Usefulness of Triiodothyronine Replacement Therapy in Patients With ST Elevation Myocardial Infarction and Borderline/Reduced Triiodothyronine Levels (from the THIRST Study)

Alessandro Pingitore, MD, PhD[a,*], Francesca Mastorci, PhD[a], Paolo Piaggi, PhD[c], Giovanni Donato Aquaro, MD[b], Sabrina Molinaro, PhD[a], Marcello Ravani, MD[b], Alberto De Caterina, MD[b], Giuseppe Trianni, MD[b], Rudina Ndreu, PhD[a], Sergio Berti, MD[b], Cristina Vassalle, PhD[b], and Giorgio Iervasi, MD[a]

The aim of the study was to investigate whether TH replacement therapy is safe and impact infarct size, left ventricular (LV) volumes and function in patients with acute myocardial infarction (AMI) and low T3 syndrome (LT3S). Thirty-seven AMI/LT3S patients were randomly treated or untreated with liothyronine (T3) therapy (maximum dosage 15 mcg/m^2/die) in addition to standardized treatment (T3-treated group, n = 19; untreated group, n = 18). TH and thyroxine (TSH) during hospital stay and at 1-month and 6 months were evaluated. At discharge and at 6 months LV volumes, ejection fraction, wall motion score index (WMSI) and infarct extent were measured by cardiac MR. T3-treated patients had a significant increase in fT3 (p = 0.003 and p <0.001) at discharge and 1-month. These patients had no signs or symptoms of hyperthyroidism or arrhythmias. At follow-up, there was a significant reduction in WMSI in both groups (T3-treated group: Δ = −0.12, p = 0.001; untreated group: Δ = −0.04, p = 0.04) and the difference value (discharge/follow-up) was significantly higher in T3-treated group than in untreated group (mean difference between groups = 0.08, 95% confidence interval [CI]: 0.01 to 0.15, p = 0.05). Also, stroke volume increased significantly in the T3-treated group (Δ = 3.4, 95% CI: 0.8 to 6, p <0.01) at follow-up. In conclusion, this is the first pilot experience in which T3 replacement therapy resulted safe and able to improve regional dysfunction in patients with STEMI/LT3S. **(Am J Cardiol 2019;123:905−912)**

Low T3 syndrome (LT3S), characterized by decreased serum triiodothyronine (T3) levels in presence of normal/mildly reduced serum thyroxine (T4) and thyroid-stimulating hormone (TSH) and increased reverse-T3 (rT3), occurs in several cardiac diseases, including acute myocardial infarction (AMI).[1−3] In AMI, changes in thyroid hormone (TH) levels are rapid during the initial 72 hours after pain onset, with maximal variations observed between the 24- to 36-hour periods.[4] LT3S is observed in up to 20% of patients with AMI and a degree of T3 downregulation is associated with higher impairment of cardiac function and higher inflammatory response.[5−7]

LT3S has been associated with worse prognosis in patients with AMI, both in the in-hospital phase and follow-up.[2,4] The effects of short-term TH administration in patients with cardiac disease and LT3S have already been studied in patients undergoing coronary artery bypass graft or affected by heart failure of different aetiologies.[8−11] In spite of much experimental evidence,[12−15] no clinical study explored safety and effects of TH replacement therapy in patients with AMI and reduced T3 plasma levels. Therefore, in this pilot study we assessed the feasibility and the effects of T3 therapy on infarct size, regional wall motion, LV ejection fraction, and LV volumes in patients with AMI and reduced T3 plasma levels.

Methods

One-hundred and ninety-five patients with STEMI (ST Elevation Myocardial Infarction) were considered eligible to be enrolled in the study on the basis of the following inclusion criteria: (1) male and female patients, of all ethnicities, admitted to the CCU for chest pain, and subsequently proven STEMI; (2) age between 30 and 70 years; (3) patients subject to percutaneous coronary revascularization and stenting of the culprit lesion alone within 12 hours from the onset of symptoms; (4) at hospital admission borderline/reduced plasma levels of triiodothyronine (fT3 </ = 2.2 pg/ml) or decrease in fT3 plasma levels more than 20% with respect to the admission levels within 72 hours after hospital arrival.

All patients were treated according to the existing guidelines for STEMI management. The mean time between symptoms of STEMI/admission to the CCU unit and

[a]Clinical Physiology Institute, CNR, Pisa, Italy; [b]G. Monasterio Foundation, Regione Toscana, CNR, Pisa, Italy; and [c]National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona. Manuscript received October 15, 2018; revised manuscript received and accepted December 7, 2018.

See page 911 for disclosure information.

