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Hypothyroidism in spontaneous coronary artery dissection: presentation, clinical and angiographic findings, management and outcomes

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ABSTRACT

Background Hypothyroidism has been suggested as a predisposing and prognostic factor in patients with spontaneous coronary artery dissection (SCAD), but evidence in this regard is very limited.

Methods This study sought to compare differences in clinical presentation, angiographic findings, management and outcomes between SCAD patients with (H-SCAD) and without (NH-SCAD) a history of hypothyroidism from the prospective nation-wide Spanish SCAD Registry.

Results Overall, 47 H-SCAD (12%) and 342 NH-SCAD patients were included. H-SCAD patients when compared with NH-SCAD patients were significantly older (57±10 vs 54±12 years, p=0.045), had more frequent dyslipidaemia (49% vs 31%, p=0.013) and a non-significant trend to more associated fibromuscular dysplasia (47% vs 30%, p=0.191). Clinical presentation did not differ between groups, with non-ST-segment elevation myocardial infarction being the more frequent diagnosis at admission (62% vs 53%, p=0.273). H-SCAD patients showed more frequent multivessel involvement (19% vs 9%, p=0.044), angiographic type 2b lesions (36% vs 23%, p=0.037), lesions at segments with side-branches (68% vs 52%, p=0.026) and tighter lesions (88±13% vs 77±21% diameter stenosis, p=0.001), but less involvement of proximal segments (5% vs 15%, p=0.044). Revascularisation was more commonly needed in H-SCAD patients (34% vs 20%, p<0.05). At late clinical follow-up (median 29 months), the H-SCAD group had a higher adverse event rate (27% vs 11%, p=0.033), mainly driven by myocardial infarction (16% vs 6%, p=0.031) and SCAD recurrence (9% vs 1%, p<0.001). On multivariable analysis, the presence of hypothyroidism remained independently associated with adverse clinical events.

Conclusions H-SCAD patients were older and had a more diffuse and aggressive angiographic phenotype, including type 2b lesions, tighter lesions and more frequent multivessel involvement. Revascularisation was more frequently needed in H-SCAD patients. Long-term outcomes were poorer in this group, mainly driven by myocardial infarction and SCAD recurrence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hypothyroidism has been suggested as a predisposing and prognostic factor in patients with spontaneous coronary artery dissection (SCAD), but evidence in this regard is still scarce.

WHAT THIS STUDY ADDS

⇒ The present study includes data from the largest European registry of patients with SCAD, with a prospective study design, a central angiographic core lab and an independent clinical events committee and demonstrates that SCAD with hypothyroidism (H-SCAD) has some unique differential characteristics. H-SCAD had more diffuse and aggressive angiographic phenotype, including type 2b lesions, tighter lesions and more frequent multivessel involvement. Revascularisation was more frequently required in H-SCAD and, importantly, long-term clinical outcomes were poorer in this group, mainly driven by myocardial infarction and SCAD recurrences.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings may help interventional cardiologists and clinicians to identify a subset of SCAD patients with higher risk of adverse events, who may benefit from a closer clinical surveillance. A systematic screening for thyroid history and function at the time of SCAD suspicion should be considered in the management of these patients.

INTRODUCTION

Spontaneous coronary artery dissection (SCAD) is an increasingly recognised cause of acute coronary syndrome (ACS), particularly in younger women without classic cardiovascular risk factors.[1–3] In the last few years, several consensus documents have been published by experts in the field,[2 4] based on data from large national registries, mainly

retrospective.[5 6] Despite the lack of solid evidence on the pathophysiology of SCAD, it is relatively well established that the combination of predisposing factors like female gender, fibromuscular dysplasia (FMD), pregnancy and acute triggers may be sufficient cause to precipitate SCAD.[4]

Thyroid hormones modulate every component of the cardiovascular system necessary for its normal development and function. Any dysregulation of thyroid function might cause alterations in the cardiovascular system.[7] The association of thyroid disorders with 'non-coronary' spontaneous arterial dissections (mainly aortic and carotid) is already well known.[8 9] In the last few years, hypothyroidism has been proposed as an emerging risk factor for SCAD with an increased prevalence of hypothyroidism in unselected patients with SCAD as compared with controls.[5 10 11] In a preliminary two-centre study, we analysed the presence of hypothyroidism in SCAD patients. We showed a female gender predilection with more distal dissections in tortuous vessels and more conservative medical management.[10]

The present study aims to assess the differences in clinical presentation, angiographic findings, management and outcomes between SCAD patients with a history of hypothyroidism (H-SCAD) and SCAD patients without a history of hypothyroidism (NH-SCAD) from a contemporary, nationwide, prospective and consecutive cohort of patients included in the Spanish Registry on SCAD (SR-SCAD).

