mass index, plasma lipids, and blood pressure: 12 women with macroprolactinemia and 14 women with prolactin levels within the reference range. Because of coexistent isolated hypercholesterolemia, all subjects were then treated with atorvastatin (20 mg daily). Glucose homeostasis markers, plasma lipids, as well as circulating levels of uric acid, high-sensitivity C-reactive protein (hsCRP), fibrinogen, homocysteine, and 25-hydroxyvitamin D were measured before entering the study and 6 months later. The treatment arms differed in baseline values of hsCRP and 25-hydroxyvitamin D, as well as in insulin sensitivity. Atorvastatin decreased total and low-density lipoprotein cholesterol levels stronger in women without than in women with macroprolactinemia. In normoprolactinemic women, atorvastatin decreased circulating levels of uric acid, hsCRP, fibrinogen, homocysteine, and increased concentrations of 25-hydroxyvitamin D, whereas in women with macroprolactinemia the drug decreased levels of hsCRP and homocysteine, as well as impaired insulin sensitivity. Both study groups differed in post-treatment insulin sensitivity and post-treatment values of prolactin before polyethylene glycol precipitation, macroprolactin, total cholesterol, low-density lipoprotein cholesterol, glycated hemoglobin, uric acid, hsCRP, fibrinogen, homocysteine, and 25-hydroxyvitamin D. In conclusion, the obtained results suggest that macroprolactinemia may attenuate cardiometabolic effects of atorvastatin. **(Am J Cardiol 2019;124:1207−1212)**

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HOMA1-IR, the homeostatic model assessment 1 of insulin resistance ratio; hsCRP, high-sensitivity C-reactive protein; IU, international unit; LDL, low-density lipoprotein; SD, standard deviation

Macroprolactin (big-big prolactin), composed mainly (90%) of complexes of prolactin and immunoglobulin G, constitutes less than 1% of circulating prolactin.[1,2] Its excess (macroprolactinemia) is estimated at 3.7% in the general population and at from 15% to 35% in subjects with hyperprolactinemia.[3] Although macroprolactinemia is generally considered an asymptomatic laboratory finding,[2,4,5] the results of some studies suggest that elevated levels of big-big prolactin may exert some prolactin-like effects. A significant number of women with elevated levels of macroprolactin complained of oligomenorrhea/amenorrhoea, galactorrhea, and subfertility.[6,7] The prevalence of macroprolactinemia in diabetic patients was higher than in the nondiabetic population.[8] Finally, compared with healthy counterparts, women with isolated macroprolactinemia had increased levels of triglycerides and high-sensitivity C-reactive protein (hsCRP), as well as lower levels of high-density lipoprotein cholesterol and 25-hydroxyvitamin D.[9] Recent studies[10,11] have revealed that monomeric prolactin, being the predominant form of circulating prolactin,[4] determines the impact of hypolipidemic agents on circulating levels of cardiometabolic risk factors. Therefore, the aim of the present study was to investigate whether macroprolactinemia modulates cardiometabolic effects of atorvastatin.

Methods

The study population was selected among adult women (aged 35 to 65 years) with elevated cholesterol levels, defined as total cholesterol concentrations more than 200 mg/dl and low-density lipoprotein (LDL) cholesterol

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See page 1211 for disclosure information.

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concentrations above 130 mg/dl, complying with the lifestyle modification for more than 3 months before entering the study. The first group included 12 women meeting the following criteria of macroprolactinemia: (1) total prolactin levels more 40 ng/ml found on 2 different occasions; (2) the prolactin recovery below 40%, and (3) postpolyethylene glycol circulating prolactin levels less than 25 ng/ml. These subjects were compared with 14 women belonging to the control group in whom prolactin levels were within the reference range (5 to 20 ng/ml). To obtain 2 groups matched for age, body mass index, plasma lipids, systolic blood pressure, and diastolic blood pressure, control subjects were selected among 85 women with hypercholesterolemia based on a computer algorithm. To limit the impact of seasonal fluctuations in vitamin D status, 6 women with macroprolactinemia and 7 control women were recruited in January and February, whereas the remaining ones in July and August. The study was approved by the local institutional review board. Written informed consent was obtained from all patients, and the study protocol followed the principles of the Declaration of Helsinki.

