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State of the coronary arteries and assessment of the role of hormone replacement therapy in patients with coronary heart disease against the background of primary manifest hypothyroidism

Aim	To study features of coronary damage and incidence of different types of acute coronary syndrome (ACS) in history associated with primary symptomatic hypothyroidism in patients with ischemic heart disease (IHD) and possible associations of replacement hormonal therapy with lipidogram indexes.
Material and methods	This retrospective study included 344 patients with IHD and functional class I–III stable angina (CCS, 1976). Of them 100 patients had primary symptomatic hypothyroidism and 244 had no hypothyroidism. Coronary angiography was performed for all patients included into this study. Routine laboratory, instrumental and clinical indexes were analyzed. Hypothyroidism was confirmed by levels of thyrotropic hormone, free triiodothyronine, and thyroxine. Comparative analysis was performed for the incidence of ACS types in history, types of coronary injury, and laboratory, instrumental and clinical indexes with assessment of potential interrelations. Statistically significant results were reported. Type of data distribution was evaluated with the Kolmogorov-Smirnov test. Quantitative data with normal (Gaussian) distribution were presented as mean (M) and standard deviation (SD). Data with attributes of non-normal distribution were presented as median (Me) with maximum and minimum values (min; max). Statistical significance of differences between means was assessed with the Mann-Whitney test. Logistic regression analysis was used in parallel for evaluating dependence of a quantitative variable on values of two or more quantitative or qualitative variables (factors). Significance level for testing of statistical hypotheses was $p<0.05$.
Results	Incidence of ST segment elevation ACS (STEACS) was significantly higher in IHD patients with hypothyroidism than in the group without hypothyroidism (61.6 and 35.6%, $p=0.03$) and also with three-vessel coronary artery disease (60.6 and 30.6%, $p=0.001$). In the IHD group with hypothyroidism, levels of total cholesterol, triglycerides, and low- and very low-density lipoproteins were significantly increased compared to the respective values in patients without hypothyroidism ($p<0.0001$). An inverse correlation was found between lipidogram indexes and L-thyroxine ($p<0.0001$).
Conclusion	The incidence of STEACS associated with primary symptomatic hypothyroidism in history was significantly higher in the patient group with IHD on the background of primary symptomatic hypothyroidism compared to the comparison group. Also, the incidence of three-vessel coronary disease was significantly greater than in the IHD patient group without hypothyroidism. A significant association was found between the replacement hormonal therapy and the best lipidogram indexes. The authors suggested that the key factor for prevention of adverse cardiovascular events in IHD with hypothyroidism is achieving control of clinical manifestations of hypothyroidism with replacement hormonal therapy.

Keywords	Ischemic heart disease; coronary angiography; hypothyroidism; lipidogram; L-thyroxine
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Comorbid associations form an integral part of the clinical portraits of older patients in contemporary cardiology, internal medicine, and other related disciplines. Although effective drug therapies and invasive interventions aimed at long-term compensation of a pathological process allow a significant number of patients with comorbidities to benefit from increased life expectancy, such treatments are

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also associated with a significant number of adverse consequences including deteriorating quality of life, increasing treatment costs for patients in particular and the health system in general, and increased repeat hospitalization rates [1, 2]. This problem is most relevant for patients with cardiovascular diseases, especially coronary artery disease (CAD) [3]. CAD is clinically associated with diabetes mellitus, chronic kidney disease, and anemia [4, 5]. A separate question of interest in relation to the comorbidity consisting in the evaluation of the influence of chronic inflammatory processes on the course of cardiovascular diseases (CVDs) [6, 7].

According to various current guidelines and studies, comorbid relationships of CVDs with endocrine diseases are represented by association with type 2 diabetes mellitus (DM). This is attributable to epidemiology (a frequent combination of DM and CVDs) and impact on the prognosis [8]. However, other equally significant associations, e.g., CVDs and hypothyroidism, are often overlooked. Hypothyroidism is a syndrome characterized by a decreased thyroid hormone level and/or reduced effects at the level of tissues [9]. There are three main mechanisms affecting how thyroid hormone imbalance acts on the course of CVDs:

- Direct genomic action on cardiomyocytes through binding with nuclear receptors, which in turn results in the regulation of the expression of a target gene;
- Non-nuclear mechanism: hormones act on the ion channels in the cardiomyocyte cell membrane;
- Extracardiac mechanism: various effects of triiodothyronine (T3) and thyroxine (T4) on peripheral blood circulation, changes in cardiovascular hemodynamics and myocardial contractility (systolic volume), etc. [10, 11].

