2015 년 8 월

박사학위논문

Impacts of combined low triiodothyronine and subclinical myocardial injury on long-term clinical outcomes in patients with chest pain

조선대학교 대학원

의 학 과

기 영 재

Impacts of combined low triiodothyronine and subclinical myocardial injury on long-term clinical outcomes in patients with chest pain

흉통 환자에서 낮은 트리아이오딘티로닌과 무증상 심근 손상이 장기 임상 결과에 미치는 영향

2015 년 8 월 25 일

조선대학교 대학원

의학과

기 영 재

Impacts of combined low triiodothyronine and subclinical myocardial injury on long-term clinical outcomes in patients with chest pain

지도교수 최 동 현

이 논문을 의학박사학위신청 논문으로 제출함.

2015 년 4 월

조선대학교 대학원

의학과

기 영 재

기영재의 박사학위논문을 인준함

위원장 조선대학교 교수 김동민 (인)

위 원 조선대학교 교수 송희상 (인)

위 원 조선대학교 교수 신병철 (인)

위 원 조선대학교 교수 박근호 (인)

위 원 조선대학교 교수 최동현 (인)

2015 년 6 월

조선대학교 대학원

CONTENTS

ABSTRACT……4

국문초록……6

Introduction……8

Methods…..……...……...……..10

Subjects……....10

Blood collection and measurement of biomarkers .....……..…10

Outcomes……11

Statistical analysis……..……11

Results……13

Discussion……16

Conclusion……20

References……21

LIST OF FIGURES

Figure 1. Overall event free survival. A. On the basis of high-sensitivity cardiac troponin-T (hs-cTnT). B. On the basis of triiodothyronine (T3)……**25**

Figure 2. Kaplan-Meier survival curve. Combined impact of high-sensitivity cardiac troponin-T (hs-cTnT) and triiodothyronine (T3) on overall events…… **26**

LIST OF TABLES

Table 1: Baseline characteristics and biochemical data on the basis of combined hs-cTnT and T3 ……...28

Table 2: The primary and secondary endpoints on the basis of combined hs-cTnT and T3 ……31

Table 3: Univariate and multivariate Cox proportional hazard model determining the significant and independent predictors for overall event, respectively……..……32

Abstract

Impacts of combined low triiodothyronine and subclinical myocardial injury on long-term clinical outcomes in patients with chest pain

Young-Jae Ki
Advisor: Prof. Dong-Hyun Choi, M.D.
Department of Medicine,
Graduate School Chosun University

Background- Low triiodothyronine (T3) levels and subclinical myocardial injury may be associated with adverse cardiac and cerebrovascular (CCV) events in individuals without clinically apparent coronary heart disease (CHD). The aim of this study was to determine the associations of a low T3 level and subclinical myocardial injury with the development of adverse CCV events in individuals without clinically apparent CHD.

Methods and Results- T3 and high-sensitivity cardiac troponin T (hs-cTnT) levels were analyzed in 250 chest pain patients free of CHD and heart failure. The primary endpoint was the composite of sudden cardiac death (SCD), ischemic stroke, newly developed atrial fibrillation (AF), pericardial effusion, and thrombosis.

Throughout a mean follow-up of 15.6 months, the primary endpoint happened in

17 (6.8%) patients. Kaplan-Meier analysis disclosed a notably higher overall occurrence rate in patients with hs-cTnT levels ≥0.014 ng/mL and in patients with T3 <60 ng/dL. An exaggerated hazard was observed in patients with combined high hs-cTnT and low T3. After adjustment, the HR for overall events in patients with high hs-cTnT/low T3 vs. normal hs-cTnT/T3 was 11.72 (95% CI: 2.83–48.57, P = 0.001).

Conclusions- In chest pain patients without clinically obvious CHD, high hs-cTnT combined with low T3 was associated with adverse cardiac/CCV events and was an independent predictor of overall events even after adjustment. Our data suggest the importance of systemic factors such as low T3 syndrome in the development of adverse cardiac/CCV events beyond advancing clinical atherosclerotic coronary disease in chest pain patients.