METHODS

The SR-SCAD (NCT03607981), a nationwide multicentre and prospective registry, includes, since 2015, consecutive patients with SCAD from 34 Spanish centres. This registry is endorsed by the Interventional Cardiology Association of the Spanish Society of Cardiology. A dedicated study protocol, database and informed consent were approved by the ethics committee at the coordinating centre. All patients gave informed consent. All coronary angiograms were meticulously reviewed by two SCAD experts in a central core laboratory, employing predefined morphological criteria specific to SCAD.[12 13] Multivessel SCAD was categorised as lesions involving at least two distinct major coronary arteries. Lesions affecting both a primary coronary segment and a side branch of the same artery were classified as single-vessel involvement, even in the absence of direct continuity between the lesions. Additionally, lesions affecting the left main stem extending into the left anterior descending artery or left circumflex artery were also considered as single-vessel involvement. The angiographic classifications by Saw and Motreff *et al* were used,[12] alongside the Mayo Clinic methodology for evaluating coronary tortuosity.[14] The study protocol encouraged the use of intracoronary imaging techniques as needed to confirm SCAD diagnosis in cases where angiographic images were unclear. Intracoronary nitroglycerin (100–200 micrograms) was recommended at the beginning of coronary angiography to exclude coronary spasm, which could obscure or alter the appearance of SCAD lesions. After careful revision of the angiogram at the core lab and the clinical data from reference centres (additional queries were sent to the sites when required), some patients were eventually excluded from the analysis if a potential alternative diagnosis to SCAD was considered more plausible. All adverse events were independently adjudicated by a clinical events committee, which reviewed anonymised source documents and images. According to the study protocol, a conservative approach to initial medical management was advised whenever feasible.[2 15] Thyroid status was specifically analysed and classified into two types: (a) hypothyroidism, if there was a previous clinical diagnosis (patients on chronic treatment with levothyroxine) or high thyroid-stimulating hormone (TSH) concentrations were detected (TSH ≥5.0 mU/mL) on admission; (b) euthyroidism, when there was no history or previous diagnosis of altered thyroid function, and the levels of TSH and free thyroxine (free T4) on admission were normal. As there were no patients with hyperthyroidism (TSH level ≤0.3 mU/mL), this group was not considered in the present analysis. This information was prospectively collected in the dedicated case report form.

Data collection

Data were prospectively collected during admission and at long-term follow-up, using standardised case report forms tailored specifically for this SCAD registry. These forms included clearly defined variables designed to capture the distinct aspects of SCAD, including acute precipitating factors, underlying predisposing conditions and conventional cardiovascular risk profiles. Demographic data, initial clinical presentation, electrocardiographic findings, echocardiographic assessments, laboratory values and coronary angiographic details were all recorded prospectively. Left ventricular ejection fraction was routinely measured using two-dimensional echocardiography prior to hospital discharge. Clinical outcomes occurring both in-hospital and during follow-up were prospectively tracked and independently adjudicated by a clinical events committee. Scheduled follow-up visits took place at 6 months and then annually for up to 5 years following the index event. If patients underwent new coronary angiography during follow-up, the images were forwarded to the central core laboratory for confirmation of SCAD recurrence or detection of coronary artery healing.

Endpoints

A prespecified *in-hospital* major adverse event (MAE) was defined as a composite of death, myocardial reinfarction, unplanned revascularisation, cardiogenic shock, ventricular arrhythmia or stroke. Similarly, the main long-term outcome—major adverse cardiac and cerebrovascular event (MACCE)—was defined as a composite of death, myocardial infarction (MI),

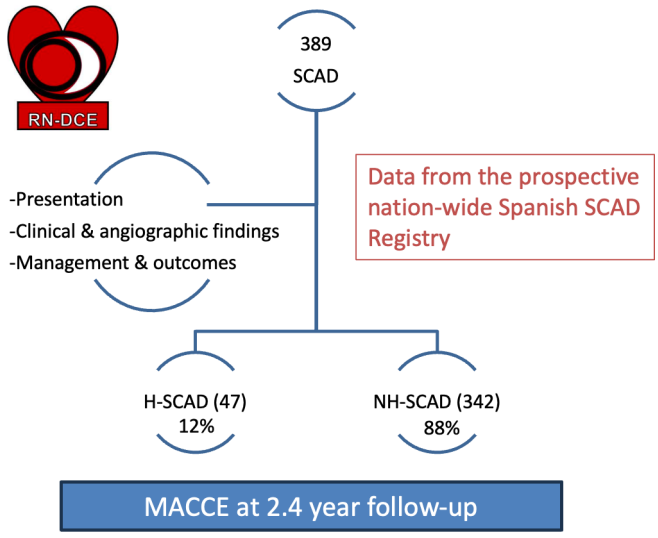


Figure 1 Flowchart of the study. H-SCAD: SCAD patients with a history of hypothyroidism; MACCE: composite of death, myocardial reinfarction, unplanned revascularisation; NH-SCAD: SCAD patients without a history of hypothyroidism; SCAD: spontaneous coronary artery dissection.

unplanned revascularisation, SCAD recurrence or stroke. These definitions were established in alignment with prior large-scale SCAD registries.[5 16 17] Reinfarction was classified according to the Third Universal Definition of Myocardial Infarction. SCAD recurrence referred to a new ACS event attributable to SCAD, affecting a different arterial segment from the original lesion. If the new event involved the same arterial segment, it was classified as SCAD progression.

Patient and public involvement

Patients and public were not specifically involved in this project.