All the above pathogenetic mechanisms lead to a deterioration of CVD in hypothyroidism. The mechanism of atherosclerosis and destabilization of dyslipidemia in patients with CAD and hypothyroidism is currently a topic of considerable interest. Researchers are interested in quantitative indicators of a decrease/increase in a particular item of the lipid profile and a more detailed study of morphological characteristics of the vascular wall. For example, a statistically significant increase in the intima-media thickness in patients with hypothyroidism was shown using Laser Doppler flowmetry [12]. The results of retrospective analyses of outcomes in patients with CAD and hypothyroidism who have undergone coronary revascularization are also worthy of consideration. A study comprising 222 patients identified a significant increase in repeat coronary revascularization compared to patients without hypothyroidism during an 8 year follow-up period (20.3% vs. 6.1%; p=0.02) [13]. However, data obtained by a study featuring a significantly higher number patients remain controversial. An analysis of PubMed and Embase publications involving a total of 555,530 patients demonstrated an increase in all-cause (including cardiovascular) mortality in patients with hypothyroidism. However, despite the presence of hypothyroidism, patients with the smallest number of associated clinical conditions did not show statistically significant differences in mortality [14]. At the same time, a Chinese meta-analysis of PubMed, Embase, and Cochrane Library publications (1,521 patients) identified associations indicating adversely affects on the lipid profile caused by elevated thyroid-stimulating hormone (TSH) in hypothyroidism. This not only has an effect on the development of endothelial dysfunction in CAD but may also negatively impact on prognosis [15].

The role of hormone replacement therapy in the pathogenesis of CAD, such as coronary heart disease, remains a separate relevant topic under discussion. Some studies conducted in small samples without prospective evaluation of treatment showed positive effects of L-thyroxine replacement therapy on the course of CAD. The published findings show a significant decrease in high-density lipoprotein cholesterol (HDL–C) and increased concentrations of nitric oxide (NO) in patients with CAD and hypothyroidism [16]. The larger samples did not clearly and definitively demonstrate positive effects of L-thyroxine on CAD. According to several researchers, there are no significant differences in the manifestation of clinical symptoms (anginal attacks), the incidence of atrial fibrillation, and other symptoms of CAD from patients treated with L-thyroxine [17–19].

However, there are no published studies carried out on a sufficient number of patients that evaluate the effect of hormone replacement therapy in hypothyroidism on the outcome of CAD and provide clear recommendations. Rather, most of the analyzed publications discuss subclinical hypothyroidism, which raises interest in the peculiarities of CAD in other forms of hypothyroidism. Although all guidelines describing the criteria for starting replacement therapy should be endorsed by endocrinological associations, such guidelines should take into account the opinions of both cardiologists and endocrinologists. Therefore, there is a need for further research to analyze the

effects of hypothyroidism on the course of CAD in more detail.

Objective

The objective of the present study was to identify possible differences in the morphology of coronary lesions in patients with an obstructive form of CAD and hypothyroidism to compare the findings with patients without hypothyroidism, evaluate possible associations of hormone replacement therapy with the indicators of lipid profile, as well as suggest possible adjustments for hormone replacement therapy in patients with CAD and clinically significant primary hypothyroidism.

Material and methods

At the first stage, 1,560 patients aged 40 to 70 were randomly examined; patients with signs of exertional angina were either admitted to or treated as outpatients at the Kerala Institute of Medical Sciences, Trivandrum, India. All the patients forming the subjects of the study were enrolled between 2016 and 2018.