Key words: triiodothyronine; troponin; death; stroke; atrial fibrillation

국 문 초 록

흉통 환자에서 낮은 트리아이오딘티로닌과 무증상 심근 손상이 장기 임상 결과에 미치는 영향

기 영 재
지 도 교 수: 최 동 현
조선대학교대학원 의학과

배경: 낮은 트리아이오딘티로닌 수준과 무증상의 심근 손상은 임상적으로 명확한 관상동맥 심장 질환이 없는 환자에서 심장 및 뇌혈관 사고 발생과 연관성이 있는 것으로 보인다. 이 연구의 목적은 임상적으로 명확한 관상동맥 심장 질환이 없는 환자에서 낮은 트리아이오딘티로닌과 무증상 심근 손상과 심장 및 뇌혈관 사고의 발생 사이의 연관성을 증명하고자 한 것이다.

방법과 결과: 관상동맥 심장 질환과 심부전이 없이 흉통을 호소하는 250명의 환자에서 트리아이오딘티로닌과 고민감도 심장 트로포닌 T 수준의 측정치를 분석하였다. 일차 종료점은 급성 심장사, 허혈성 뇌졸중, 새롭

게 발생한 심방세동, 심낭삼출 및 혈전증의 복합으로 정하였다. 15.6 개월의 평균 추적 기간 동안 17 명 (6.8%)의 환자에서 일차 종료점 사건이 발생하였다. 카플란-메이어 분석을 통해 분석하였을 때 고민감도 심장 트로포닌 T 수준 ≥0.014 ng/mL 와 트리아이오딘티로닌 수준 <60 ng/dL 인 환자군에서 유의하게 높은 발생률을 관찰할 수 있었다. 높은 고민감도 심장 트로포닌 T 와 낮은 트리아이도딘티로닌을 동시에 만족하는 환자군에서 이러한 위험도가 더욱 증가되는 것 또한 관찰할 수 있었다. 높은 고민감도 심장 트로포닌 T 와 낮은 트리아이도딘티로닌을 동시에 만족하는 환자군을 모두 정상인 환자군과 비교하였을 때 위험도는 11.72 (95% CI: 2.83–48.57, *P* = 0.001)이었다.

결론: 본 연구의 결론은 임상적으로 명확한 관상동맥 심장 질환이 없이 흉통을 호소하는 환자들에서 고민감도 심장 트로포닌 T 가 높고 트리아이오딘티로닌 수준이 낮은 경우 심장 및 뇌혈관 사고를 예측할 수 있는 독립적인 예측 인자라는 것이다.

Introduction

Thyroid hormones play a vital role in the physiological aspects of the cardiovascular systems, one of their primary targets, in healthy subjects.[1, 2] Indeed, several studies provide evidence of a connection between altered thyroid circumstances and the development and progression of cardiac disease.[3] _ENREF_1 Appropriate cardiovascular function depends on thyroid hormone homeostasis. Bioactive triiodothyronine (T3) is a potent controller of the inotropic and lusitropic properties of the heart through its effects on myosin isoforms and calcium-managing proteins.[2, 4] Low T3 syndrome is defined as low levels of circulating T3 in individuals with normal or slightly decreased thyrotropin (TSH) and thyroxine (T4) concentrations.

Among several biomarkers recently recognized for their ability to noninvasively detect subclinical myocardial injury,[5] cardiac troponin-T (cTnT) has been known to be independently associated with coronary heart disease (CHD) _ENREF_6.[6, 7] Therefore, cTnT is a recommended biomarker for use in the detection of myocardial infarction (MI) and in acute coronary syndromes.[8] Indeed, several authors have proposed that somewhat elevated troponin values may designate subclinical cardiac injure and that hs-cTnT may presently permit for the detection of early phases of myocardial damage masked in the past.[9, 10] We previously reported that T3 levels were inversely associated with hs-cTnT levels in patients with no clinically evident CHD.[11] However, no information is available

regarding the impact of a low T3 level and subclinical myocardial injury on long-term clinical outcomes.

The aim of current investigation was to determine the associations of a low T3 level and subclinical myocardial injury with the occurrence of adverse cardiac and cerebrovascular (CCV) events in individuals without clinically apparent CHD.