The exclusion criteria were as follows: monomeric hyperprolactinemia, kidney or hepatic failure, thyroid disorders, diabetes, acute and chronic inflammatory processes, cardiovascular disease (with the exception of mild arterial hypertension), gestation or breastfeeding, as well as any pharmacotherapy.

During the entire study, all enrolled subjects were given atorvastatin (20 mg once daily at bedtime) for 6 months. Both groups of patients were also requested to further comply with the lifestyle modification (total fat intake <30% of total energy intake, saturated fat intake <7% of energy consumed, cholesterol intake <200 mg per day, an increase in fiber intake to 15 g per 1,000 kcal, moderate to vigorous exercise for at least 30 minutes per day). Treatment compliance was assessed by tablet counts once monthly at control visits, aimed at investigating possible drug-induced side effects. Compliance with lifestyle modification was checked at each visit by analysis of 3 days' eating diaries and direct questioning.

All venous blood samples for laboratory were collected from 7.30 to 8.30 A.M. after 12-hour overnight fasting in a quiet and air-conditioned room (constant temperature of 23°C to 24°C). Glucose levels were additionally determined in samples collected 2 hours after consumption of 75 g of glucose. Seasonal and other external conditions were similar for all participants. Plasma levels of glucose, total cholesterol, high-density lipoprotein cholesterol, LDL cholesterol, triglycerides, uric acid, prolactin, insulin, hsCRP, fibrinogen, homocysteine, and 25-hydroxyvitamin D,[9–12] as well as glycated hemoglobulin[12] were measured before and after 6 months of therapy. The homeostasis model assessment 1 of insulin resistance index (HOMA1-IR), assessing the grade of insulin sensitivity, was calculated by multiplying plasma insulin [mIU/L] by plasma glucose [mg/dl] and dividing by 405. Macroprolactin content was determined as previously described.[9,19]

Data with skewed distributions were natural-log transformed to overcome heteroscedasticity. Between- and within-group comparisons were carried out by 2-sample *t* tests and Student's paired *t* tests, respectively. Qualitative data were compared using the chi-square test. Correlations between the measured variables were studied using Pearson's correlation coefficient (r). Differences were regarded as statistically significant if 95% confidence intervals did not include the null value and/or 2-tailed p values were less than 0.05.

Results

At baseline, there were no significant differences between the participants with and without macroprolactinemia in age, body mass index, smoking habits, fasting and 2-hour postload plasma glucose, glycated hemoglobin, plasma lipids, uric acid, fibrinogen and homocysteine (Table 1). Expectedly, both study groups differed in prolactin concentrations before polyethylene glycol precipitation and in macroprolactin content but not in prolactin concentrations after polyethylene glycol precipitation. Compared with normoprolactinemic subjects, women with isolated macroprolactinemia had increased plasma levels of hsCRP, higher values of HOMA1-IR and glycated hemoglobin, and decreased levels of 25-hydroxyvitamin D (Table 1 and Supplementary Table 1).

No significant adverse effects were observed and all subjects completed the study.

In both study groups, atorvastatin decreased total and LDL cholesterol (Table 2 and Supplementary Table 2). In women with normal prolactin levels, atorvastatin reduced plasma levels of uric acid, hsCRP, fibrinogen, and homocysteine, and increased concentrations of 25-hydroxyvitamin D. In women with macroprolactinemia, the drug reduced macroprolactin content, hsCRP, and homocysteine, as well as increased HOMA1-IR. Atorvastatin did not affect body mass index. The impact of atorvastatin on total cholesterol, LDL cholesterol, glycated hemoglobin, uric acid, hsCRP, fibrinogen, homocysteine, and 25-hydroxyvitamin D was more pronounced, whereas the effect on HOMA1-IR was weaker in women with normal prolactin levels than in women with macroprolactinemia. There were differences in post-treatment values of total cholesterol, LDL cholesterol, 2-hour postchallenge plasma glucose, HOMA1-IR, glycated hemoglobin, uric acid, hsCRP, fibrinogen, homocysteine, and 25-hydroxyvitamin D (Table 2).