Inclusion criteria:

- Diagnosis of CAD, functional class (FC) II–IV stable angina (CCS, 1976);
- Consent to undergo coronary angiography given at the time of inclusion to study the morphology of coronary lesions. Clinically significant stenosis was a narrowing of the lumen by more than 50% [20];
- Diagnosis of clinically significant primary hypothyroidism confirmed by T4 and TSH levels [21];

Exclusion criteria:

- Refusal to undergo coronary angiography;
- Acute forms of CAD at the time of inclusion (ACS, life-threatening rhythm disorders);
- FC III–IV (NYHA) chronic heart failure, decompensated heart failure;
- Atrial flutter / fibrillation;
- Chronic kidney disease, GFR <30 mL / min;
- Liver cirrhosis;
- Decompensated diabetes mellitus;
- Degenerative joint diseases;
- Grade III obesity;
- Other severe diseases;
- Smoking.

Lesions (stenosis) were detected in one, two, or three coronary arteries; the extent of stenosis was indicated. Additionally, bicycle ergometry was performed following the Bruce protocol and a modified Bruce protocol on an 8000 Marquette system (GE Medical System). Biochemical studies included natriuretic peptide (Vidas IFA), HbA1c (TOSOH), troponin, myoglobin (Cobas e411ECLIA), as well as lipid profile and thyroid hormones TSH, T3, T4 (COBAS 6000). The electrocardiogram was registered in 12 standard leads using a Mac 1200 Marquette device (GE Medical System). The echocardiogram was performed using Vivid E9 and Vivid 1 devices (Wipro GE Medical System).

As a result, 1,316 patients meeting exclusion criteria were excluded from the study.

Two groups were formed: the index group (CAD with hypothyroidism, n=100) and the control group (CAD without hypothyroidism, n=244). All included patients received CAD therapy following the standard clinical guidelines [11], including beta-blockers, antiplatelet treatment, and statins. Patients with contraindications to these groups of drugs and / or side effects were excluded from the study. Patients in the index group received hormone replacement therapy (L-thyroxine). Furthermore, 66% of patients had compensated clinically significant hypothyroidism, while 24% had newly detected hypothyroidism. Hypothyroidism was decompensated in 10% of cases.

A cross-sectional comparative analysis of the parameters of interest was carried out. Possible correlations between thyroid hormones and coronary performance and history of various acute cardiovascular events were analyzed.

Prior to being included in the study, patients were briefed following the ethical principles established by the Declaration of Helsinki (World Medical Association, 2013). All patients who participated in the study signed informed consent. The Ethics Committee of the Kerala Institute of Medical Sciences approved the study on May 2, 2020.

The data underlying the statistically significant results presented in this paper were processed using STATISTICA 10.0. software. The nature of data distribution was evaluated using the Kolmogorov-Smirnov test. Normally distributed (Gaussian) quantitative data were expressed in terms of mean (M) and standard deviation (SD). Data with signs of non-normal distribution were presented as median (Me), minimum and maximum values (min; max). The statistical significance of differences between the mean values was assessed using the Mann-Whitney test. A logistic regression analysis was used to evaluate the relationship between the value of a quantitative characteristic and the values of two or more quantitative or qualitative characteristics

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(factors). The significance threshold for the statistical hypotheses was p <0.05.

Results

With the exception of dyslipidemia, the clinical characteristics of the included patients given in Table 1 show no significant differences in these parameters. Age and sex characteristics of patients are provided in Table 2. Here, although the groups were comparable in age composition, the index group included more female patients in all age categories, while males prevailed in the control group. The comparative analysis of the clinical data presented in Table 3 shows statistically significant differences in all parameters of interest except for T3, troponin, and HDL–C.

At the first stage of the study, a comparative analysis of the morphological characteristics of the coronary lesions was carried out (Figure 1). Although three-vessel CAD was prevalent in both groups (p<0.001), it was more common in the group of patients with hypothyroidism than in patients with CAD without hypothyroidism (p<0.001). There were no significant differences in the rates of RCA and LAD+LCX lesions between the groups (p>0.05).

The rates of ACS variation in patients included in the study are shown in Figure 2. The rates of STE-ACS were statistically significantly different between the groups (p=0.03). There were no significant differences in the rates of NSTE-ACS (p=0.9). A comparative retrospective analysis was performed to evaluate the rates of coronary revascularization (Figure 3). There were no statistically significant differences between the groups (p>0.05).