Methods

Subjects

A total of 365 consecutive patients with chest pain who underwent TSH, free thyroxine (FT4), T3, and hs-cTnT measurements in the emergency room or outpatient department of the cardiovascular center of Chosun University Hospital between November 2011 and January 2012 were included in current investigation with endorsement from the Chosun University Hospital Research Ethics Committee (2014-05-003). Patients who were diagnosed with overt hyperthyroidism or CHD were excluded. Therefore, 250 patients were included in this analysis.

Blood collection and measurement of biomarkers

Venous blood samples were obtained in K2-EDTA coated tubes (BD Vacutainer Systems, Franklin Lakes, NJ, USA) and serum separator blood-drawing tubes (Franklin Lakes, NJ, USA). TSH, T3 and FT4 concentrations were determined by the immunoradiometric assay (IRMA) and radioimmunoassay (RIA) using RIA-gnost® FT4, TSH, and T3 kits (CISbio international, Cedex, France). We used a cobra E 5005® gamma counter (PACKard, USA). The tests were executed within 2 hours after sample collection (normal range: TSH 0.25–4 mIU/L, FT4 0.7–1.8 ng/dL, and T3 60–190 ng/dL). The levels of hs-cTnT were measured using the

Cobas 6000 (Roche Diagnostics, Penzberg, Germany) with a lower limit of detection of 0.003 ng/mL within 2 hours after sample collection.

Outcomes

Clinical information was gained from outpatient records or telephone interviews. The primary endpoint was a composite of sudden cardiac death (SCD), ischemic stroke, newly developed atrial fibrillation (AF), pericardial effusion, and thrombosis. SCD was defined as death by terminal rhythm disorders verified on electrocardiography (ECG), death observed by a witness within 1 hour of cardiac symptoms onset, or unexpected death, presumably or possibly of cardiac origin. Ischemic stroke was defined as a neurologic deficit lasting longer than 24 hours. Cerebral computed tomography or magnetic resonance imaging was available in all ischemic stroke patients.

Statistical analysis

All values are expressed as mean ± SD or as number (percentages). Baseline characteristics were compared between groups using one-way ANOVA for continuous variables and the chi-square test for non-continuous variables. Event-free survival curves were constructed using the Kaplan-Meier method, and outcomes were compared using the log-rank test.

Independent predictors of overall events were analyzed using Cox proportional hazards regression. Baseline clinical, biochemical, and angiographic data with a *P*

value <0.05 were entered into a forward stepwise multivariate Cox proportional hazards model. Statistical analyses were carried out using SPSS 12.0 (SPSS Inc., Chicago, Illinois), and a *P* value of <0.05 was considered statistically significant.

Results

Baseline biomarker values

Mean TSH, T3, FT4, and hs-cTnT levels in the overall population were 5.97 ± 15.0 mIU/L (median, 1.92 mIU/L, IQR 1.02–3.31), 84.9 ± 36.1 ng/dL (median 81.7 ng/dL, IQR 58.1–110.0), 1.18 ± 0.42 ng/dL (median, 1.15 ng/dL, IQR 0.98–1.38), and 0.013 ± 0.021 ng/mL (median 0.003 ng/mL, IQR 0.003–0.017), respectively. 115 subjects (46%) had quantifiable levels (>0.003 ng/mL) of hs-cTnT. Overall, 28% of participants had high hs-cTnT levels (≥0.014 ng/mL).

Clinical characteristics

The mean age of patient was 60.2 years, and 42.4% were male (Table 1). Patients were stratified into 4 groups according to cut-off values of 0.014 ng/mL for hs-cTnT and 60 ng/dL for T3: normal hs-cTnT/T3, normal hs-cTnT/low T3, high hs-cTnT/normal T3, and high hs-cTnT/low T3. Baseline clinical characteristics and biochemical data on the basis of combined hs-cTnT and T3 levels are described in Table 1. High hs-cTnT/low T3 was associated with older age, higher low-density lipoprotein (LDL) -cholesterol levels, and a lower estimated glomerular filtration rate (eGFR). Patients with high hs-cTnT/normal T3 were more likely to have left ventricular hypertrophy (LVH) and higher levels of FT4, and showed greater utilization of renin-angiotensin system blockers and insulin. The group with normal

hs-cTnT/T3 levels had higher levels of high-density lipoprotein (HDL) -cholesterol.