In subjects with elevated levels of big-big prolactin, prolactin concentrations before polyethylene glycol precipitation and macroprolactin content correlated with (1) plasma levels of hsCRP ($r = 0.37$, $p < 0.01$ and $r = 0.35$, $p < 0.01$, respectively); (2) plasma levels of 25-hydroxyvitamin D ($r = -0.34$, $p < 0.05$ and $r = -0.32$, $p < 0.05$, respectively); (3) HOMA1-IR ($r = 0.32$, $p < 0.05$ and $r = 0.30$, $p < 0.05$, respectively); and (4) 2-hour postload plasma glucose ($r = 0.26$, $p < 0.05$ and $r = 0.29$, $p < 0.05$, respectively). The impact on plasma lipids or glucose homeostasis markers did not correlate with the effect on uric acid, hsCRP, fibrinogen, homocysteine, and 25-hydroxyvitamin D. In women with macroprolactinemia, treatment-induced changes in hsCRP, homocysteine, and HOMA1-IR correlated with baseline levels of prolactin before polyethylene glycol precipitation (hsCRP: $r = -0.40$, $p < 0.001$; homocysteine: $r = -0.28$, $p < 0.05$; HOMA1-IR: $r = 0.35$ $p < 0.01$) and baseline

Table 1
Baseline characteristics of participants

Variable	Women with macroprolactinemia (n = 12)	Control women (n = 14)	Difference [95% confidence interval]
Age [years; mean (SD)]	50 (8)	51 (7)	1 [−5, 7]
Smokers	25%	29%	–
Body mass index [kg/m^2; mean (SD)]	27.9 (5.1)	27.4 (4.9)	−0.5 [−4.6, 3.6]
Systolic blood pressure [mm Hg; mean (SD)]	135 (12)	134 (14)	−1 [−10, 8]
Diastolic blood pressure [mm Hg; mean (SD)]	87 (6)	85 (5)	−2 [−6, 2]
Prolactin before polyethylene glycol precipitation [ng/ml; mean (SD)]	68 (15)	12 (7)	−56 [−65, −47]*
Prolactin after polyethylene glycol precipitation [ng/ml; mean (SD)]	12 (6)	11 (6)	−1 [−6, 4]
Macroprolactin [mean (SD)]	81 (11) %	8 (5) %	−73 [−80, −66]*
Total cholesterol [mg/dl; mean (SD)]	252 (34)	256 (29)	4 [−21, 29]
LDL-cholesterol [mg/dl; mean (SD)]	159 (23)	161 (20)	2 [−15, 19]
HDL-cholesterol [mg/dl; mean (SD)]	49 (8)	51 (8)	2 [−4, 8]
Triglycerides [mg/dl; mean (SD)]	203 (40)	190 (32)	−13 [−42, 16]
Fasting glucose [mg/dl; mean (SD)]	93 (9)	91 (8)	−2 [−9, 5]
2-h postchallenge glucose [mg/dl; mean (SD)]	139 (20)	129 (18)	−10 [−25, 5]
Glycated hemoglobin [mean (SD)]	5.4 (0.4)%	5.3 (0.3)%	−0.1 [−0.4, 0.2]
HOMA1-IR [mean (SD)]	2.8 (0.7)	2.0 (0.7)	−0.8 [−1.4, −0.2]*
Uric acid [μmol/L; mean (SD)]	401 (75)	382 (61)	−19 [−74, 36]
hsCRP [mg/L; mean (SD)]	2.5 (0.6)	2.0 (0.5)	−0.5 [−0.9, −0.1]*
Fibrinogen [mg/dl; mean (SD)]	380 (70)	365 (56)	−15 [−66, 36]
Homocysteine [μmol/L; mean (SD)]	22 (7)	22 (6)	0 [−5, 5]
25-hydroxyvitamin D [ng/ml; mean (SD)]	23 (7)	29 (7)	6 [1, 11]*

* statistically significant difference between both groups.
CI = confidence interval; HDL = high-density lipoprotein; HOMA1-IR = the homeostatic model assessment 1 of insulin resistance ratio; hsCRP = high-sensitivity C-reactive protein; IU = international unit; LDL = low-density lipoprotein; SD = standard deviation.

macroprolactin content (hsCRP: $r = -0.42$, $p < 0.001$; homocysteine: $r = -0.31$, $p < 0.05$; HOMA1-IR: $r = 0.28$ $p < 0.05$). All other correlations were insignificant.