*Corresponding author: Tel: +39050-3152605; Fax: +39050-3153303.
E-mail address: pingi@ifc.cnr.it (A. Pingitore).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.12.020

randomization was 9 ± 3 hours. Due to their potential interference with TH metabolism and results interpretation, patients already assuming the following drugs were excluded from the study: (1) TH replacement therapy, antithyroid drugs; (2) amiodarone; (3) corticosteroids; (4) oral anticoagulant therapy; (5) sympathomimetic drugs; (6) oral contraceptives or estro-progestinic hormone replacement; (7) potentially hepatotoxic drugs (e.g., metotrexate). Other exclusion criteria were the following: (1) previous myocardial infarction; (2) previous evidence of moderate-to-severe compromised left ventricular function (Ejection fraction <40%); (3) hemodynamic instability, ventricular fibrillation, or sustained ventricular tachycardia, cardiogenic shock, decompensate heart failure (NYHA IV class) on admission; (4) use of inotropic drugs; (5) known thyroid disease; (6) patients presenting atrial fibrillation or with previous documentation of paroxysmal or persistent atrial fibrillation; (7) severe systemic diseases; (8) systemic inflammatory autoimmune disease; (9) patients with mechanical cardiac valves, pace-makers or infusion pumps, magnetic materials like metallic clips and prosthesis; (10) patients refusing or unable to supply written informed consent. Forty-two patients that satisfied both inclusion and exclusion criteria refused to participate to the study.

Therefore, according to the above-mentioned criteria, the final enrolled population consisted of 37 patients (mean age 68 ± 2 years, female n = 6, 16%). Out of these, 19 patients were treated with T3 (T3-treated group) and the 18 were untreated (untreated group). Of the 19 T3-treated patients, 8 had fT3 <2.2 pg/ml at hospital admission whereas the remaining 11 had fT3 reduction of 20%. Patients underwent continuous EKG Holter monitoring during hospital stay and at 6-month follow-up. This study protocol was carried out in accordance with Good Clinical Practice and the Declaration of Helsinki statements concerning medical research in Humans. The local Ethical Committee approved this study protocol (study registration number 266). Written Signature on the Informed Consent Form was obtained before randomization. The THIRST Study (Thyroid Hormone Replacement Therapy in ST elevation myocardial infarction) was registered in the European Clinical Trials Database with the following number: EudraCT: 2009-010869-23.

This is a phase II, randomized, treated/untreated patients study. Patients were randomly assigned to 2 distinct groups: (1) substitutive treatment (T3-treated, 19 patients), (2) traditional treatment (untreated, 18 patients). The outcomes of this study, feasibility and the effects on cardiac function and morphology of T3 treatment are listed as secondary objectives in the trial registry protocol.

The treatment medications supplied for this trial was a synthetic analogue of native triiodothyronine (Liothyronine Sodium, LIOTIR, AMSA s.r.l.). Liothyronine Sodium is already sold in Italy as LIOTIR. The drug was assumed per os as drops dissolved in a small quantity of water, each drop containing 0.7 mcg of sodium Liothyronine. For patients taking Liothyronine Sodium, the maximum daily dosage was 15 mcg/m^2/day, to be assumed 3 times during the day, in the morning (8 to 9 A.M.) after blood sampling, at 04:00 P.M. and 10:00 P.M. Treatment with Liothyronine Sodium started during the in-hospital period (Acute phase), after 72 hours from hospital admission, and lasted for 6 months after hospital discharge (follow-up phase). The initial Liothyronine daily mean dose was 22.23 mcg (range 19.87 to 26.53 mcg) and 11.97 mcg (range 10.62 to 13.12 mcg) at the end of treatment. Specifically, the initial dose was 15 mcg/m^2/day in patients <65 years, 12 mcg in patients with age between 65 and 70 years, and 10 mcg in those with age >70 years. This range of doses has been chosen based on the results on daily production of T3.[16,17] All patients were subjected to TH and TSH plasma levels checks every day during hospital stay and at 1 and 6 months after hospital discharge. In presence of borderline/elevated fT3 plasma levels (>/= 4.2 pg/ml) and/or evidence of TSH levels below the referral limits (0.3 microUI/ml) were followed by the assumption of a half dosage of ongoing treatment for 10 days. After this period, a new TH dosage was performed and TH treatment was discontinued in the case of persistent abnormalities of fT3 and/or TSH plasma levels.

Whenever the patient manifested symptoms or signs suggestive of hyperthyroidism (e.g., palpitation, anxiety, significant weight loss, etc), a new TH dosage was provided to assess TH status and further clinical or instrumental exams were performed if necessary.

Both in the acute phase (at admission, after 3 days, and at discharge) and at follow-up (1- and 6 months), patients underwent blood sampling for biochemical assays. Blood samples were withdrawn between 8 A.M. and 9 A.M. from an antecubital vein, after a 20-minute period of supine rest. Plasma samples for BNP and cTnI were calculated according to a procedure previously described.[18] Glutamate Oxaloacetate Transaminase (GOT), Alanine Aminotransferase (ALT), lipid profile (total cholesterol, tryglicerides, high density lipoproteins, and HDL), and myoglobin were measured with standard clinical chemistry laboratory analyzer (CX Chemistry Analyzer (Beckman, CA). Levels of low density lipoproteins (LDL) were calculated with the Friedewald equation.

Serum TSH and fT3, as well as free T4 (fT4), were measured using an AIA 600 analyzer (Eurogenetics-Tosoh, Turin, Italy). Reference values for our laboratory are 0.3 to 3.8 mIU/l for TSH, 2.1 to 4.2 ng/l for fT3, and 7.1 to 18.5 ng/l for fT4.

CMR was performed using a 1.5 T whole-body scanner (GE Medical Systems, Milwaukee, WI) at discharge and at 6 month's follow-up. CMR methodology and parameters has been already defined in previous studies.[19,20] CMR data analysis has been performed by 2 independent experts and the intraobserver and interobserver agreement were 98% and 95%, respectively.