Statistical analysis

Quantitative variables are described as mean±SD or median (IQR), according to their distributions. Categorical variables are presented as numbers (percentages). Continuous variables were analysed using the Student's t-test or the Mann-Whitney U test for comparisons between groups according to the nature of their distributions. Categorical variables were analysed using Pearson's χ^2 or Fisher's exact tests. Kaplan-Meier analyses were performed to assess clinical outcomes in the two groups and the results were compared with log-rank analyses. A Cox regression model was designed to search for independent factors related to MACCE at follow-up in the entire cohort. For this purpose, variables presenting a p value <0.1 in the univariate analysis were included. In addition, variables that had been identified in previous studies as prognostic variables in SCAD were also included in the model (hypertension, peripartum context, FMD, type 2 intramural haematoma (IMH), severe coronary tortuosity, conservative versus percutaneous coronary intervention (PCI) initial treatment and treatment with beta-blockers at discharge).[13 16] HRs with 95% CIs were calculated. A p value <0.05 was considered statistically significant. All statistical tests were performed using Stata V.12 software (StataCorp, College Station, Texas, USA).

RESULTS

From June 2015 to December 2020, a total of 389 patients with SCAD were prospectively included (encompassing 441 SCAD lesions). Overall, there were 342 patients in the

Table 1 Baseline clinical characteristics

	Global (n=389)	Hypothyroidism (n=47, 12%)	No hypothyroidism (n=342, 88%)	P Value
Age, years	54±11	57±10	54±12	0.045
Sex (female)	344 (88%)	44 (94%)	300 (88%)	0.236
Hypertension	139 (36%)	21 (45%)	118 (35%)	0.172
Dyslipidaemia	128 (33%)	23 (49%)	105 (31%)	0.013
Diabetes mellitus	21 (5%)	4 (9%)	17 (5%)	0.317
Cigarette smoking	171 (44%)	14 (30%)	157 (46%)	0.055
Connective tissue disease	2 (0.5%)	0	2 (0.6%)	0.599
Chronic inflammatory disease	18 (5%)	3 (6%)	15 (4%)	0.541
Fibromuscular dysplasia	34/106 (32%)	7/15 (47%)	27/91 (30%)	0.191
Depression	79 (20%)	11 (23%)	68 (20%)	0.574
Anxiety	70 (18%)	9 (19%)	61 (18%)	0.826
Menopause	190/344 (55%)	29/44 (66%)	163/300 (54%)	0.153
Presentation as STEMI	156 (40%)	17 (36%)	139 (41%)	0.557
Presentation as NSTEMI	211 (54%)	29 (62%)	182 (53%)	0.274
Identifiable trigger	158 (41%)	21 (45%)	137 (40%)	0.545

Categorical variables are expressed as n (%).
NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

NH-SCAD group (87%) and 47 patients in the H-SCAD group (12%). Among the total of 47 patients included in the hypothyroidism group, 16 patients (34%) had an elevated TSH value at the time of diagnosis of SCAD, so that two-thirds of the patients included in this group were euthyroid at the time of the SCAD episode. Regarding TSH values at the time of SCAD-related hospital admission, the mean TSH value in the global cohort (n=289) was 2.4 mU/mL (IQR 1.2–2.7). In the subgroup of patients with hypothyroidism, the mean TSH was 3.2 mU/mL (IQR 1.5–5.7). Figure 1 shows the flowchart of the study.

Baseline clinical characteristics

Baseline characteristics are summarised in table 1. Patients with H-SCAD, when compared with NH-SCAD patients were significantly older (57±10 vs 54±12 years, p=0.045), had more dyslipidaemia (49% vs 31%, p=0.013) and a non-significative (NS) numeric difference in FMD (47% vs 30%, p=NS). The clinical presentation did not differ between groups, with non-ST-segment elevation MI being the more frequent diagnosis at admission (62% vs 53%, p=NS).

Angiographic findings

Angiographic findings are shown in table 2. In both groups, the left anterior descending coronary artery was the most frequently affected vessel (41% vs 45%, p=NS). The H-SCAD group showed more frequently multivessel involvement (19% vs 9%, p=0.044) or lesions located in side branches coronary segments (68% vs 52%, p=0.026), had tighter lesions (88±13% vs 77±21% diameter stenosis, p=0.001) and more lesions presenting as long IMH type 2b (36% vs 23%, p=0.037), but with less proximal segment involvement (5% vs 15%, p=0.044), as compared with the

Table 2 Angiographic findings

	Global (N=389, 441 lesions)	Hypothyroidism (n=47, 59 lesions)	No hypothyroidism (n=342, 382 lesions)	P Value
Affected coronary artery*				
Left main	10 (2%)	1 (1.7%)	9 (2.4%)	0.751
LAD	196 (44%)	24 (41%)	172 (45%)	0.532
LCX	141 (32%)	19 (32%)	122 (32%)	0.967
RCA	94 (21%)	15 (25%)	79 (21%)	0.408
Dominance				0.485
Right	353 (91%)	44 (94%)	309 (90%)	
Left	27 (7%)	2 (4%)	25 (7%)	
Codominance	9 (2%)	1 (2%)	8 (2%)	
Proximal segment involvement*	59 (13%)	3 (5%)	56 (15%)	0.044
Distal segment involvement*	167 (38%)	20 (34%)	147 (38%)	0.499
Side branch involvement*	240 (54%)	40 (68%)	200 (52%)	0.027
Multisegment (>1 syntax segment)*	92 (23%)	9 (18%)	83 (24%)	0.373
Multivessel involvement	41 (11%)	9 (19%)	32 (9%)	0.044
Diameter stenosis (%)*	79±21	88±13	77±21	0.001
Lesion length (mm)*	37±24	42±24	37±24	0.241
Angiographic classification*				
Type 1	84 (19%)	12 (20%)	72 (19%)	0.786
Type 2a	162 (37%)	14 (24%)	148 (39%)	0.026
Type 2b	109 (25%)	21 (36%)	88 (23%)	0.037
Type 3	38 (9%)	4 (7%)	34 (9%)	0.589
Type 4	48 (11%)	8 (14%)	40 (10%)	0.478
IMH type 2 versus other patterns	271 (61%)	25 (53%)	215 (63%)	0.201
Severe coronary tortuosity	49 (13%)	6 (13%)	43 (13%)	0.97
Coronary ectasia	47 (12%)	6 (13%)	41 (12%)	0.878
Initial TIMI flow*	2.2±1.1	2.0±1.2	2.2±1.1	0.24
Initial TIMI flow 0–1**	114 (26%)	18 (31%)	96 (25%)	0.38