Discussion

Compared with control subjects, women with macroprolactinemia were characterized by increased circulating levels of hsCRP, higher values of HOMA1-IR and decreased levels of 25-hydroxyvitamin D. Similar differences were reported previously between women with elevated content of big-big prolactin not selected for plasma lipids and healthy young women with normal lipid levels.[9] The participants of the present study were older (50 ± 8 years) than women participating in the previous one (34 ± 7 years) and no patient was enrolled in both studies. Moreover, all participants of the present study had hypercholesterolemia and, to minimize the impact of plasma lipids on cardiometabolic effects of atorvastatin, both groups were matched for the lipid profile. Based on the obtained results, it seems that macroprolactinemia may by itself, irrespective of age and plasma lipids, predispose women to the development of cardiovascular and metabolic disorders.

The present study has shown for the first time that macroprolactinemia impairs cardiometabolic effects of atorvastatin. In women with normal prolactin levels, the drug decreased plasma levels of uric acid, hsCRP, fibrinogen, and homocysteine and increased the plasma concentration of 25-hydroxyvitamin D, whereas in women with macroprolactinemia atorvastatin action was limited to a decrease in hsCRP and homocysteine, less pronounced than in women without macroprolactinemia. Moreover, in subjects with macroprolactinemia, atorvastatin affected insulin sensitivity in an unfavorable way. The finding that the strength of pleiotropic effects of the drug correlated with baseline concentrations of both total prolactin and macroprolactin, but not with levels of postpolyethylene glycol prolactin suggests that the different impact of atorvastatin in both study arms reflects a specific effect of macroprolactinemia. These findings are an argument letting us disagree with the view that macroprolactinemia is a benign condition not having any clinical significance.[2,4,5] Taking into account that uric acid, hsCRP, fibrinogen, homocysteine, and vitamin D are important cardiometabolic risk factors,[13–17] between-group differences in post-treatment concentrations of all these markers indicate that the presence of macroprolactinemia may weaken or even prevent cardiometabolic benefits associated with statin therapy.

The impact of macroprolactin excess on cardiometabolic effects of atorvastatin was less expressed than that of true hyperprolactinemia, impairing hypolipidemic effects, as well as completely abolishing pleiotropic effects of this drug.[9] Interestingly, despite similar mean total prolactin content, clinical symptoms of prolactin excess were reported more often in individuals (mainly women) with isolated monomeric hyperprolactinemia than in subjects with macroprolactinemia.[18] Isolated monomeric hyperprolactinemia led also to the development of more severe sexual dysfunction than isolated macroprolactinemia did.[19] The results of all studies indicate that elevated levels of big-big prolactin produce similar, although less pronounced, effects to monomeric hyperprolactinemia, suggesting that macroprolactin probably possesses weak prolactin-like properties. These properties may either result from a direct affinity of macroprolactin for

Table 2
The effect of atorvastatin on body mass index, plasma lipids, glucose homeostasis markers, as well as on cardiometabolic risk factors in women with macroprolactinemia and women with prolactin levels within the reference range