One of the most important tools used to assess the course and prognosis of the disease in patients with CAD is lipid profiling. Given that all patients in the index group received hormone replacement therapy (L-thyroxine) and taking into account the absence of a clear and unambiguous opinion on the role of replacement therapy in hypothyroidism against CAD, a possible correlation between doses of L-thyroxine and relevant parameters of the lipid profile was analyzed. Doses of L-thyroxine ranged from 12.5 to 125 μg/day (Me=43.05 [12.5;125] μg/day). The results of a statistical analysis carried out to determine a possible optimal association between L-thyroxine doses and lipid profile indicators are presented in Table 4.

The analysis demonstrated that the strongest correlation between L-thyroxine and the lipid profile occurs within the mean daily range of 75–125 μg. In this subgroup, the mean dose was 90.7 μg/day (635.3 μg/week). Patients of both groups were comparable according to the lipid-lowering therapy parameters. The mean dose of statins (atorvastatin) was 80 mg/day during the hospital stay. Considering the mean daily dose of replacement therapy, the

Table 1. General characteristics of patients

Parameter	CAD and hypothyroidism, n = 100	CAD without hypothyroidism, n = 244	p
Age, years	58±5	56±7	0.07
BMI, kg/m^2	29.7±3.5	24.6±1	<0.0001
Diabetes mellitus, n (%)	48 (48)	122 (50)	0.7
Hypertensive heart disease, n (%)	69 (69)	156 (64.3)	0.8
Dyslipidemia, n (%)	77 (77)	90 (37)	<0.001
CKD, n (%)	29 (29)	78 (32)	<0.7
Anemia, n (%)	12 (12)	26 (11)	0.9
COPD, n (%)	24 (24)	58 (24)	0.7
Stable angina FC II, n (%)	18.2	22.4	0.4
Stable angina FC III, n (%)	67.4	59.1	0.09
Stable angina FC IV, n (%)	14.4	18.5	0.5

BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FC, functional class.

Table 2. Distribution of patients of the study groups depending on age and sex

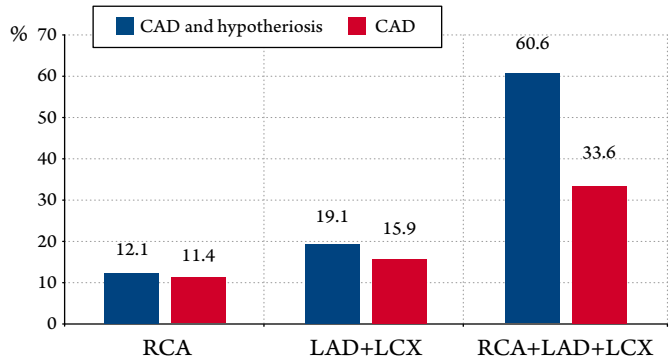
Age and sex		Patient groups: CAD and hypothyroidism, n=100		CAD without hypothyroidism, n=244		p
		n	%	n	%	
41–50 years old	Total	16	16	38	15.5	–
	Male	7	7	29	11.8	0.04
	Female	9	9	9	3.6	0.01
51–60 years old	Total	41	41	110	45.2	–
	Male	17	17	70	28.6	0.03
	Female	24	24	40	16.3	0.04
61–70 years old	Total	43	43	96	39.3	–
	Male	21	21	56	22.9	0.1
	Female	22	22	40	16.3	0.02
Total	Total	100	100	244	100	–
	Male	45	44	155	63.5	<0.001
		55	55	89	36.4	<0.001

