# Percutaneous Coronary Intervention for Chronic Total Occlusion versus Percutaneous Coronary Intervention for Non-Complex Coronary Lesions: Is There a Different Impact on Thyroid Function?

Çağın Mustafa Üreyen[a]    Kahraman Coşansu[b]    Mustafa Gökhan Vural[b]    Sait Emir Şahin[c]
Mehmet Akif Çakar[b]    Harun Kılıç[b]    Mustafa Tarık Ağaç[b]    Hüseyin Gündüz[b]
Ramazan Akdemir[b]    Ersan Tatlı[b]

[a]Department of Cardiology, University of Health Sciences, Education and Research Hospital, Antalya, Turkey;
[b]Department of Cardiology, Sakarya University, Education and Research Hospital, Sakarya, Turkey; [c]Cerrahpaşa
Medical Faculty, İstanbul University, İstanbul, Turkey

### Highlights of the Study

- We demonstrated that percutaneous coronary intervention (PCI) for coronary chronic total occlusion lesions increased the risk of overt hyperthyroidism in patients with subclinical hyperthyroidism at baseline when compared to PCI for non-complex coronary lesions.
- No significant risk was observed in euthyroid patients.

## Abstract

*Objective:* This study assessed whether high levels of iodide administered during percutaneous coronary intervention (PCI) for chronic total occlusion (CTO) differentially influenced thyroid function compared to PCI for non-complex coronary lesions. *Subjects and Methods:* A total of 615 patients were enrolled in the study; 205 underwent elective PCI for CTO lesions (Group I) and 410 underwent elective PCI for non-complex lesions including non-CTO, non-bifurcation, non-calcified, and non-tortuous lesions (Group II). Patients were monitored for development of incidental thyroid dysfunction between 1 and 6 months after PCI. *Results:* The patients in Group I were administered a median of 255 mL of contrast medium during PCI for CTO; a median of 80 mL was administered to the patients in Group II during non-complex PCI ($p = 0.001$). Ten (5.4%) of the 186 euthyroid patients in Group I and 19 (5%) of the 379 euthyroid patients in Group II developed subclinical hyperthyroidism ($p = 0.854$). However, 7 (50%) of the 14 subclinical hyperthyroid patients in Group I and only 3 (12%) of the 25 subclinical hyperthyroid patients in Group II developed overt hyperthyroidism ($p = 0.019$). *Conclusion:* In euthyroid patients, PCI for coronary CTO lesions did not increase the risk for subclinical hyperthyroidism when compared to PCI for non-complex coronary lesions. However, in patients with subclinical hyperthyroidism at baseline, PCI for coronary CTO lesions significantly increased the development of overt hyperthyroidism when compared to PCI for non-complex coronary lesions.

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Çağın Mustafa Üreyen
Department of Cardiology, University of Health Sciences
Antalya Education and Research Hospital, Varlık Mahallesi, Kazım Karabekir Caddesi
TR–07100 Muratpaşa, Antalya (Turkey)
E-Mail drcaginureyen@gmail.com

## Introduction

Exposure to iodinated contrast media (ICM) is frequent in daily medical practice, particularly due to the 4- to 8-fold increase in computed tomography (CT) and cardiac catheterization over the past 2 decades [1]. An iodine-containing contrast medium of 100 mL contains 3,500 μg of free iodide, which is 22.5 times the recommended daily intake. These high levels of iodide might suppress thyroid hormone synthesis (the Wolff-Chaikoff effect) or cause hyperthyroidism (the Jod-Basedow phenomenon) [2]. The prevalence of ICM-induced thyroid dysfunction remains under-researched. ICM-induced thyroid dysfunction incidence ranges from 0.05 to 5% and is more common in patients with pre-existing thyroid disease [3].

Coronary chronic total occlusion (CTO) is defined as TIMI grade 0 flow (no flow) in the occluded segment of a coronary artery that persists for >3 months [4]. Revascularization of coronary CTO is a significant component of contemporary interventional cardiology. In the early 2000s, the procedural success rate was around 65–70%, but this has increased to up to 90% in the last decade due to improvements in technology and techniques, albeit with increased costs, procedure and fluoroscopy times, and ICM exposure than non-CTO percutaneous coronary intervention (PCI) [5–8].