Clinical outcomes

Overall, 17 (6.8%) primary endpoint events occurred for the period of a mean follow-up of 15.6 months (4 SCDs, 5 ischemic strokes, 1 pericardial effusion, 5 newly developed AF, 1 pulmonary thromboembolism, and 1 thrombus in the left atrial appendage) (Table 2).

Kaplan-Meier analysis disclosed that the high hs-cTnT group (≥0.014 ng/mL) had a notably higher overall event rate than the low hs-cTnT group (<0.014 ng/mL) (18.6% vs. 2.2%, log-rank: $P < 0.0001$). In addition, a significantly higher overall event rate was observed in the lower T3 group (<60 ng/dL) compared to that in the higher T3 group (≥60 ng/dL) (12.7% vs. 4.8%, log-rank: $P = 0.0164$) (Figure 1).

Combined impact of hs-cTnT and T3 on clinical outcomes

Kaplan-Meier analysis showed a significantly high overall event rate in the high hs-cTnT/low T3 group (log-rank: $P < 0.0001$, Figure 2). A combined analysis of overall event on the basis of hs-cTnT and T3 levels showed an exaggerated risk with combined higher hs-cTnT and lower T3 (HR for overall events: 15.81, 95% CI: 4.07–61.34, P <0.001)

Independent predictors of overall events

In the univariate analysis, high hs-cTnT/low T3, high hs-cTnT/normal T3, eGFR <

60 mL/min/1.73 m^2, and LVH were significantly associated with overall events in our cohort. To identify independent predictors of overall events, the significant univariate variables were entered into a Cox proportional hazards model. In this model, the variables that emerged as independent risk factors for overall events in chest pain patients free of CHD and heart failure were high hs-cTnT/low T3 and high hs-cTnT/normal T3 (Table 3).

Discussion

The major result of the current investigation was the relationship between high hs-cTnT or low T3 and overall events in chest pain patients with no clinically apparent CHD. We also found that patients with both high hs-cTnT and low T3 were at an amplified hazard for the happening of overall events.

Current indications for the measurement of cTnT and cardiac troponin I generally spotlight on detection and risk stratification in patients with suspected MI. Elevated troponin concentrations have been related to cardiovascular events.[6] In the usual examinations, troponin is able to be detected in 0.7% of the population and is related to MI and death.[6, 12] However, the high-sensitivity troponin test allows troponin to be detected at much lesser levels than past detection limits. This examination advances the sensitivity for identifying MI, early subsequent the beginning of symptoms at the expense of reduced specificity.[13, 14] With the hs-cTnT, the recognition of circulating cTnT is possible in nearly all patients with chronic coronary artery disease or CHF. In addition, 25% to 67% of grown persons from the common population have quantifiable troponin levels with this examination.[15-19] In the ARIC (Atherosclerosis Risk in Communities) study, hs-cTnT was detected in 2/3 of group devoid of clinically evident CHD.[19] Lately, numerous studies have demonstrated that troponin concentrations tested with the highly sensitive test independently predict cardiovascular events.[17-19] The

augmented sensitivity of this analysis makes possible the assessment of the cardiovascular phenotype associated with low circulating concentration of troponin in symptom-free patients, including links to subclinical cardiovascular disease and latent clinical events.

Patients with hypothyroidism may present with signs and symptoms indicative of MI, such as elevated creatine kinase and ECG abnormalities, or may sporadically have simultaneous heart disease, detection of acute coronary syndrome critical for appropriate management.[20, 21] Relationships between increased troponin and hypothyroidism have been reported in 2 cases.[21, 22] Gunduz et al. reported a patient with hypothyroidism and chest pain, electrocardiographic alterations, and elevated cardiac enzymes with a normal coronary angiography (CAG).[21] In this case, the elevation in troponin was assigned to the hypothyroidism. Buschmann et al. described a patient suffered cardiac symptoms, electrocardiographic alterations, elevated cardiac enzymes and a normal CAG; however, in this case, magnetic resonance imaging demonstrated a tiny area of myocardial damage.[22] Ness-Abramof et al. implied that cardiac troponin T was not elevated in hypothyroid patients with no cardiac symptoms. In their investigation, nevertheless, concentrations of cardiac troponin T were gauged by the classic technique rather than by hs-cTnT.[23]

We reported previously that the T3 concentrations were inversely associated with hs-cTnT levels in patients with no clinically evident CHD.[11] However, no information is available regarding the impact of a low T3 level and subclinical

myocardial injury on long-term clinical outcomes. This is the first clinical outcome study in which hs-cTnT and T3 were assessed in patients suffered chest pain and without clinically evident CHD. Though hypothyroidism is generally thought to be associated with cardiovascular events via atherosclerosis, our results suggest that low T3 syndrome, may contribute to cardiovascular events by alternative mechanisms.