Alpha was set at 0.05. Analyses were performed using SPSS (Version 22.0. Armonk, NY: IBM Corp). Data are presented as mean ± SD, or mean with its 95% confidence interval (CI). The normality of data distribution was assessed by the Shapiro-Wilk test. Individual changes at each follow-up visit were calculated as the follow-up visit value minus the baseline visit value, and analyzed by paired Student's *t* test. A paired *t* test was used to calculate intragroup differences, while differences between categorical variables were done by Chi-square analysis. Differences between groups in the change of each clinical parameter

Table 1
Clinical characteristics in overall population and in T3-treated and untreated patients

Variable	Entire population (n = 37)	T3-treated		p value
		YES (n = 19)	NO (n = 18)	
Age (years)	65.0 ± 9.1	66.9 ± 8.0	63.1 ± 9.9	0.20
Woman (%)	6 (16%)	2 (11%)	4 (22%)	<0.001
Body mass index (Kg/m^2)	26.8 ± 4.4	27.6 ± 4.0	26.0 ± 4.9	0.28
Family history of coronary artery disease	12 (32%)	5 (26%)	7 (39%)	<0.05
Hypertension	15 (41%)	8 (42%)	7 (39%)	0.25
Diabetes mellitus	2 (5%)	2 (11%)	0 (0)	<0.05
Hypercholesterolemia	22 (59%)	11 (58%)	11 (61%)	0.25
Smoker	21 (57%)	9 (47%)	12 (67%)	0.41
Chronic kidney disease	0	0	0	NA
Chronic obstructive pulmonary disease	0	0	0	NA
Anterior myocardial infarction (%)	20 (54%)	13 (68%)	7 (39)	0.62
Heart rate in hospital (bpm)	14 (5 to 80)	14 (5 to 108)	13 (9 to 80)	0.18
Heart Rate at sixth month (bpm)	20 (0 to 54)	13 (0 to 50)	20 (4 to 65)	0.71
Ectopic ventricular beat in hospital	14 (5 to 80)	14 (5 to 108)	13 (9 to 80)	0.92
Ectopic ventricular beat at sixth month	20 (0 to 54)	13 (0 to 50)	20 (4 to 65)	0.34
Brain natriuretic peptide at discharge (ng/l)	176 (105 to 282)	219 (105 to 305)	148 (86 to 282)	0.60
Brain natriuretic peptide at first month (ng/l)	59 (32 to 100)	59 (34 to 83)	55 (20 to 153)	0.75
Brain natriuretic peptide at sixth month (ng/l)	45 (33 to 63)	48 (33 to 54)	41 (28 to 107)	0.96
Cardiac troponin I (ng/l)	51.1 (31.4 to 104.6)	51.1 (31.4 to 156.8)	60.7 (29.6 to 103.9)	0.68

Data are expressed ad mean ± SD or number (%), except for HR, EVB, BNP, and cTnI measures that are reported as median and IQR due to skewed distribution and analysed between groups by the Mann-Whitney U test. Troponin has been measured 3 times a day in the first 3 days and the higher value has been reported in the study. The total number of EVB per day was reported. Hypercholesterolemia was defined when the value of total cholesterol was > 200 mg/dl

were assessed using the Student's unpaired *t* test after testing the equality of variances between groups using the Levene's test.

Results

Clinical, biohumoral, and instrumental data of patients are shown in Table 1. All T3-treated patients swallowed T3 for all the period of follow up. During follow-up at 1-month, T3 daily dose was halved in 4 patients due to increased T3 circulating level over the range of normality; in all patients, however, T3 treatment continued up to 6 months. In addition, there were no major cardiac events in any patients during follow-up.

As shown in Figure 1, fT3 reduction was of 23% (CI: 21 to 25) in overall population at day 3 of hospital admission. In the Table 2, intragroup and intergroup changes are reported. Compared to baseline, T3-treated patients had a significant increase in fT3 circulating levels at discharge and at the first month of follow-up. Compared to baseline, untreated patients had a significant decrease in fT3 circulating levels at discharge, but no change at the first month of follow-up. At first month of follow-up, the increase in fT3 observed in the T3-treated group was greater than that of untreated group, whereas, at 6-months follow-up, fT3 circulating levels were not significantly different between the 2 groups. TSH was significantly higher in untreated in comparison to T3-treated patients at discharge and at the first month follow-up (Figure 1). fT4 was not significantly different in the 2 groups and did not change significantly in acute phase and follow-up.

As shown in the Table 3, the 2 groups did not differ about LV function and volumes, and the extent of necrosis, as documented by cardiac MR, at discharge and follow-up. When we considered per patient differences in SV, WMSI, left ventricular end-diastolic (LVED), and left ventricular end-systolic (LVES) Volumes (V), LGE, and ejection fraction (EF) before and after treatment. WMSI reduced in all patients out of 2, likewise stroke volume (SV), LGE reduced in all patients, and EF increased in all out of 1; LVEDV increased in the major part of patients, whereas LVESV reduced. In the Table 2, intragroup and intergroup changes are reported. At follow-up, there was a significant reduction in WMSI in both groups, but the discharge/follow-up decrease in WMSI was significantly greater in the T3-treated group (Figure 2). Considering necrosis extent, at follow-up there was a significant reduction in the global extent of necrosis, in both groups, but with no difference between groups. Similarly, stroke volume (SV) increased significantly in T3-treated group at follow-up, and there was a tendency (between-group p = 0.06) toward a higher increase in SV in the T3-treated patients compared to the untreated patients. In the overall population, we did not observe any correlation between fT3 levels and CMR outcomes at 6 months.