Variable	Women with macroprolactinemia	Control women	Difference [95% confidence interval]
Body mass index [kg/m^2; mean (SD)]			
Baseline	27.9 (5.1)	27.4 (4.9)	−0.5 [−4.6, 3.6]
After 6 months	28.3 (4.7)	27.5 (5.0)	−0.8 [−4.7, 3.1]
Change	0.4 (0.6)	0.1 (0.4)	−0.3 [−0.7, 0.1]
Prolactin before polyethylene glycol precipitation [ng/ml; mean (SD)]			
Baseline	68 (15)	12 (7)	−56 [−65, −47]*
After 6 months	62 (14)	10 (5)	−52 [−60, −44]*
Change	−6 (7)	−2 (4)	4 [−1, 9]
Prolactin after polyethylene glycol precipitation [ng/ml; mean (SD)]			
Baseline	12 (6)	11 (6)	−1 [−6, 4]
After 6 months	12 (5),	10 (5)	−2 [−6, 2]
Change	0 (2)	−1 (1)	−1 [−3, 1]
Macroprolactin [mean (SD)]			
Baseline	81 (11)%	8 (5)%	−73 [−80, −66]*
After 6 months	81 (7)%	0 (4)%	−81 [−85, −77]*
Change	0 (8)%	−8 (12)%	−8 [−1, 17]
Total cholesterol [mg/dl; mean (SD)]			
Baseline	252 (34)	256 (29)	4 [−21, 29]
After 6 months	214 (23)†	195 (21)†	−19 [−37, −1]*
Change	−38 (18)	−61 (20)	−23 [−39, −7]‡
LDL-cholesterol [mg/dl; mean (SD)]			
Baseline	159 (23)	161 (20)	2 [−15, 19]
After 6 months	120 (18)†	102 (17)†	−18 [−32, −4]*
Change	−39 (15)	−59 (14)	−20 [−32, 8]‡
HDL-cholesterol [mg/dl; mean (SD)]			
Baseline	49 (8)	51 (8)	2 [−4, 8]
After 6 months	52 (9)	55 (8)	3 [−4, 10]
Change	3 (5)	4 (5)	1 [−3, 5]
Triglycerides [mg/dl; mean (SD)]			
Baseline	203 (40)	190 (32)	−13 [−42, 16]
After 6 months	193 (35)	173 (29)	−20 [−46, 6]
Change	−10 (16)	−17 (15)	−7 [−20, 6]
Fasting glucose [mg/dl; mean (SD)]			
Baseline	93 (9)	91 (8)	−2 [−9, 5]
After 6 months	96 (8)	93 (8)	−3 [−9, 3]
Change	3 (2)	2 (2)	−1 [−3, 1]
2-h postchallenge glucose [mg/dl; mean (SD)]			
Baseline	139 (20)	129 (18)	−10 [−25, 5]
After 6 months	145 (18)	132 (14)	−13 [−25, −1]*
Change	6 (5)	3 (4)	−3 [−7, 1]
HOMA1-IR [mean (SD)]			
Baseline	2.8 (0.7)	2.0 (0.7)	−0.8 [−1.4, −0.2]*
After 6 months	3.4 (0.7)†	2.1 (0.6)	−1.3 [−1.8, −0.8]*
Change	0.6 (0.4)	0.1 (0.2)	−0.5 [−0.8, −0.2]‡
Glycated hemoglobin [mean (SD)]			
Baseline	5.4 (0.4)%	5.3 (0.3)%	−0.1 [−0.4, 0.2]
After 6 months	5.6 (0.4)%	5.3 (0.3)%	−0.3 [−0.5, −0.1]*
Change	0.2 (0.1)%	0.0 (0.1)%	−0.2 [−0.3, −0.1]‡
Uric acid [μmol/L; mean (SD)]			
Baseline	401 (75)	382 (61)	−19 [−74, 36]
After 6 months	373 (60)	325 (53)†	−48 [−94, −2]*
Change	−28 (18)	−57 (24)	−29 [−12, −46]‡
hsCRP [mg/L; mean (SD)]			
Baseline	2.5 (0.6)	2.0 (0.5)	−0.5 [−0.9, −0.1]*
After 6 months	1.9 (0.6)†	1.0 (0.4)†	−0.9 [−1.3, −0.5]*
Change	−0.6 (0.4)	−1.0 (0.4)	−0.4 [−0.7, −0.1]‡
Fibrinogen [mg/dl; mean (SD)]			
Baseline	380 (70)	365 (56)	−15 [−66, 36]
After 6 months	370 (76)	312 (60)†	−58 [−113, −3]*
Change	−10 (8)	−53 (18)	43 [31, 55]‡

(*continued*)

Table 2 (***Continued***)

Variable	Women with macroprolactinemia	Control women	Difference [95% confidence interval]
Homocysteine [μmol/L; mean (SD)]			
Baseline	22 (7)	22 (6)	0 [−5, 5]
After 6 months	17 (5)†	12 (6)†	−5 [−9, −1]*
Change	−5 (3)	−10 (5)	−5 [−8, −2]‡
25-hydroxyvitamin D [ng/ml; mean (SD)]			
Baseline	23 (7)	29 (7)	6 [1, 11]*
After 6 months	25 (8)	35 (5)†	10 [5, 15]*
Change	2 (3)	6 (4)	4 [1, 7]‡

* statistically significant difference between both groups.