A possible mechanism by which low thyroid function induces myocardial damage is through the impairment of coronary blood flow, because thyroid hormones influence the vasoreactive properties of vessels.[24, 25] Other mechanisms include myocardial fibrosis and a gene program resembling that of pathological hypertrophy.[26-28]

Recently, we demonstrated that a high T3 level was an independent predictor of the extent of transmural infarction in patients with ST segment elevation myocardial infarction (STEMI).[29] Previous results seem to be considered as somewhat conflicting findings. However, these differences may be due to study population disparity (active infarction vs. chronic subclinical myocardial damage) between investigations. This work suggests that high hs-cTnT/low T3 is an indicator of poor clinical outcomes in chest pain patients without clinically obvious CHD.

This study was limited by the somewhat small sample size and this was a retrospective study. Our inclusion criteria (patients suffered chest pain who underwent hs-cTnT, TSH, FT4, and T3 measurements) introduce the possibility of

a selection bias.

Conclusion

In conclusion, in chest pain patients without clinically obvious CHD, high hs-cTnT combined with low T3 was associated with adverse cardiac/CCV events and was an independent predictor of overall events even after correction for other factors. Our data suggest the importance of systemic factors such as low T3 syndrome in the development of adverse cardiac/CCV events beyond advancing clinical atherosclerotic coronary disease in chest pain patients.

References

[1] Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation 1993;87:1435-41.

[2] Klein I, Ojamaa K. Thyroid hormone and the cardiovascular system. The New England journal of medicine 2001;344:501-9.

[3] Gerdes AM, Iervasi G. Thyroid replacement therapy and heart failure. Circulation 2010;122:385-93.

[4] Katzeff HL, Powell SR, Ojamaa K. Alterations in cardiac contractility and gene expression during low-T3 syndrome: prevention with T3. The American journal of physiology 1997;273:E951-6.

[5] Melander O, Newton-Cheh C, Almgren P, Hedblad B, Berglund G, Engstrom G, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA : the journal of the American Medical Association 2009;302:49-57.

[6] Daniels LB, Laughlin GA, Clopton P, Maisel AS, Barrett-Connor E. Minimally elevated cardiac troponin T and elevated N-terminal pro-B-type natriuretic peptide predict mortality in older adults: results from the Rancho Bernardo Study. Journal of the American College of Cardiology 2008;52:450-9.

[7] Januzzi JL, Jr., Bamberg F, Lee H, Truong QA, Nichols JH, Karakas M, et al. High-sensitivity troponin T concentrations in acute chest pain patients evaluated with cardiac computed tomography. Circulation 2010;121:1227-34.

[8] Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.

[9] Morrow DA, Antman EM. Evaluation of high-sensitivity assays for cardiac troponin. Clinical chemistry 2009;55:5-8.

[10] Sabatine MS, Morrow DA, de Lemos JA, Jarolim P, Braunwald E. Detection of acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35. European heart journal 2009;30:162-9.

[11] Kim BB, Ku YH, Han JY, Ha JM, Park G, Choi DH, et al. Relation of triiodothyronine to subclinical myocardial injury in patients with chest pain. The American journal of cardiology 2013;111:1087-91.

[12] Wallace TW, Abdullah SM, Drazner MH, Das SR, Khera A, McGuire DK, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958-65.

[13] Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. The New England journal of medicine 2009;361:858-67.

[14] de Lemos JA, Morrow DA, deFilippi CR. Highly sensitive troponin assays and the cardiology community: a love/hate relationship? Clinical chemistry 2011;57:826-9.