Categorical variables are expressed as n (%).
*Analysis performed per lesion.
IMH, intramural haematoma; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

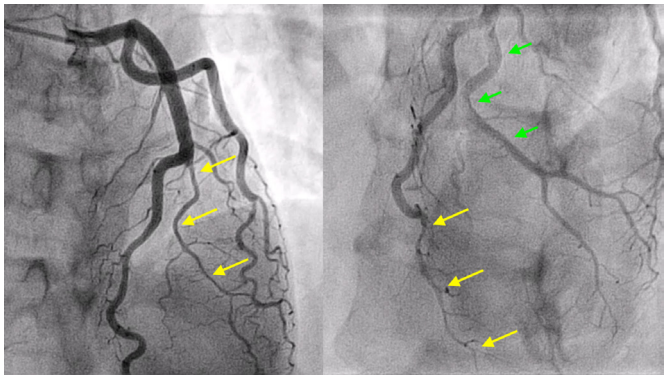


Figure 2 Representative case of H-SCAD and recurrence. A 54-year-old female with a history of hypothyroidism presented with a lateral non-ST elevation myocardial infarction. Coronary angiography revealed a diffuse lesion (type 2B) in the diagonal branch (panel A, yellow arrows, online supplemental video 1**)** and conservative management was decided. The same patient was admitted 2 years later due to anterior non-ST elevation myocardial infarction. Coronary angiography revealed a recurrence of SCAD with a severe diffuse lesion (type 2B) involving the mid-distal left anterior descending artery (panel B, yellow arrows, online supplemental video 2) and the healing of the previously dissected diagonal branch (panel B, green arrows, online supplemental video 2); again, conservative management was done. H-SCAD, SCAD patients with a history of hypothyroidism; SCAD, spontaneous coronary artery dissection.

NH-SCAD group. Figure 2 illustrates a representative case of H-SCAD.

Management and outcomes

Management and outcomes are summarised in table 3. Regarding the initial revascularisation strategy, patients with H-SCAD were more frequently managed with percutaneous coronary intervention (34% vs 20%, p=0.031). The complications related to invasive coronary angiogram, including catheter-induced iatrogenic dissection and IMH progression related to PCI, were similar in both groups. There were no significant differences in medical treatment at hospital discharge, including the prescription of dual antiplatelet therapy (61% vs 57%, p=NS) and beta-blockers (85% vs 79%, p=NS). The rate of in-hospital MAE was numerically higher in the H-SCAD group, although this difference did not reach statistical significance (13% vs 6%, p=0.0587). With a median follow-up of 29 months, the MACCE rate was higher in the H-SCAD group (27% vs 11%, p=0.033), mainly driven by MI (16% vs 6%, p=0.031) and SCAD recurrence (9% vs 1%, p<0.001). Figure 3 shows MACCE-free survival curves estimated by the Kaplan-Meier method according to history of hypothyroidism. Table 4 summarises univariable and multivariate Cox regression analysis of MACCE predictors at follow-up. In crude Cox regression analysis, hypothyroidism was associated with an increased risk of MACCE at follow-up (crude HR 2.83 (95% CI 1.5 to 5.5, p=0.002)). After adjustment for baseline differences in the study groups (including age, dyslipidaemia, proximal involvement, multivessel involvement, % diameter stenosis, type 2 intramural haematoma and conservative management), hypothyroidism continued to be associated with an increased risk of MACCE at follow-up (adjusted HR 4.0 (95% CI 1.8 to 8.7, p=0.001)). In addition, in the multivariable model, only history of hypothyroidism (HR 3.21 (95% CI 1.6 to 6.6, p=0.001)) and treatment with dual antiplatelet therapy at discharge (HR 2.56 (95% CI 1.2 to 5.5, p=0.016)) were identified as independently related to an increased risk of MACCE at follow-up, see table 4.

DISCUSSION

The present work includes data from the largest European registry of patients with SCAD, with a prospective study design, a central angiographic core lab and an independent clinical events committee. The main findings of the study are the following: (1) patients with H-SCAD are older and have a more diffuse and aggressive angiographic phenotype, including tighter lesions and more frequent angiographic type 2b IMH pattern and multivessel involvement than patients with NH-SCAD; (2) the H-SCAD group more often required initial management with percutaneous coronary intervention and (3) long-term outcomes were markedly poorer in H-SCAD patients, mainly driven by MI and SCAD recurrences, compared with NH-SCAD patients.