Discussion

The main results of this study show that there were no signs or symptoms of hyperthyroidism, and in particular; T3-treatment did not increase heart rate and did not induce arrhythmias, and there were no cardiac events in the follow-up in patients with AMI and reduced T3 plasma levels. Furthermore, the reduction in regional contractile dysfunction, as documented by the reduced WMSI, was significantly higher in T3-treated in comparison to untreated

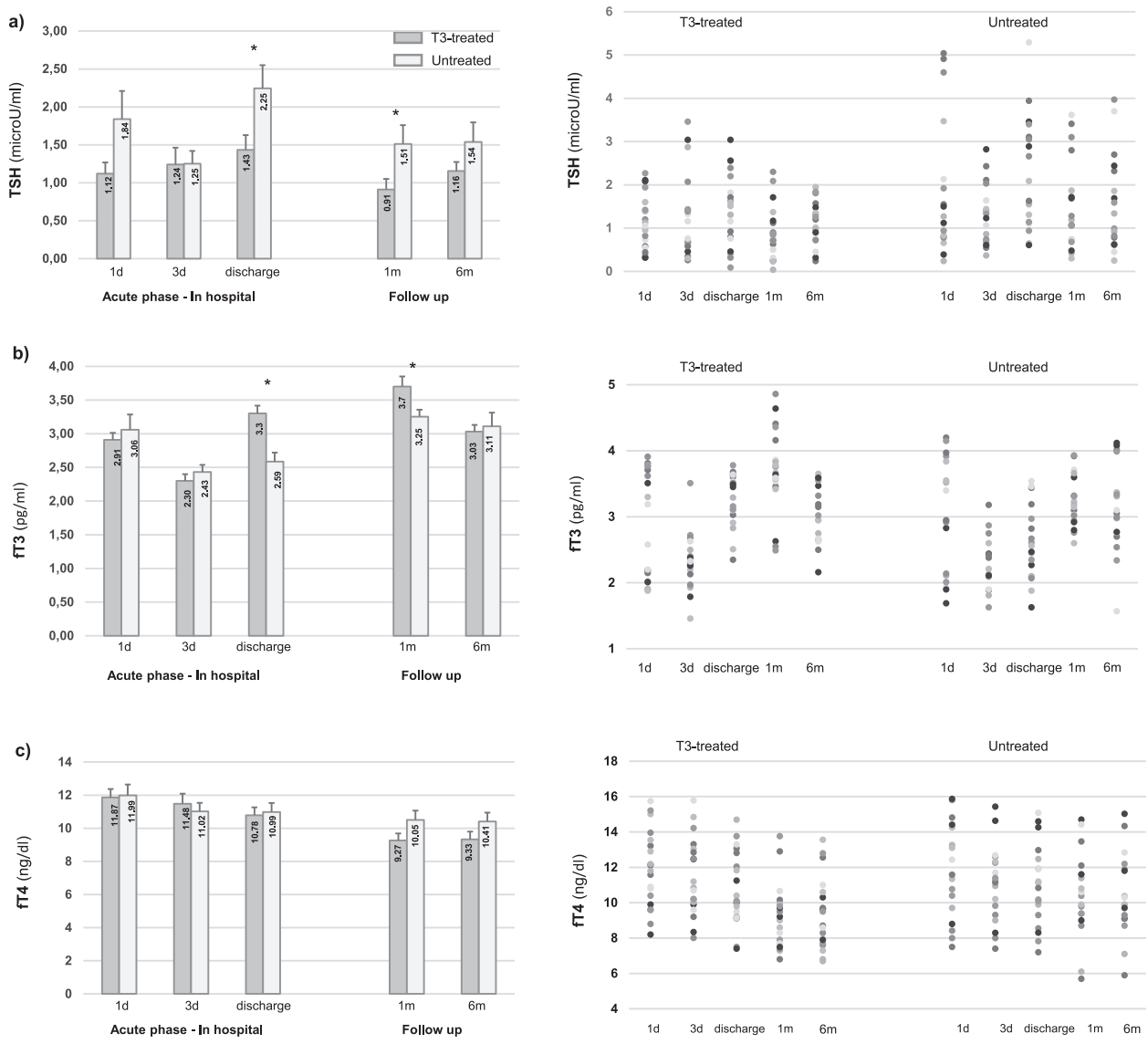

Figure 1. The amount of TSH (a), fT3 (b), and fT4 (c) hormones in T3-treated and untreated patients during hospital stay and at follow-up. Data are presented as mean ± SD.
* p <0.05
** p <0.01