[15] Latini R, Masson S, Anand IS, Missov E, Carlson M, Vago T, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242-9.

[16] Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. The New England journal of medicine 2009;361:2538-47.

[17] de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA : the journal of the American Medical Association 2010;304:2503-12.

[18] deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA : the journal of the American Medical Association 2010;304:2494-502.

[19] Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. Circulation 2011;123:1367-76.

[20] Strachan SR, Afolabi O, Brown N, Gray D. Chest pain, enzymes and hypothyroidism. Postgraduate medical journal 2000;76:168-9.

[21] Gunduz H, Arinc H, Yolcu M, Akdemir R, Kanat M, Uyan C. A case of hypothyroidism mimicking acute coronary syndrome. The international journal of cardiovascular imaging 2006;22:141-5.

[22] Buschmann IR, Bondke A, Elgeti T, Kuhnle Y, Dietz R, Mockel M. Positive cardiac troponin I and T and chest pain in a patient with iatrogenic hypothyroidism and no coronary artery disease. International journal of cardiology 2007;115:e83-5.

[23] Ness-Abramof R, Nabriski DA, Shapiro MS, Tripto-Shkolnik L, Katz B, Weiss E, et al. Cardiac troponin T is not increased in patients with hypothyroidism. Internal medicine journal 2009;39:117-20.

[24] Scott JC, Balourdas TA, Croll MN. The effect of experimental hypothyroidism on coronary blood flow and hemodynamic factors. The American journal of cardiology 1961;7:690-3.

[25] Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. Thyroid : official journal of the American Thyroid Association 2000;10:665-79.

[26] Chen WJ, Lin KH, Lee YS. Molecular characterization of myocardial fibrosis during hypothyroidism: evidence for negative regulation of the pro-alpha1(I) collagen gene expression by thyroid

hormone receptor. Molecular and cellular endocrinology 2000;162:45-55.

[27] Yao J, Eghbali M. Decreased collagen gene expression and absence of fibrosis in thyroid hormone-induced myocardial hypertrophy. Response of cardiac fibroblasts to thyroid hormone in vitro. Circulation research 1992;71:831-9.

[28] Dillmann W. Cardiac hypertrophy and thyroid hormone signaling. Heart failure reviews 2010;15:125-32.

[29] Kim DH, Choi DH, Kim HW, Choi SW, Kim BB, Chung JW, et al. Prediction of infarct severity from triiodothyronine levels in patients with ST-elevation myocardial infarction. The Korean journal of internal medicine 2014;29:454-65.