† statistically significant difference between post-treatment and baseline values in the same group.

‡ statistically significant difference between the changes in both groups.CI = confidence interval; HDL = high-density lipoprotein; HOMA1-IR = the homeostatic model assessment 1 of insulin resistance ratio; hsCRP = high-sensitivity C-reactive protein; IU = international unit; LDL = low-density lipoprotein; SD = standard deviation.

peripheral prolactin receptors or, as suggested previously,[8] from the impact of monomeric prolactin dissociating in small amounts from high molecular weight complexes of prolactin and immunoglobulins.

Another interesting finding of the present study was dimorphism in the effect of the investigated drug on glucose homeostasis markers. Atorvastatin treatment did not affect glucose homeostasis in patients with normal prolactin levels but slightly increased HOMA1-IR in subjects with macroprolactinemia. Moreover, despite similar baseline values, post-treatment levels of 2-hour postload plasma glucose, HOMA1-IR, and glycated hemoglobin were higher in women with macroprolactinemia than in women with normal prolactin levels. Different effects on glucose homeostasis are in line with observations that high levels of big-big prolactin are more frequently observed in subjects with than in subjects without diabetes, as well as that the coexistence of macroprolactinemia in patients with diabetes is associated with higher concentrations of glycated hemoglobin.[8] It is possible that a small unfavorable effect of macroprolactinemia on carbohydrate metabolism may be unmasked by treatment with HMG-CoA reductase inhibitors, being drugs slightly increasing the risk of new-onset type 2 diabetes mellitus.[20]

Taking into account that the effect of atorvastatin on uric acid, hsCRP, homocysteine, and 25-hydroxyvitamin D was unrelated to the changes in plasma lipids, cardiometabolic effects of atorvastatin seem to reflect its pleiotropic properties. However, we can only speculate about molecular mechanisms explaining our findings. Statins inhibit production of farnesyl-pyrophosphate and geranylgeranyl-pyrophosphate, which are isoprenoid intermediates playing an important role in the post-translational prenylation of small Guanosine-5′-triphosphate (GTP)-binding proteins, including Rho, Rab, Rac, Ral, and Rap.[21] This action may be less expressed in subjects with macroprolactinemia, because prolactin stimulates G proteins in various target tissues.[22] Statins were also found to inhibit nuclear factor-κB pathway and leukocyte function-associated antigen-1 intercellular adhesion molecule-1 interaction,[23,24] whereas prolactin administration was found to stimulate the nuclear factor-κ-B pathway and adhesion of circulating mononuclear cells to endothelial cells, the effect mediated by leukocyte function-associated antigen-1.[25,26]

Some study limitations need to be mentioned. The most important limitation is a small number of women participating in this research, causing that the results should be considered as only pilot ones. Moreover, because of short treatment duration, it is probable that a longer lasting therapy results in a stronger effect of atorvastatin than observed in the present study. Furthermore, the study measured only surrogates of outcome, not investigating morbidity and mortality. Finally, because all subjects received the same HMG-CoA reductase inhibitor, it cannot be completely ruled out that the impact of atorvastatin does not represent a class effect but is associated with its specific properties.

In conclusion, atorvastatin administered to normoprolactinemic women decreased plasma levels of uric acid, hsCRP, fibrinogen, and homocysteine and increased plasma levels of 25-hydroxyvitamin D, whereas in women with macroprolactinemia, the drug decreased only hsCRP and homocysteine, as well as slightly impaired insulin sensitivity. The impact on hsCRP, homocysteine and insulin sensitivity correlated with baseline values of total prolactin and macroprolactin. These findings suggest that macroprolactinemia may attenuate cardiometabolic effects of atorvastatin.

Disclosures

The authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.07.017.

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