patients when the difference in WMSI at discharge vs follow-up was assessed. In addition, cardiac MR showed the reduction in the necrotic area in both groups, although the discharge/follow-up difference between the 2 groups was not significant, and there was a tendency towards a higher increase in SV when assessing the discharge/follow-up difference between groups. WMSI is commonly used in the clinical practice to assess the extent of left ventricular dysfunction and, also, as an indirect marker to assess the extent of myocardial damage. In a previous CMR study, we documented that WMSI had a prognostic role in addition to necrosis extent and LV enlargement.[20] Previous studies showed that the better the reduction in WMSI the higher the probability of survival and this is mainly true in patients with severe LV dysfunction.[21,22] We actually cannot evaluate whether the entity of variation we observed in the present study has clinical relevance. However, we have to consider that LV function was mainly preserved in overall population and, therefore, the improvement in cardiac function has been expected to be low. Vice-versa, in patients with moderate-to-severe LV, we expect a higher reduction in WMSI that means higher LV salvage. Accordingly, previous animal studies showed that T3 treatment reduced necrotic area, improving, thus, regional systolic function.[23,24] Moreover, in the study of Lymvaios, the recovery of global LV function was associated to low levels of T3 both at 48 hours after AMI and at 6 months.[25] In this study, we did not observe any improvement in the global LV function, neither there was any effect mediated by T3 on LV remodeling. However, we enrolled patients mostly with a preserved global LV function and normal LV volumes, with a low probability to progress through postischemic remodeling. In addition, we did not observe any relationship between the levels of T3 and cardiac CMR variables in

Table 2
Changes (Δ) in each variable and in each group with intragroup and intergroup comparisons

	T3-treated								
	YES (n = 19)				NO (n = 18)				
	Mean	95% Lower CL for mean	95% Upper CL for mean	p value (intragroup)	Mean	95% Lower CL for mean	95% Upper CL for mean	p value (intragroup)	p value (intergroup)
Δ Free thyroxine 3 day	−0.4	−0.7	−0.1	0.005	−0.6	−1.0	−0.2	0.003	0.38
Δ Free thyroxine at discharge	0.5*	0.2	0.9	0.003	−0.5*	−0.9	−0.1	0.03	0.0003*
Δ Free thyroxine first month	0.9*	0.5	1.4	0.0003	0.2*	−0.2	0.6	0.34	0.02*
Δ Free thyroxine sixth months	0.3	−0.1	0.6	0.12	0.1	−0.5	0.6	0.84	0.47
Δ Free triiodothyronine 3 day	−0.4	−1.1	0.3	0.26	−1.0	−1.6	−0.3	0.008	0.22
Δ Free triiodothyronine at discharge	−1.1	−1.9	−0.3	0.009	−1.0	−1.9	−0.1	0.03	0.88
Δ Free triiodothyronine first month	−2.6	−3.5	−1.7	<0.0001	−1.5	−2.5	−0.5	0.005	0.08
Δ Free triiodothyronine sixth months	−2.5	−3.6	−1.5	0.0001	−1.6	−2.5	−0.6	0.002	0.16
Δ Thyroid-stimulating hormone 3 day	0.1	−0.3	0.5	0.52	0.0	−1.1	1.1	0.95	0.78
Δ Thyroid-stimulating hormone at discharge	0.3	−0.1	0.7	0.09	0.4	−0.5	1.3	0.34	0.84
Δ Thyroid-stimulating hormone first month	−0.2	−0.5	0.0	0.11	−0.3	−0.8	0.1	0.15	0.63
Δ Thyroid-stimulating hormone sixth months	0.0	−0.2	0.3	0.79	−0.3	−0.8	0.2	0.26	0.24
Δ Global late gadolinium enhancement	−4.6	−6.6	−2.6	0.0001	−2.7	−4.7	−0.7	0.01	0.16
Δ Left ventricular end-diastolic volume	2.0	−1.9	5.8	0.30	−0.4	−6.1	5.3	0.89	0.47
Δ Left ventricular end-systolic volume	−1.8	−4.6	1.1	0.21	1.0	−2.0	4.0	0.47	0.16
Δ Wall motion score index	−0.119*	−0.182	−0.056	0.001	−0.044*	−0.087	−0.002	0.04	0.05*
Δ Stroke volume	3.4	0.8	6.0	0.013	−1.0	−5.0	3.1	0.62	0.06
Δ Left ventricular ejection fraction	3.1	−0.5	6.7	0.09	0.7	−2.4	3.8	0.66	0.29

Table 3
CMR parameters of the entire population and in T3-treated patients (YES and NO) at discharge and at sixth month

		T3-treated	
Cardiac magnetic resonance parameters at discharge	Entire population (n = 37)	YES (n = 19)	NO (n = 18)	p value
Left ventricular end-diastolic volume (ml/m^2)	88.84 ± 14.71	89.56 ± 18.78	88.07 ± 9.14	0.76
Left ventricular end-systolic volume (ml/m^2)	39.91 ± 12.70	40.67 ± 14.08	39.10 ± 11.42	0.71
Left ventricular ejection fraction (%)	53.43 ± 10.04	52.89 ± 9.72	54 ± 10.63	0.74
Stroke volume (ml/kg)	47.97 ± 8.43	47.67 ± 6.16	48.29 ± 10.49	0.83
Late gadolinium enhancement extent (% of mass)	17 ± 9.87	19 ± 10.80	14.89 ± 8.58	0.21
Cardiac magnetic resonance parameters at sixth month				
Left ventricular end-diastolic volume (ml/m^2)	90.06 ± 14.96	91.52 ± 17.60	88.52 ± 11.87	0.55
Left ventricular end-systolic volume (ml/m^2)	39.51 ± 15.20	38.91 ± 16.60	40.14 ± 14.02	0.81
Left ventricular ejection fraction (%)	55.35 ± 8.80	56 ± 8.70	54.67 ± 9.11	0.65
Stroke volume (ml/kg)	49.66 ± 7.13	51.09 ± 7.052	48.14 ± 7.09	0.21
Late gadolinium enhancement extent (% of mass)	13.30 ± 8.28	14.37 ± 8.68	12.17 ± 7.93	0.43