Whether PCI increases the risk of thyroid dysfunction is an important question because even subclinical thyroid dysfunction can negatively affect the cardiovascular system [9–12]. This study evaluates whether the much higher levels of ICM administered during PCI for CTO may differentially influence thyroid function when compared to PCI for non-complex coronary lesions such as non-CTO, non-bifurcation, non-calcified, and non-tortuous lesions.

## Subjects and Methods

### Study Design and Patient Population

This observational, retrospective cohort study was carried out on patients who visited a tertiary referral centre in an iodine-deficient area of Sakarya, Turkey, between July 2015 and December 2017. A flowchart of patient enrollment is shown in Figure 1. Group I comprised 205 patients who underwent PCI for CTO lesions. All Group I participants were routinely assessed for thyroid function before the coronary procedure and reassessed from 1 to 6 months after the procedure. Group II comprised a pool of 410 patients who underwent elective, non-complex PCI within the same time period. These participants were also assessed for thyroid function before and 1–6 months after non-complex PCI. None of the patients in either group had a history of thyroid disease, nor had they used an anti-thyroid drug or thyroid replacement medication. Patients newly diagnosed with subclinical hypo- or hyperthyroidism during the pre-procedural assessment and who had not used any anti-thyroid or thyroid replacement medication were included in the study.

### Thyroid Function Tests

Serum thyroid-stimulating hormone (TSH), free thyroxine ($FT_4$) and free tri-iodothyronine ($FT_3$) levels were measured using an Access 2 Immunoassay System (Beckman Coulter, USA). The normal range for TSH, FT4, and FT3 values is 0.34–5.86 IU/mL, 0.61–1.12 ng/dL, and 2.5–3.9 pg/mL, respectively. These values were measured before and 1–6 months after the procedure. A decrease in TSH below the assay reference range with a normal $FT_4$ and $FT_3$ was considered subclinical hyperthyroidism, and an increase in $FT_4$ and $FT_3$ above the assay reference range in addition to suppressed TSH in patients with clinical symptoms was considered overt hyperthyroidism. An increase in TSH above the assay reference range with a normal $FT_4$ and $FT_3$ was considered subclinical hypothyroidism, while a decrease in $FT_4$ and $FT_3$ below the assay reference range accompanied by an elevated TSH in patients with clinical symptoms was considered overt hypothyroidism.

### Coronary Angiography and Iodinated Contrast Media

All cardiovascular procedures were performed using a Toshiba Infinix 8000V or Infinix 8000G5 (Toshiba Medical Systems, Nasushiobara, Japan). The ICM used in the study was iohexol (Omnipaque®, 300 mg iodine/mL, GE Healthcare, USA), a low-osmolar and non-ionic ICM.

### Statistical Analysis

Data analyses were performed with the Statistical Package for Social Sciences v24 for Windows (SPSS Inc., Chicago, IL, USA). The Student $t$ test and the Mann-Whitney U test were used to compare means and medians in the 2 groups. The $\chi^2$ test or the Fisher exact test, where appropriate, was used to compare proportions and percentages in the groups. The correlation of age to changes in TSH after ICM exposure was calculated with the Pearson test. $p < 0.05$ was considered statistically significant.

## Results

Baseline characteristics of study participants are presented in Table 1. No differences were observed between groups other than age and extent of ICM exposure. The mean age of Group I and Group II was 60.9 and 62.7 years, respectively ($p = 0.042$). The patients in Group I were administered a median of 255 mL (interquartile range [IQR] 195–300 mL) of ICM during CTO PCI, whereas a median of 80 mL (IQR 65–90 mL) was delivered to those in Group II ($p < 0.001$); this difference was found to be statistically significant. Post-procedural thyroid function tests were conducted between 1 and 6 months after ICM exposure. The median time for