The thyroid gland and the heart share a common embryological origin and an intimate and complex functional relationship. Thyroid hormone function affects the entire cardiovascular system due to receptors being present in the myocardium and vascular endothelium tissue. There are two main routes for thyroid hormone action: the transcriptional genomic effects and the non-genomic effects, the latter targeting directly different cell structures.[7] Thyroid hormones exert their effect on the vasculature via both the vascular smooth muscle and endothelial cell levels.[18] Non-genomic, indirect effects of thyroid hormones include ion channel activation (Na^+, K^+ and Ca^{2+}) and regulation of specific signal transduction pathways. Activation of phosphatidylinositol 3-kinase and serine/threonine protein kinase pathways causes the production of endothelial nitric oxide, leading to a reduction in systemic vascular resistance through its effects on vascular smooth muscle cells.[18 19] Decreased level of thyroid hormones, even at the subclinical level, has deleterious cardiovascular effects with a 20–80% increased risk of vascular morbidity and mortality.[18 20]

In a previous preliminary two-centre study, we described that hypothyroidism was more frequently found in patients with ACS secondary to SCAD than in patients with ACS due to atherothrombotic disease.[10] As previously reported and corroborated in the present study, hypothyroidism prevalence increases with age and is associated with a small but significant increase in lipid parameters.[18] However, the small differences found in

Table 3 Management and outcomes

	Global (n=389)	Hypothyroidism (n=47, 12%)	No hypothyroidism (n=342, 88%)	P Value
Initial management				0.031
Conservative	305 (78%)	31 (66%)	273 (80%)	
PCI	84 (22%)	16 (34%)	69 (20%)	
Complication related to ICA	44 (11%)	7 (15%)	37 (11%)	0.408
Catheter-induced iatrogenic dissection	11 (2.8%)	1 (2.1%)	10 (2.9%)	0.758
IMH extension related to PCI	24/84 (29%)	5/16 (31%)	19/69 (28%)	0.766
Left ventricular ejection fraction (LVEF)	57±9	58±7	57±10	0.308
Reduced LVEF (<50%)	53 (14%)	3 (6%)	50 (15%)	0.123
Treatment at discharge				
Aspirin	354 (93%)	44 (96%)	310 (92%)	0.408
DAPT	221 (58%)	28 (61%)	193 (57%)	0.659
Beta-blocker	304 (79%)	39 (85%)	265 (79%)	0.351
ACEIs/ARB	196 (51%)	26 (57%)	170 (51%)	0.451
Statins	288 (75%)	37 (80%)	251 (75%)	0.397
In-hospital MAE (n=389)	25 (6%)	6 (13%)	19 (6%)	0.059
Death	7 (2%)	1 (2%)	6 (2%)	0.857
Myocardial reinfarction	11 (3%)	2 (4%)	9 (3%)	0.529
Unplanned revascularisation	17 (4%)	4 (9%)	13 (4%)	0.139
Ventricular arrhythmia	5 (1.3%)	1 (2%)	4 (1%)	0.585
Cardiogenic shock	7 (1.8%)	2 (4%)	5 (1.5%)	0.177
Stroke	1 (0.3%)	0	1 (0.3%)	0.711
Time of follow-up (months)	29±15	29±16	29±14	0.899
MACCE at follow-up (n=355)	46 (13%)	12 (27%)	34 (11%)	0.033
Death	9 (2.5%)	3 (7%)	6 (2%)	0.059
Myocardial re-infarction	27 (8%)	7 (16%)	20 (6%)	0.031
Unplanned revascularisation	22 (6%)	4 (9%)	18 (6%)	0.423
SCAD recurrence	7 (2%)	4 (9%)	3 (1%)	<0.001
Stroke	4 (1.1%)	0	4 (1.3%)	0.444

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; DAPT, dual antiplatelet therapy; ICA, invasive coronary angiogram; IMH, intramural haematoma; MACCE, Major adverse cardiac and cerebrovascular event; MAE, major adverse event; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.

mean age (57 years vs 54 years of age) and prevalence of dyslipidaemia (49% vs 31%) do not seem to explain, per se, the increase in events in the H-SCAD group. This fact, together with the more frequent multivessel involvement, more aggressive angiographic pattern and more frequent SCAD recurrence rate, might suggest a greater weakness of the coronary artery wall in this group of patients. Of note, the differences in clinical outcomes persisted after meticulous multivariable analyses to adjust for potential confounders. This further suggests the relevance of hypothyroidism in the prognosis of these patients.