Table 3. Clinical characteristics of the subjects

Parameter	CAD and hypothyroidism, n=100	CAD without hypothyroidism, n=244	p
T3, ng/mL	0.9 (0.02; 3.7)	1.3 (0.7; 88)	0.5
T4, ng/dL	1.09 (0.8; 10.3)	2.3 (0.2; 3.7)	<0.0001
TSH, μIU/mL	9.06 (0.07; 100)	1.9 (0.3; 5)	<0.0001
Troponin T, pg/mL	699.5 (5; 6930)	692.2 (5.1; 10000)	0.9
Myoglobin, ng/mL	19.4 (1.1; 170)	32.4 (0.5; 500)	0.04
Glucose, mg/dL	185.7 (82; 292)	160.7 (83; 207)	<0.0001
HbA1C, %	6.3 (5.2; 11.8)	5.4 (5.1; 8.9)	<0.0001
GFR, mL/min/1.73m2	88.7 (76; 102.7)	95.8 (89.2; 105.7)	<0.0001
TC, mg/dL	232.08 (177; 405)	177.9 (101; 316)	<0.0001
TG, mg/dL	148.1 (50; 330)	103.5 (31; 713)	<0.0001
HDL-C, mg/dL	41.4 (16; 65)	42.9 (17; 76)	0.1
LDL-C, mg/dL	161.01 (110; 303)	114.3 (45; 246)	<0.0001
VLDL, mg/dL	29.3 (10; 66)	20.3 (6; 142)	<0.0001
AI	5.8 (3; 14)	4.1 (2; 12)	<0.0001
L-thyroxine (μg/day)	43.05 (12.5; 200)		

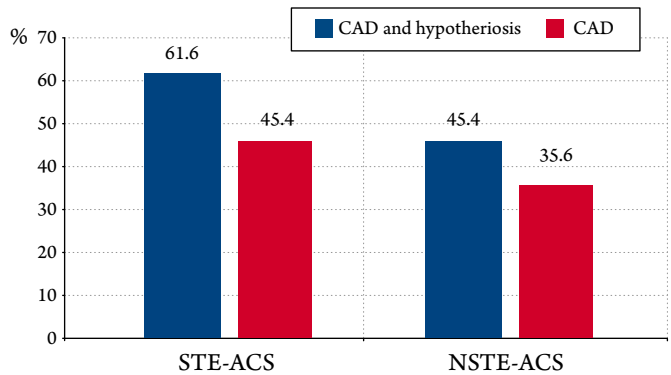
p – level of significance; BMI – body mass index; T3 – triiodothyronine; T4 – thyroxine; TSH – thyroid-stimulating hormone; HbA1c – glycated hemoglobin; GFR – glomerular filtration rate; TC – total cholesterol; TG – triglycerides; HDL – high-density lipoproteins; LDL – low-density lipoproteins; VLDL – very-low-density lipoproteins; AI – atherogenic index.

Figure 1. Comparative analysis of coronary artery lesions, %



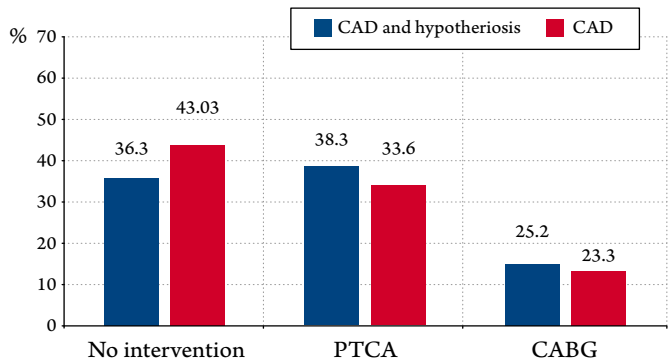
RCA, right coronary artery; LAD, left anterior descending artery; LAD + LCX, left anterior descending artery + left circumflex artery.

Figure 2. History of ACS in study patients, %



STE-ACS – ST segment elevation acute coronary syndrome; NSTE-ACS – non-ST segment elevation acute coronary syndrome.

Figure 3. Rate of coronary revascularization, %



PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.

correlation of this dose with the lipid profile indicators was analyzed, and the statistical significance for each item of the lipid profile was verified in the index subgroup. The results are presented in Table 5.

The analysis also revealed statistically significant correlations between total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL–C), and very-low-density lipoprotein (VLDL) cholesterol and the use of L-thyroxine. It should be noted that this regression model was constructed based on data of 84% of CAD and hypothyroidism patients. There was no statistically significant correlation between the doses of L-thyroxine and the parameters of the lipid profile in 10% of patients with decompensated hypothyroidism.