**Fig. 1.** Flowchart of patient enrollment. CTO, chronic total occlusion; PCI, percutaneous coronary intervention.
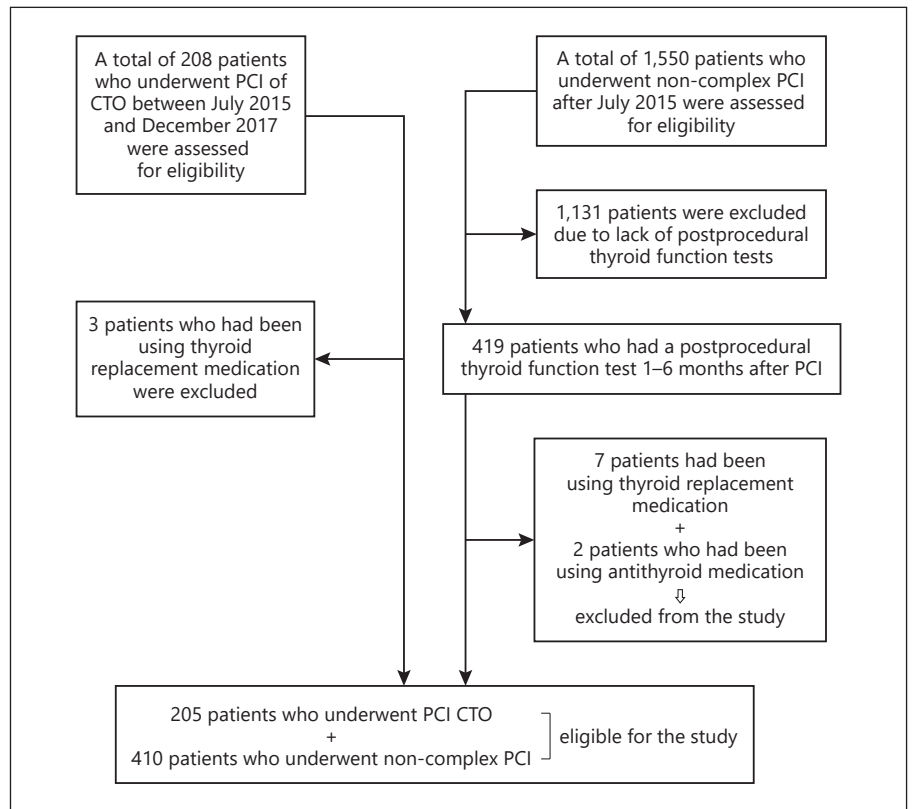
Flowchart boxes:

- A total of 208 patients who underwent PCI of CTO between July 2015 and December 2017 were assessed for eligibility
- A total of 1,550 patients who underwent non-complex PCI after July 2015 were assessed for eligibility
- 1,131 patients were excluded due to lack of postprocedural thyroid function tests
- 3 patients who had been using thyroid replacement medication were excluded
- 419 patients who had a postprocedural thyroid function test 1–6 months after PCI
- 7 patients had been using thyroid replacement medication + 2 patients who had been using antithyroid medication ⇩ excluded from the study
- 205 patients who underwent PCI CTO + 410 patients who underwent non-complex PCI — eligible for the study

**Table 1.** Baseline characteristics of the study population

| Variables | Group 1 (n = 205) | Group 2 (n = 410) | p |
|---|---|---|---|
| Age, years (mean ± SD) | 60.9±10.2 | 62.7±10.2 | 0.042 |
| Male sex | 173 (84.4) | 320 (78) | 0.063 |
| Diabetes mellitus | 83 (40.5) | 163 (39.8) | 0.861 |
| Hypertension | 101 (49.3) | 191 (46.6) | 0.530 |
| Hyperlipidemia | 106 (51.7) | 200 (48.8) | 0.494 |
| Current smoker | 68 (33.2) | 140 (34.1) | 0.809 |
| Ex-smoker | 77 (37.6) | 144 (35.1) | 0.552 |
| A history of: | | | |
| MI | 117 (57.1) | 219 (53.4) | 0.390 |
| PCI | 125 (61) | 232 (56.6) | 0.298 |
| CVA | 19 (9.3) | 33 (8) | 0.608 |
| PAD | 22 (10.7) | 32 (7.8) | 0.227 |
| CHF | 42 (20.5) | 76 (18.5) | 0.562 |
| Baseline thyroid status | | | |
| Euthyroid | 186 (90.8) | 379 (92.4) | 0.642 |
| Subclinical hyperthyroidism | 14 (6.8) | 25 (6.1) | |
| Subclinical hypothyroidism | 5 (2.4) | 6 (1.5) | |
| Median time of postprocedural thyroid function tests, days (IQR) | 147 (132–168) | 152 (138–169) | 0.197 |
| Median amount of ICM administered, mL (IQR) | 255 (195–300) | 80 (65–90) | <0.001 |