As previously suggested,[8 9] a specific wall weakness could be the link between thyroid disorders and vascular dissections of several territories (including aortic or vertebral). Several studies have shown that thyroid hormones regulate endothelial nitric oxide production and vascular tone and that patients with hypothyroidism (both overt and subclinical) exhibit impaired endothelial function, which improves with hormone replacement therapy.[18] Overt and subclinical hypothyroidism are associated with diastolic hypertension, impaired vascular function and increased carotid intima hyperplasia.[18] Furthermore, endothelial-dependent vasodilation is reduced in hypothyroidism but improves with levothyroxine treatment, as does pulse wave velocity, a surrogate measure of arterial stiffness.[18] Several factors could contribute to this distinct arterial stiffness and endothelial dysfunction in hypothyroidism patients, including hyperlipidaemia and a proinflammatory state.[18] However, the intrinsic mechanisms by which the arterial wall becomes weaker remain mere hypotheses to date. Although there are no data on specific histological changes at the level of the

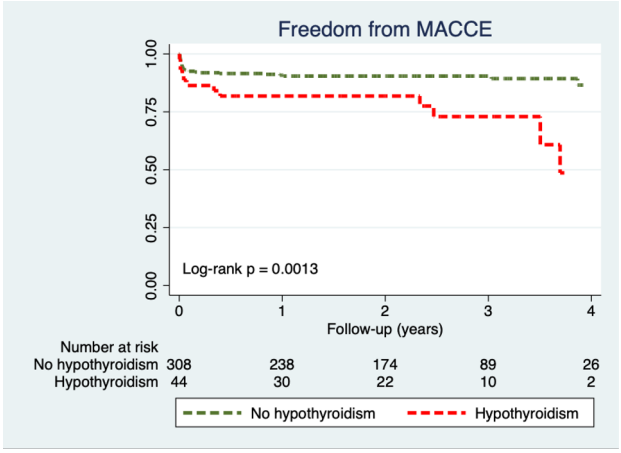


Figure 3 MACCE-free survival curves estimated by the Kaplan-Meier method according to history of hypothyroidism. MACCE, composite of death, myocardial reinfarction, unplanned revascularisation.

coronary wall, it has been suggested that the presence of a myxedematous deposit could be involved.[21] Thus, in hypothyroidism, interstitial water and sodium retention in the vascular wall has been described, with a deposit of hydrophilic mucopolysaccharides, increased number of fibroblasts, decreased degradation of hyaluronic acid and an increase in its synthesis by fibroblasts.[21 22] An increase in hyaluronic acid in the initial phases of plaque erosion has also been postulated. All these changes, in turn, could induce endothelial dysfunction and a certain degree of systemic inflammation.[23 24] These findings could explain the relationship between hypothyroidism and SCAD with bleeding and thrombus formation at the interface between the media and the adventitia, a greater tendency to recur and lower spontaneous healing during follow-up. Figure 4 represents a proposed histopathological model of hypothyroid involvement in the arterial wall.

Although the percentage of screening for FMD was relatively low in this cohort (27%), a numerical difference is again found in favour of greater association with FMD in the H-SCAD group (47% vs 30%, NS), similar to that described in our preliminary study.[10] It should be kept in mind that FMD has been associated with an increased risk of SCAD and adverse events.[6] Interestingly, in FMD, there is also an increase in fibroblasts in the arterial media with elevated collagen synthesis that progressively replaces the muscle cells and weakens the arterial wall.[25] This might also contribute to explaining the outcomes in the H-SCAD subgroup. However, it is well known that observational association does not imply causality and our findings should be considered as hypothesis generating.

Not only thyroid hormones but also other hormonal changes appear to play an important role in SCAD. Pregnancy-related SCAD (P-SCAD), most often within the first postpartum month, has a more severe clinical and angiographic presentation. Variations in haemodynamic and hormonal factors might contribute to SCAD events in susceptible women.[26 27] It is noteworthy that, despite the well-documented association between pregnancy and hypothyroidism, and its possible association with maternal and fetal outcomes,[28 29] a higher prevalence of hypothyroidism in P-SCAD patients has not been reported to date.[26] These findings could be explained by the lack of subclinical hypothyroidism inclusion criteria in most of the previous studies, considering only hypothyroidism as a diagnostic criterion despite the increased cardiovascular risk associated with subclinical hypothyroidism.

Regarding angiographic features, in our study, the H-SCAD group presented twice as much multivessel involvement, which may be a reflection of widespread vascular fragility. This presentation has some distinctive clinical and angiographic characteristics; however, composite clinical outcomes in the acute setting seem

Table 4 Univariable and multivariate Cox regression analysis of MACCE predictors at follow-up

	Univariate HR (95% CI)	Multivariate HR (95% CI)
Hypertension*	0.99 (0.5 to 1.8, p=0.95)	
Peripartum*	2.62 (0.4 to 19, p=0.343)	
Hypothyroidism	2.83 (1.5 to 5.5, p=0.002)	3.21 (1.6 to 6.6, p=0.001)
Fibromuscular dysplasia*	0.94 (0.3 to 2.6, p=0.906)	
Type 2 IMH*	1.45 (0.8 to 2.8, p=0.262)	
Severe coronary tortuosity*	1.49 (0.7 to 3.2, p=0.305)	
Conservative management (vs PCI)*	0.68 (0.3 to 1.3, p=0.254)	
DAPT at discharge	2.55 (1.2 to 5.4, p=0.014)	2.56 (1.2 to 5.5, p=0.016)
Betablockers at discharge*	1.48 (0.6 to 3.8, p=0.412)	

SCAD recurrence, or stroke.
*Variables without significant differences in the bivariate comparison of the present study but included in the model considering previous scientific evidence on SCAD.
DAPT, dual antiplatelet therapy; IMH, intramural haematoma; MACCE, composite of death, myocardial reinfarction, unplanned revascularisation; PCI, percutaneous coronary intervention; SCAD, spontaneous coronary artery dissection.