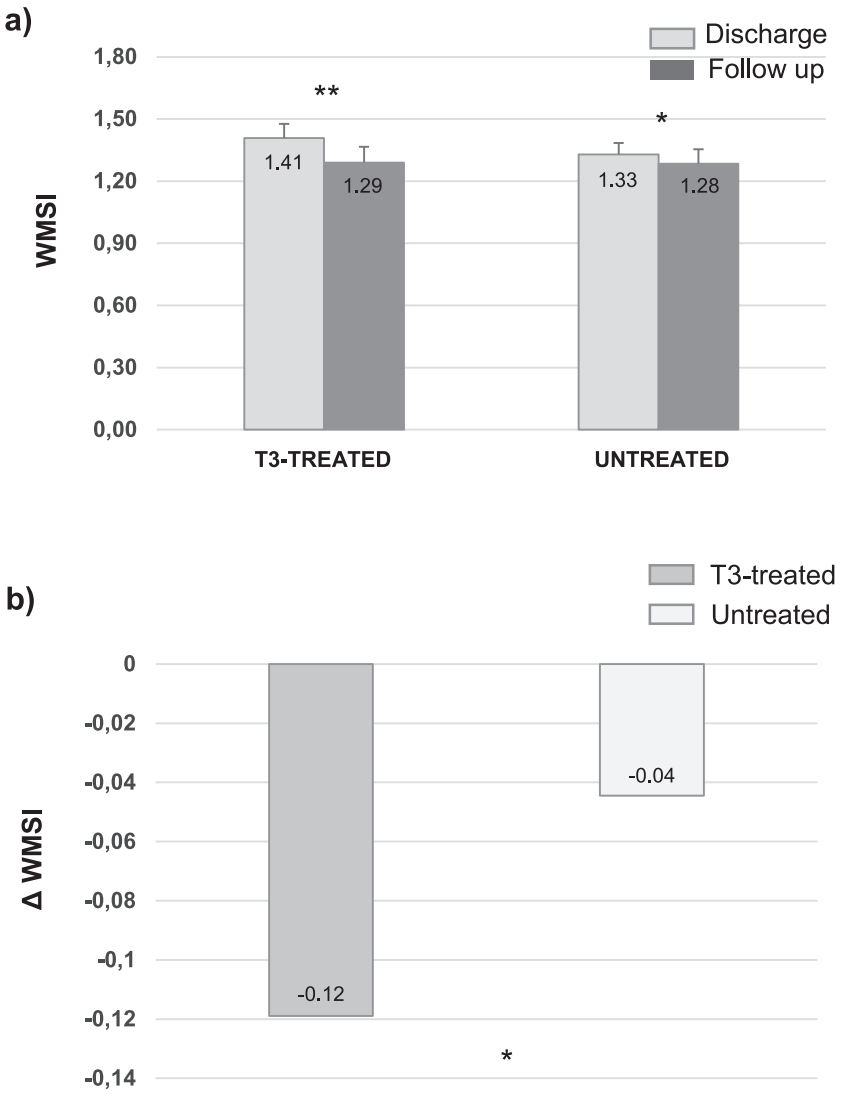

Figure 2. Wall-motion score index (WMSI) in T3-treated and untreated patients expressed as absolute value at discharge and at follow up (a), and as discharge/follow-up difference (b). Data are presented as mean ± SD.
*p <0.05
**p <0.01

overall population both at hospital discharge and at 6 months. This may be due to the fact that T3 treatment reduced the differences in T3 value among patients and therefore, changed the potential relationship between T3 levels, and systolic function. In addition, our population consisted mainly of patients with preserved left ventricular global function.

The main limitation is the low number of patients. The initial power calculations included 100 patients per group to detect a significant difference between groups on the incidence of major or minor events at a 2-sided alpha level of 0.05 with a power greater equal to 0.84, assuming an incidence of major or minor events equal to 20% in patients treated with sodium liothyronine and 40% in patients treated with placebo. However, we have had important difficulties to enroll patients. This was due to the strict inclusion and exclusion criteria adopted for the study, and the difficulty to get accepted the T3 treatment in patients and family doctors. Indeed, 42 patients that satisfied inclusion criteria refused to participate to the study. This is the reason of the long period of enrollment and the reason to interrupt the study and to limit the objects of this pilot study on the effect of T3 treatment on cardiac function and morphology only that are secondary endpoints as defined in the clinical trials registry protocol. The reason to use strict inclusion and exclusion criteria was mainly linked to the need to have a high safety profile. In fact, since the THIRST study is the first in which AMI patients have been treated with biologically active T3, we enrolled only clinically and hemodynamically stable patients, who had had an uncomplicated AMI. Furthermore, in an attempt to maintain a high safety profile, we used a relatively low dosage of T3. However, the use of low dose of T3 was also for a potential physiological reason, considering that supra-physiological T3 doses led to increased mortality in rodent models very likely due to exaggerated activation of AKT.[26] In this

context, the results of the Coronary Drug showed that DT4, the inactive form of thyroxine and administered in patients with AMI, induced adverse outcomes, in particular arrhythmias.[27] Patients, however, were treated with 6 mg/day D-T4, that is equivalent to approximately 225 μg of L-T4, that, in turn, corresponds to more than double the endogenous production of T4.[16] It was later found that the D-T4 preparation (Choloxin; Flint Laboratories) used in the Coronary Drug Project was contaminated with a high level of active L-T4.[28]