Values express n (%), unless otherwise indicated. CHF, congestive heart failure; CVA, cerebrovascular accident; ICM, iodinated contrast medium; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; SD, standard deviation; IQR, interquartile range.
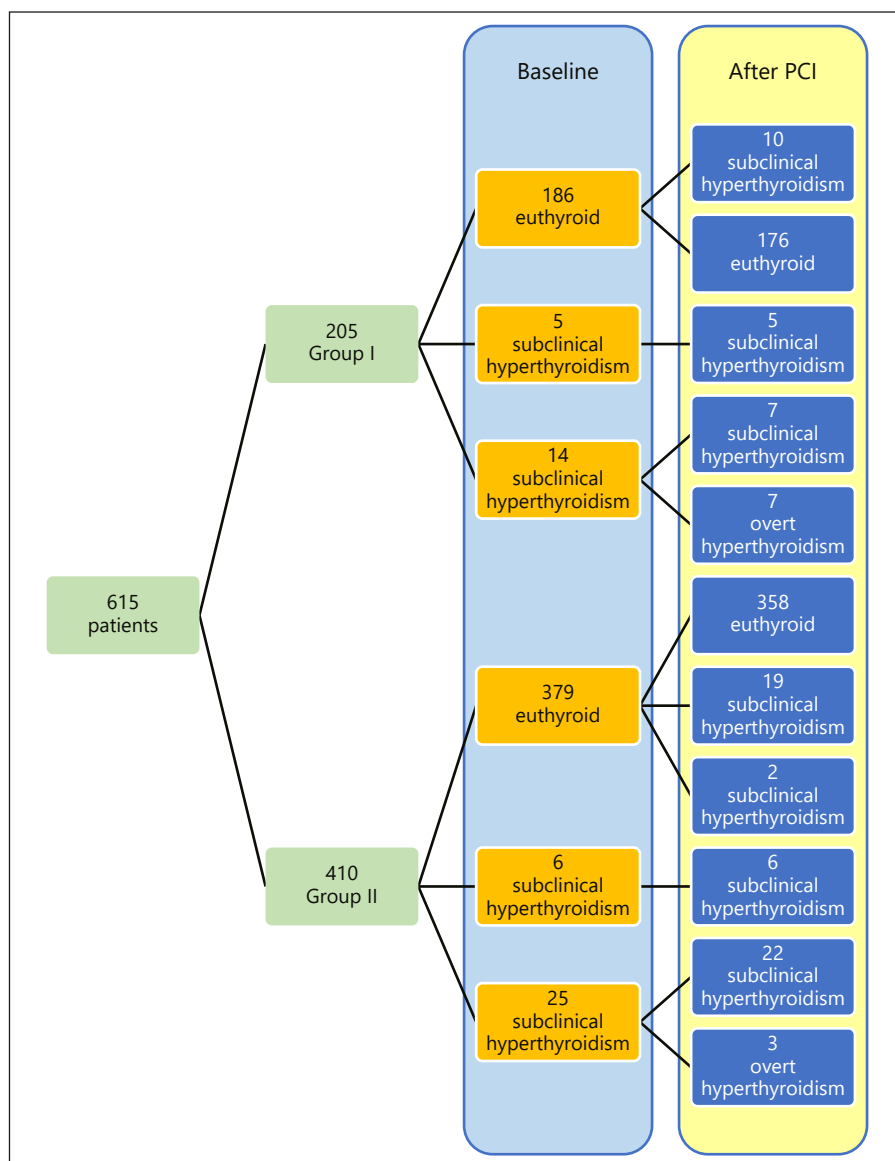
**Fig. 2.** Flowchart of changes in thyroid function in patients who underwent percutaneous coronary intervention (PCI) for chronic total occlusion or non-complex coronary lesions.