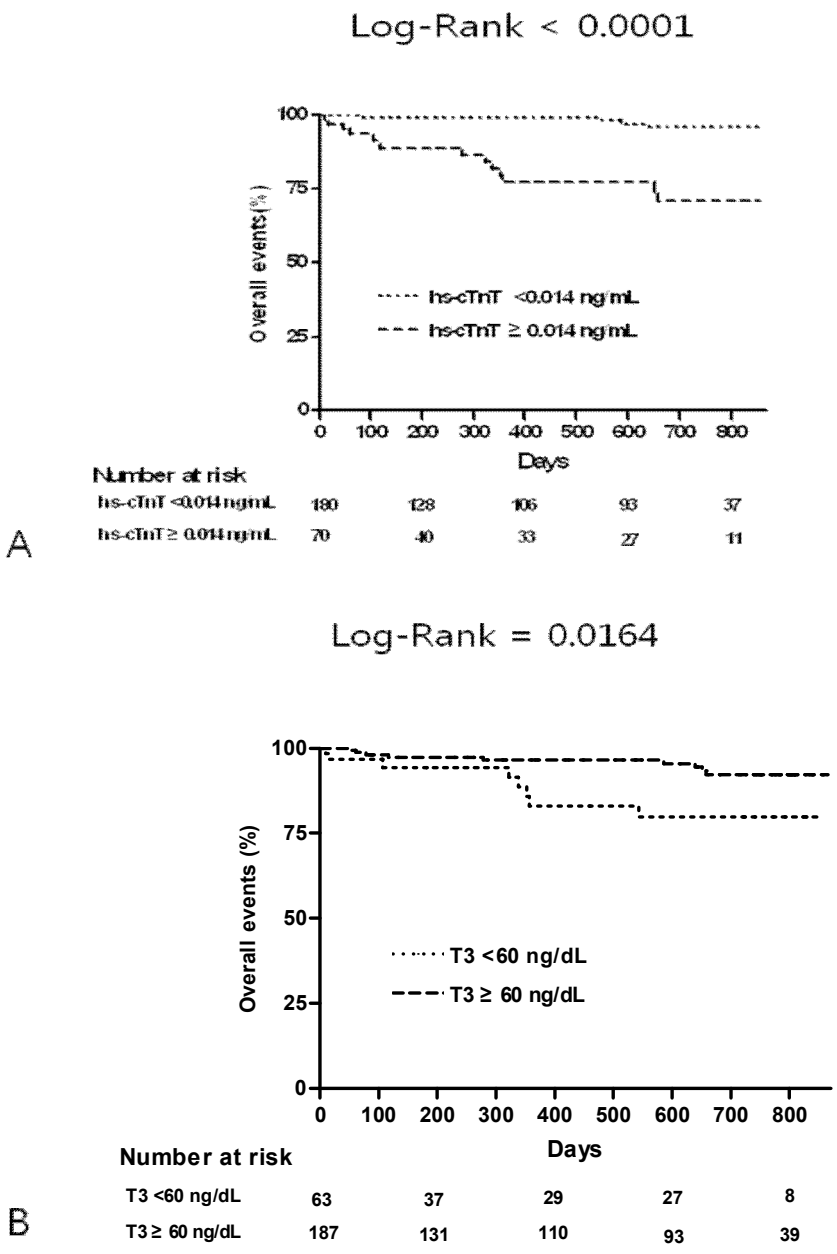

Figure 1. Overall event free survival. A. On the basis of high-sensitivity cardiac troponin-T (hs-cTnT). B. On the basis of triiodothyronine (T3)

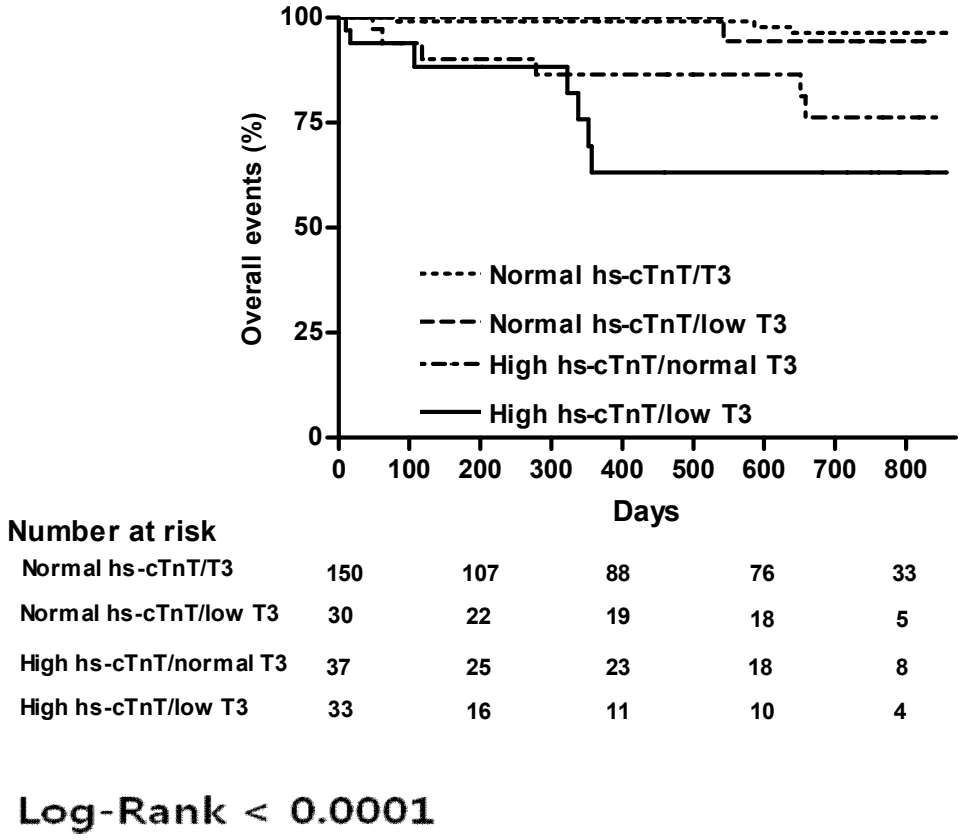

Figure 2. Kaplan-Meier survival curve. Combined impact of high-sensitivity cardiac troponin-T (hs-cTnT) and triiodothyronine (T3) on overall events