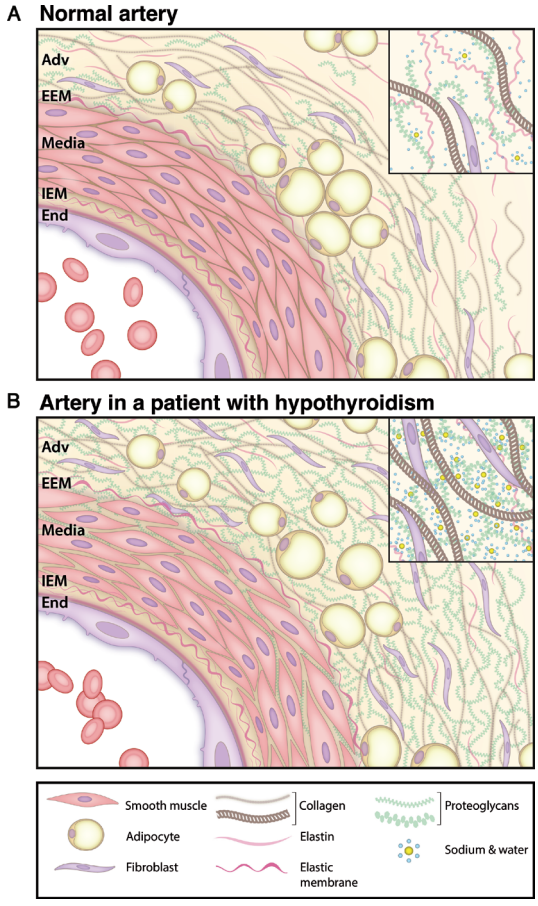


Figure 4 Proposed histopathological model of hypothyroid involvement in the arterial wall. **(A)** illustrates a normal coronary artery wall. **(B)** shows the postulated changes in the arterial wall of hypothyroid patients with interstitial water and sodium retention, with a deposit of hydrophilic mucopolysaccharides, increased number of fibroblasts, decreased degradation of hyaluronic acid and an increase in its synthesis by fibroblasts. Adv, adventitial layer; EEM, elastic external membrane; EIM, elastic internal membrane; End, endothelium.

to be similar to those seen in patients with single-vessel SCAD. However, the relatively small sample size, especially in the H-SCAD group, should be kept in mind.[17]

Different studies have shown the type 2 IMH angiographic pattern as a predictor of adverse events[16 30] compared with lesions with double lumen, not only in the early phase after SCAD diagnosis but also in the long-term follow-up. Jackson *et al* showed that these lesions have larger false lumen/IMH, probably associated with greater pressure, promoting a more susceptible scenario for subsequent SCAD extension and events. In the present study, the H-SCAD group presented more frequently with this angiographic pattern. Moreover, lesions in this group seemed to be tighter, which could explain at least in part the more frequent use of percutaneous coronary interventions and the higher rate of recurrences at follow-up.

There was just a NS pointing at a higher rate of in-hospital MAE in the H-SCAD group, mainly due to unplanned revascularisation and cardiogenic shock. Similarly, in the long-term follow-up (median 2.4 years), the H-SCAD group presented worse outcomes with a higher rate of myocardial re-infarction and SCAD recurrence. The present study has inherent design limitations and therefore should be just considered as hypothesis generating and ideally endorsed and confirmed in larger cohorts (difficult to achieve in the field of SCAD). However, our data strongly suggest that the presence of hypothyroidism may identify a high-risk subgroup of SCAD patients. Consequently, systematic screening for thyroid history and function at the time of the SCAD event should be considered in the management of these patients.

Study limitations

Among the limitations of the study, we should acknowledge those inherent to a non-randomised observational design and the relatively small sample size (like any other work in relatively rare entities, such as SCAD), mainly in the H-SCAD group. We estimated a relatively small statistical power (75%) to find differences between groups in MACCE. In addition, we should acknowledge the variability of thyroid management across centres, lack of data about the aetiology, duration or treatment of hypothyroidism and also the possibility of a selection bias in an entity where the initial diagnosis can easily be overlooked. Moreover, the current cohort did not incorporate patients who did not survive their initial SCAD presentation. Thus, it is possible that some patients with a more severe presentation profile have not been correctly diagnosed and referred. However, this study enabled us to evaluate and compare the characteristics and natural history of H-SCAD with that of NH-SCAD, in an objective manner, according to real-world management and during a long-term, prospective, clinical follow-up.

CONCLUSIONS

Patients with SCAD and hypothyroidism appear to have a more diffuse and aggressive angiographic phenotype, including more frequent multivessel involvement, type 2b angiographic lesions and tighter lesions. This group of patients more frequently requires initial management with percutaneous coronary intervention. Patients with SCAD and hypothyroidism may have a poorer clinical outcome, driven by an increased risk of MI and SCAD recurrence.