**Table 2.** Changes in thyroid function after percutaneous coronary intervention

| | Group I, $n$ (%) | Group II, $n$ (%) | $p$ value |
|---|---|---|---|
| Baseline euthyroid to subclinical hyperthyroidism | 10 (5.4) | 19 (5) | 0.854 |
| Baseline subclinical hyperthyroidism to overt hyperthyroidism | 7 (50) | 3 (12) | 0.019 |
| Baseline euthyroid to subclinical hypothyroidism | 0 (0) | 2 (0.5) | 1.000 |

post-procedural thyroid function tests in Group I was 147 days (4.9 months) and that for Group II was 152 days (5.1 months). There was no statistically significant difference in the median date of post-procedural thyroid function tests between the 2 groups ($p = 0.197$).

In Group I, 186 patients (90.8%) were euthyroid, 14 (6.8%) had subclinical hyperthyroidism, and 5 (2.4%) had subclinical hypothyroidism at baseline. In Group II, 379 patients (92.4%) were euthyroid, 25 (6.1%) had subclinical hyperthyroidism, and 6 (1.5%) had subclinical hypo-

thyroidism at baseline. Of the 186 euthyroid patients in Group I, 10 (5.4%) developed subclinical hyperthyroidism after PCI, whilst 19 (5%) of the 379 euthyroid patients in Group II developed subclinical hyperthyroidism, a difference that was not statistically significant ($p = 0.854$). However, 7 (50%) of the 14 subclinical hyperthyroid patients in Group I developed overt hyperthyroidism after PCI, whereas only 3 (12%) of the 25 subclinical hyperthyroid patients in Group II developed overt hyperthyroidism ($p = 0.019$). None of the euthyroid patients in Group I developed subclinical hypothyroidism, whereas 2 (0.5%) of the euthyroid patients in Group II developed subclinical hypothyroidism, a difference that was not statistically significant ($p = 1.000$) (Table 2). None of the patients in either group with subclinical hypothyroidism at baseline developed overt hypothyroidism (Fig. 2).

Age was the only parameter that varied significantly between the groups. In the univariate analysis, however, changes in TSH values after ICM exposure as calculated by subtraction of post-procedural TSH from pre-procedural TSH were not associated with age ($p = 0.557$).

### Discussion

While a few studies have investigated how ICM after coronary angiography affects thyroid function [13–15], to the best of our knowledge, there has not yet been an evaluation of the effect of the extremely supraphysiological levels of iodide administered during PCI for coronary CTO. PCI for coronary CTO lesions is a complex and more technically demanding procedure that results in increased total procedure and fluoroscopy times, higher costs, and greater ICM exposure. This procedure may thus have a more pronounced effect on thyroid function than a standard, non-complex PCI. In this study, we enrolled euthyroid, subclinical hyperthyroid, and subclinical hypothyroid patients.

Under normal physiological conditions, active transport of iodine into the thyroid gland via the sodium-iodine symporter is stimulated by TSH [16]. The subsequent synthesis and release of FT4 and FT3 are tightly regulated by the thyroid gland. In susceptible individuals, however, exposure to supraphysiological levels of iodide may overcome these regulatory processes and lead to hypothyroidism (the Wolff-Chaikoff effect) or hyperthyroidism (the Jod-Basedow phenomenon) [13, 17–20]. Exposure to excess iodine results in a transient decrease in thyroid hormone synthesis due to an acute Wolff-Chaikoff effect. In rats undergoing persistent excess exposure to iodine, thyroid function returned to normal levels within 24–48 h, known as escape from acute Wolff-Chaikoff effect [21]. In humans, TSH levels peaked at 3–5 days and decreased gradually thereafter [20]. Belloni et al. [22] found that intravenous ICM in children with congenital heart disease resulted in a decrease in TSH levels after 48 h of CT but returned to within normal limits by discharge. Escape from acute Wolff-Chaikoff effect occurring after 8–10 days has also been observed [23]. In this study, thyroid function was only re-evaluated after >1 month, which could explain why iodine-induced hypothyroidism was only observed in 2 of our patients.