The low T3 regimen dose we adopted may reduce the potential positive effects of this treatment on cardiac function and morphology. Therefore, if we consider that patients assuming T3 have had similar plasma T3 levels than those not assuming T3, we could speculate that the maximal T3 daily dose could be increased till a maximum of 20 mcg/m2 b.s., in order to reach borderline high normal values of circulating T3, but always paying special attention to avoid iatrogenic thyrotoxicosis. In this line, the evidence of spontaneous return of serum T3 to normal in untreated group after 1-month follow-up suggests that T3 substitutive treatment after AMI could be restricted to a shorter time than that utilized in the present study, in accord with recent experimental data.[29]

In conclusion, oral administration of low T3 dose resulted safe and able to reduce regional dysfunction. These results are pioneer, being THIRST Study the first and pilot experience to treat AMI/Low T3 Syndrome patients with T3 replacement therapy. Therefore, more data and studies are needed to assess the potential cardioprotective benefit of this therapy by trying to answer several issues including the type of hormone to administer, T3 or T4 or a combination, the kind of patients who truly benefit TH treatment, the timing to start and finish this treatment, and the clinical targets of this approach.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.12.020.

1. Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. *Circulation* 2010;122:385–393.
2. Friberg L, Drvota V, Bjelak AH, Eggertsen G, Ahnve S. Association between increased levels of reverse triiodothyronine and mortality after acute myocardial infarction. *Am J Med* 2001;111:699–703.
3. Pingitore A, Landi P, Taddei MC, Ripoli A, L'Abbate A, Iervasi G. Triiodothyronine levels for risk stratification of patients with chronic heart failure. *Am J Med* 2005;118:132–136.
4. Friberg L, Werner S, Eggertsen G, Ahnve S. Rapid down-regulation of thyroid hormones in acute myocardial infarction: is it cardioprotective in patients with angina. *Arch Intern Med* 2002;162:1388–1394.
5. Li L, Guo CY, Yang J, Jia EZ, Zhu TB, Wang LS, Cao KJ, Ma WZ, Yang ZJ. Negative association between free triiodothyronine level and international normalized ratio in euthyroid subjects with acute myocardial infarction. *Acta Pharmacol Sin* 2011;32:1351–1356.
6. Ozcan KS, Osmonov D, Toprak E, Güngör B, Tatlısu A, Ekmekçi A, Kaya A, Tayyareci G, Erdinler İ. Sick euthyroid syndrome is associated with poor prognosis in patients with ST segment elevation myocardial infarction undergoing primary percutaneous intervention. *Cardiol J* 2014;21:238–424.
7. Jabbar A, Pingitore A, Pearce SH, Zaman A, Iervasi G, Razvi S. Thyroid hormones and cardiovascular disease. *Nat Rev Cardiol* 2017;14:39–55.
8. Novitzky D, Cooper DK, Swanepoel A. Inotropic effect of triiodothyronine (T3) in low cardiac output following cardioplegic arrest and cardiopulmonary bypass: an initial experience in patients undergoing open heart surgery. *Eur J Cardiothorac Surg* 1989;3:140–145.
9. Moruzzi P, Doria E, Agostoni PG. Medium-term effectiveness of L-thyroxine treatment in idiopathic dilated cardiomyopathy. *Am J Med* 1996;101:461–467.
10. Hamilton MA, Stevenson LW, Fonarow GC, Steimle A, Goldhaber JI, Child JS, Chopra IJ, Moriguchi JD, Hage A. Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. *Am J Cardiol* 1998;81:443–447.
11. Pingitore A, Galli E, Barison A, Iervasi A, Scarlattini M, Nucci D, L'abbate A, Mariotti R, Iervasi G. Acute effects of triiodothyronine (T3) replacement therapy in patients with chronic heart failure and low-T3 syndrome: a randomized, placebo-controlled study. *J Clin Endocrinol Metab* 2008;93:1351–1358.
12. Pantos C, Mourouzis I, Saranteas T, Clavé G, Ligeret H, Noack-Fraissignes P, Renard PY, Massonneau M, Perimenis P, Spanou D, Kostopanagiotou G, Cokkinos DV. Thyroid hormone improves postischaemic recovery of function while limiting apoptosis: a new therapeutic approach to support hemodynamics in the setting of ischaemia-reperfusion? *Basic Res Cardiol* 2009;104:69–77.
13. Chen YF, Kobayashi S, Chen J, Redetzke RA, Said S, Liang Q, Gerdes AM. Short term triiodo-L-thyronine treatment inhibits cardiac myocyte apoptosis in border area after myocardial infarction in rats. *J Mol Cell Cardiol* 2008;44:180–187.