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REFERENCES

1 Hayes SN, Kim ESH, Saw J, *et al*. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. *Circulation* 2018;137:e523–57.
2 Hayes SN, Tweet MS, Adlam D, *et al*. Spontaneous Coronary Artery Dissection. *J Am Coll Cardiol* 2020;76:961–84.
3 Saw J, Aymong E, Mancini GBJ, *et al*. Nonatherosclerotic coronary artery disease in young women. *Can J Cardiol* 2014;30:814–9.
4 Adlam D, Alfonso F, Maas A, *et al*. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *Eur Heart J* 2018;39:3353–68.
5 García-Guimaraes M, Bastante T, Macaya F, *et al*. Spontaneous coronary artery dissection in Spain: clinical and angiographic characteristics, management, and in-hospital events. Rev Esp Cardiol (Engl Ed) 2021;74:15–23.
6 Saw J, Starovoytov A, Aymong E, *et al*. Canadian Spontaneous Coronary Artery Dissection Cohort Study: 3-Year Outcomes. *J Am Coll Cardiol* 2022;80:1585–97.
7 Grais IM, Sowers JR. Thyroid and the heart. *Am J Med* 2014;127:691–8.
8 Rosenmann E, Yarom R. Dissecting aneurysm of the aorta and hypothyroidism. *Isr J Med Sci* 1994;30:510–3.
9 Pezzini A, Del Zotto E, Mazziotti G, *et al*. Thyroid autoimmunity and spontaneous cervical artery dissection. *Stroke* 2006;37:2375–7.
10 Camacho Freire SJ, Díaz Fernández JF, Gheorghe LL, *et al*. Disección coronaria espontánea e hipotiroidismo. *Revista Española de Cardiología* 2019;72:625–33.
11 Ionescu CN, Chrissoheris M, Caraccciolo EA. Spontaneous coronary artery dissection and severe hypothyroidism. *J Invasive Cardiol* 2009;21:E60–2.
12 Motreff P, Malcles G, Combaret N, *et al*. How and when to suspect spontaneous coronary artery dissection: novel insights from a single-centre series on prevalence and angiographic appearance. *EuroIntervention* 2017;12:e2236–43.
13 Mori R, Macaya F, Giacobbe F, *et al*. Clinical outcomes by angiographic type of spontaneous coronary artery dissection. *EuroIntervention* 2021;17:516–24.
14 Eleid MF, Guddeti RR, Tweet MS, *et al*. Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circ Cardiovasc Interv* 2014;7:656–62.
15 Kim ESH. Spontaneous Coronary-Artery Dissection. *N Engl J Med* 2020;383:2358–70.
16 Garcia-Guimaraes M, Masotti M, Sanz-Ruiz R, *et al*. Clinical outcomes in spontaneous coronary artery dissection. *Heart* 2022;108:1530–8.
17 Salamanca J, García-Guimarães M, Sabaté M, *et al*. Multivessel spontaneous coronary artery dissection: Clinical features, angiographic findings, management, and outcomes. *Int J Cardiol* 2023;370:65–71.
18 Razvi S, Jabbar A, Pingitore A, *et al*. Thyroid Hormones and Cardiovascular Function and Diseases. *J Am Coll Cardiol* 2018;71:1781–96.
19 Carrillo-Sepúlveda MA, Ceravolo GS, Fortes ZB, *et al*. Thyroid hormone stimulates NO production via activation of the PI3K/Akt pathway in vascular myocytes. *Cardiovasc Res* 2010;85:560–70.
20 Jabbar A, Razvi S. Thyroid disease and vascular risk. *Clin Med (Lond)* 2014;14 Suppl 6:s29–32.
21 Parving HH, Helin G, Garbarsch C, *et al*. Acid glycosaminoglycans in myxoedema. *Clin Endocrinol (Oxf)* 1982;16:207–10.
22 Shishiba Y, Yanagishita M, Hascall VC. Effect of thyroid hormone deficiency on proteoglycan synthesis by human skin fibroblast cultures. *Connect Tissue Res* 1988;17:119–35.
23 Taddei S, Caraccio N, Virdis A, *et al*. Low-grade systemic inflammation causes endothelial dysfunction in patients with Hashimoto's thyroiditis. *J Clin Endocrinol Metab* 2006;91:5076–82.
24 Taddei S, Caraccio N, Virdis A, *et al*. Impaired endothelium-dependent vasodilatation in subclinical hypothyroidism: beneficial effect of levothyroxine therapy. *J Clin Endocrinol Metab* 2003;88:3731–7.
25 Michelis KC, Olin JW, Kadian-Dodov D, *et al*. Coronary artery manifestations of fibromuscular dysplasia. *J Am Coll Cardiol* 2014;64:1033–46.
26 Tweet MS, Hayes SN, Codsi E, *et al*. Spontaneous Coronary Artery Dissection Associated With Pregnancy. *J Am Coll Cardiol* 2017;70:426–35.
27 Mori R, Macaya F, Giacobbe F, *et al*. Association between hormone therapy and short-term cardiovascular events in women with spontaneous coronary artery dissection. *Revista Española de Cardiología (English Edition)* 2023;76:165–72.
28 Maraka S, Ospina NMS, O'Keeffe DT, *et al*. Subclinical Hypothyroidism in Pregnancy: A Systematic Review and Meta-Analysis. *Thyroid* 2016;26:580–90.
29 Bein M, Yu OHY, Grandi SM, *et al*. Levothyroxine and the risk of adverse pregnancy outcomes in women with subclinical hypothyroidism: a systematic review and meta-analysis. *BMC Endocr Disord* 2021;21:34.
30 Cerrato E, Giacobbe F, Quadri G, *et al*. Antiplatelet therapy in patients with conservatively managed spontaneous coronary artery dissection from the multicentre DISCO registry. *Eur Heart J* 2021;42:3161–71.