It has been demonstrated that ICM exposure causes incidental hyperthyroidism [13, 17–19]. This study recapitulated these findings, with ICM exposure resulting in incidental hyperthyroidism in approximately 5% of patients from both groups; however, there was no statistical difference regarding the development of subclinical hyperthyroidism among euthyroid patients from either group despite the greater amount of ICM used in Group I.

Our results suggest that PCI for coronary CTO lesions does not increase the risk of developing subclinical hyperthyroidism when compared to PCI for non-complex coronary lesions in euthyroid patients. However, progression to overt hyperthyroidism was significantly higher for patients with subclinical hyperthyroidism at baseline in Group I than in Group II. This indicates that the higher doses of ICM during PCI for coronary CTO increase the risk of overt hyperthyroidism in patients with subclinical hyperthyroidism at baseline but not in patients with normal thyroid function. No published reports have addressed this discrepancy thus far.

In the literature, study populations exposed to ICM were virtually all euthyroid at baseline; studies on patients with subclinical hyper- or hypothyroidism are scarce [14]. No article has yet focused on patients with subclinical hyperthyroidism who were then exposed to ICM, and the rate of development of overt hyperthyroidism remains unknown in this population. Our findings demonstrate a high rate of development of overt hyperthyroidism in patients with subclinical hyperthyroidism at baseline with both PCI for CTO and non-complex PCI. This could be explained by the fact that patients with subclinical hyperthyroidism potentially present with untreated Graves' disease, multi-nodular goiter, or thyroid autonomy. It suggests that physicians need to be more careful about performing PCI, particularly for CTO, on patients with subclinical hyperthyroidism at baseline, as our data indicates an increased risk for developing overt hyperthyroidism in this cohort. A recent update on contrast media safety recommended that pa-

tients consult an endocrinologist before undergoing any procedure with ICM; this would uncover any subclinical thyroid dysfunction such as untreated Graves' disease, multi-nodular goitre, or thyroid autonomy, and therefore reduce the likelihood of thyrotoxicosis [24]. Further studies are needed to delve into the incidence of overt hyperthyroidism in patients with subclinical hyperthyroidism after exposure to ICM in more depth, to determine whether prophylaxis or pre-treatment could mitigate thyroid dysfunction after an ICM procedure.

In this study, patients had a post-procedural thyroid function test between 1 and 6 months after ICM exposure (a median of 5 months). Existing studies have also demonstrated an increased incidence of hyperthyroidism in the months following ICM [2, 17, 19, 25, 26]. This time interval was specifically addressed in monitoring the development of incidental hyperthyroidism post-ICM in this study.

This study has some limitations. First, this report details a retrospective, single-centre study. Second, all patients were assessed only for biochemical parameters. An ultrasonograhic examination of the thyroid gland to measure gland volume and check for nodular lesions prior to ICM may have ascertained which patients were at an increased risk of developing thyroid dysfunction. Third, post-procedural thyroid function was re-evaluated only once at a median of 5 months after the ICM exposure but did not assess variations immediately following ICM exposure that may have presaged clinical thyroid dysfunction. Fourth, only a limited number of patients presented with subclinical hyperthyroidism in this study. Further studies focusing on the influence of ICM on thyroid function in patients with subclinical hyperthyroidism at baseline are needed.

## Conclusion

This study demonstrated that PCI for coronary CTO lesions did not increase the risk of developing subclinical hyperthyroidism when compared to PCI for non-complex coronary lesions in euthyroid patients. However, a significantly increased risk for developing overt hyperthyroidism was observed in patients with subclinical hyperthyroidism at baseline. Cardiologists must therefore be aware of the potential for thyroid-specific complications after ICM. We recommend a more thorough medical assessment of thyroid function before commencing any coronary intervention. The possibility of worsening thyroid dysfunction in patients with subclinical hyperthyroidism at baseline needs to be taken into account when administering high doses of iodide during PCI for coronary CTO lesions.

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Üreyen/Coşansu/Vural/Şahin/Çakar/
Kılıç/Ağaç/Gündüz/Akdemir/Tatlı