14. Forini F, Kusmic C, Nicolini G, Mariani L, Zucchi R, Matteucci M, Iervasi G, Pitto L. Triiodothyronine prevents cardiac ischemia/reperfusion mitochondrial impairment and cell loss by regulating miR30a/p53 axis. *Endocrinology* 2014;155:4581–4590.
15. de Castro AL, Fernandes RO, Ortiz VD, Campos C, Bonetto JH, Fernandes TR, Conzatti A, Siqueira R, Tavares AV, Schenkel PC, Bellló-Klein A, da Rosa Araujo AS. Thyroid hormones improve cardiac function and decrease expression of pro-apoptotic proteins in the heart of rats 14 days after infarction. *Apoptosis* 2016;21:184–194.
16. Pilo A, Iervasi G, Vitek F, Ferdeghini M, Cazzuola F, Bianchi R. Thyroidal and peripheral production of 3,5,3′-triiodothyronine in humans by multicompartmental analysis. *Am J Physiol* 1990;258:E715–E726.
17. Celi FS, Zemskova M, Linderman JD, Smith S, Drinkard B, Sachdev V, Skarulis MC, Kozlosky M, Csako G, Costello R, Pucino F. Metabolic effects of liothyronine therapy in hypothyroidism: a randomized, double-blind, crossover trial of liothyronine versus levothyroxine. *J Clin Endocrinol Metab* 2011;96:3466–3474.
18. Passino C, Pingitore A, Landi P Fontana M, Zyw L, Clerico A, Emdin M, Iervasi G. Prognostic value of combined measurement of brain natriuretic peptide and triidothyronine in heart failure. *J Card Fail* 2009;15:35–40.
19. Aquaro GD, Camastra G, Monti L, Lombardi M, Pepe A, Castelletti S, Maestrini V, Todiere G, Masci P, di Giovine G, Barison A, Dellegrottaglie S, Perazzolo Marra M, Pontone G, Di Bella G. Reference values of cardiac volumes, dimensions, and new functional parameters by MR: A multicenter, multivendor study. *J Magn Reson Imaging* 2017;45:1055–1067.
20. Di Bella G, Siciliano V, Aquaro GD, Molinaro S, Lombardi M, Carerj S, Landi P, Rovai D, Pingitore A. Scar extent, left ventricular end-diastolic volume, and wall motion abnormalities identify high-risk patients with previous myocardial infarction: a multiparametric approach for prognosis. *Eur Heart J* 2013;34:104–111.
21. Picano E, Sicari R, Landi P, Cortigiani L, Bigi R, Coletta C, Galati A, Heyman J, Mattioli R, Previtali M, Mathias W Jr, Dodi C, Minardi G, Lowenstein J, Seveso G, Pingitore A, Salustri A, Raciti M. Prognostic value of myocardial viability in medically treated patients with global left vetnricular dysfunction early after an acute myocardial uncomplicated myocardial infarction: a dobutamine stress echocardiography study. *Circulation* 1998;98:1078–1084.
22. Fath-Ordoubadi F, Pagano D, Marinho NV, Keogh BE, Bonser RS, Camici PG. Coronary revascularization in the treatment of moderate and severe postischemic left ventricular dysfunction. *Am J Cardiol* 1998;82:26–31.

23. Ojamaa K, Kenessev A, Shenov R, Klein I. Thyroid hormone metabolism and cardiac gene expression after acute myocardial infarction in the rat. *Am J Physiol Endocrinol Metab* 2000;279:E1319–E1324. Klein I.
24. KK1 Henderson, S Danzi, Paul JT, Leya G, Klein I, Samarel AM. Physiological replacement of T3 improves left ventricular function in an animal model of myocardial infarction-induced congestive heart failure. *Circ Heart Fail* 2009;2:243–252.
25. Lymvaios I, Mourouzis I, Cokkinos DV, Dimopoulos MA, Toumanidis ST, Pantos C. Thyroid hormone and recovery of cardiac function in patients with acute myocardial infarction: a strong association? *Eur J Endocrinol* 2011;165:107–114.
26. Mourouzis I, Mantzouratou P, Galanopoulos G, Kostakou E, Roukounakis N, Kokkinos AD, Cokkinos DV, Pantos C. Dose-dependent effects of thyroid hormone on post-ischemic cardiac performance: potential involvement of Akt and ERK signaling. *Mol Cell Biochem* 2012;363:235–243.
27. Stamler J. The coronary drug project. Findings leading to further modifications of its protocol with respect to dextrothyroxine. The coronary drug project research group. *JAMA* 1972;220:996–1008.
28. Jr Young WF, CA Gorman, Jiang NS, Machacek D, Hay ID. L-thyroxine contamination of pharmaceutical D-thyroxine: probable cause of therapeutic effect. *Clin Pharmacol Ther* 1984;36:781–787.
29. Nicolini G, Forini F, Kusmic C, Pitto L, Mariani L, Iervasi G. Early and short term triiodothyronine supplementation prevents adverse post-ischemic cardiac remodeling: role of transforming growth factor-β1 and anti-fibrotic miRNA signaling. *Mol Med* 2016;21:900–911.