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Discussion

The role of comorbidities in CVDs is widely discussed in the scientific literature. The relationship between hypothyroidism and CAD is an issue common to the cardiovascular and endocrine systems, involving many clinical and pathogenetic correlations. The role of primary subclinical and clinically significant hypothyroidism in the progression of CAD has long been the subject of discussion. Although the effect of thyroid imbalance on the coronary system within this relationship remains a pressing issue, the available data are controversial. Although some authors identify a connection between the progression of dyslipidemia and that of coronary atherosclerosis, other sources indicate no statistically significant associations between hypothyroidism and the severity of coronary atherosclerosis [11]. Our study obtained statistically significant data indicating the prevalence of three-vessel CAD in the group of patients with CAD and primary clinically significant hypothyroidism compared to those with CAD and without hypothyroidism. More statistically significant cases of STE-ACS history were observed in the index group than in the group of patients without hypothyroidism. These findings, which complement the information currently available on this issue, point to the adverse impact of clinically significant primary hypothyroidism on the course of CAD. In this connection, there is sufficient evidence support the belief that primary hypothyroidism worsens the course of CAD [22].

The impact of hypothyroidism on the course of dyslipidemia is widely discussed in the literature. The literature analysis revealed a high risk of progression of dyslipidemia in such patients [23, 24]. Given the lack of a generally accepted opinion in the literature, it seems essential to study the role of hormone replacement therapy of primary hypothyroidism in relation to the course of CAD caused by coronary atherosclerosis. While experts from the American Association of Clinical Endocrinologists and the American Thyroid Association state that replacement therapy should be initiated when TSH is more than 10 mIU/L, recommending that lower physiological levels (4.5 to 10.0 mIU/L) in the senior be considered individually in relation to the administration of L-thyroxine, these endocrinological guidelines have yet to be endorsed by the cardiology community.

The logistic regression analysis revealed associations between the levels of TC, TG, LDL–C and VLDL and the administration of L-thyroxine at a mean daily dose of 90.7 mg/day in the group of patients with CAD and hypothyroidism. This association, which was identified in the cross-sectional study, is not predictive. However, we consider that more intensive lipid-lowering therapy combined with hormone replacement therapy is possible in this group of patients. It is also worth pointing out that, since this mathematical model was obtained in the course of a cross-sectional study, a longitudinal study is required to evaluate treatment efficacy.

Table 4. Correlation between dose ranges of L-thyroxine and lipid profile

Lipid profile components	Dose of L-thyroxine, μg/day		
	25-50	50-75	75-125
TC	r= –0.001	r= –0.1	r= –0.4
TG	r= –0.02	r=0.1	r= –2.4
HDL-C	r=0.05	r=0.01	r=0.3
LDL-C	r= –0.03	r=0.002	r= –0.5
VLDL	r= –0.001	r= –0.1	r= –0.3

Parameters of the model: t=1.4; b=0.6; r=0.5; r2=0.3, p=<0.001.
TC – total cholesterol; TG –triglycerides; HDL-C – high density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; VLDL – very low density lipoprotein;
t – Student's test; b – regression equation coefficient;
r –correlation coefficient; r2 – determination coefficient.

Table 5. Analysis of correlation of lipid profile and mean daily dose of L-thyroxine

Component	L-thyroxine (90.7 μg/day)				
	t	b	r	r^2	p
TC	5.8	-0.5	-0.5	-0.2	<0.0001
TG	8.8	-0.5	-0.5	-0.3	<0.0001
HDL-C	-1.7	-0.1	0.1	0.02	0.08
LDL-C	5.2	0.4	-0.4	-0.2	<0.0001
VLDL	6.7	0.5	-0.5	-0.3	<0.0001

TC – total cholesterol; TG – triglycerides; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; VLDL – very-low-density lipoprotein.

The findings appear to indicate an adverse prognosis for patients with CAD and clinically significant primary hypothyroidism. Prospective studies should be carried out to develop interventions that can influence prognosis and evaluate their efficacy.

Conclusion

More statistically significant cases of STE-ACS history were observed in the group of patients with CAD and clinically significant primary hypothyroidism than in the control group. There were also more statistically significant cases of three-vessel coronary artery disease in the index group than in patients with CAD but without hypothyroidism. A statistically significant association was found between hormone replacement therapy and the optimal lipid profile values. We suggest that the key factor in preventing adverse cardiovascular events in CAD and hypothyroidism consists in a compensation of the clinical manifestations of hypothyroidism using hormone replacement therapy.

No conflict of interest is reported.

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