Table 1. Baseline characteristics and biochemical data on the basis of combined hs-cTnT and T3

Characteristics	Total (N=250)	Normal hs-cTnT /T3 (N=150)	Normal hs-cTnT /low T3 (N=30)	High hs-cTnT /normal T3 (N=37)	High hs-cTnT /low T3 (N=33)	P-value
Age (years)	60.2±16.5	55.7±15.8	61.6±14.5	66.5±12.9	72.5±16.9	<0.001
Men	42.4%	46.7%	33.3%	40.5%	33.3%	0.349
Hypertension	35.2%	32.0%	23.3%	45.9%	48.5%	0.073
LVH †	13.2%	10.0%	3.3%	32.4%	15.2%	0.001
Diabetes	26.0%	21.3%	30.0%	35.1%	33.3%	0.215
Smoker‡	20.8%	24.0%	16.7%	21.6%	9.1%	0.261
TSH (mIU/L)	5.97±15.0	3.29±8.1	7.98±8.5	6.36±16.1	3.96±12.28	0.082
Free T4 (ng/dL)	1.18±0.4	1.20±0.4	0.92±0.6	1.27±0.5	1.21±0.5	0.003
T3 (ng/dL)	84.9±36.1	102.9±28.8	44.2±11.2	86.1±24.9	38.8±13.2	<0.001
hs-cTnT (ng/mL)	0.013±0.021	0.004±0.002	0.005±0.002	0.032±0.018	0.052±0.020	<0.001
eGFR (ml/min/1.73	71.2±20.5	73.4±14.5	75.2±20.6	66.4±28.2	62.8±29.6	0.014

m^2)*						
LDL-C (mg/dL)	105.5±31.4	107.4±33.5	71.7±28.7	109.6±21.4	112.2±17.4	<0.001
HDL-C (mg/dL)	47.0±12.4	48.8±12.5	42.2±11.8	44.8±11.5	42.9±12.2	0.041
CCB	10.4%	7.3%	10.0%	16.2%	18.2%	0.171
RAAS blocker	18.4%	16.7%	6.7%	32.4%	21.2%	0.044
Diuretics	5.6%	6.7%	0.0%	2.7%	9.1%	0.327
Beta blocker	9.2%	8.7%	10.0%	10.8%	9.1%	0.979
OHA	12.0%	12.0%	20.0%	10.8%	6.1%	0.396
Insulin	1.2%	0.0%	3.3%	5.4%	0.0%	0.031
Statin	12.4%	10.7%	13.3%	18.9%	12.1%	0.596
Warfarin	2.4%	2.0%	0.0%	5.4%	3.0%	0.508
SBP (mmHg)	117±12.7	117±11.8	116±12.0	120±15.1	118±14.2	0.543
DBP (mmHg)	72±8.8	72±8.8	71±6.5	74±9.5	74±9.6	0.501

†LVH calculated by electrocardiographic Cornell criteria.

‡'Smoker' means active smokers as well as ex-smokers, in whom smoking is stopped less than 1 year before enrollment.

*eGFR was calculated using the Modification of Diet in Renal Disease formula; GFR = 186.3 x (serum creatinine)$^{-1.54}$ x (age)$^{-0.203}$ x (0.742 if female).

hs-cTnT denotes high-sensitivity cardiac troponin T; T3, Triiodothyronine; LVH, left ventricular hypertrophy; TSH, thyroid stimulating hormone; T4, thyroxin; eGFR, estimated glomerular filtration rate ; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CCB, calcium channel blocker; RAAS, renin angiotensin aldosterone system; OHA, oral hypoglycemic agent; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Cut-off level of hs-cTnT and T3; 0.014 ng/mL and 60 ng/dL, respectively.

Table 2. The primary and secondary endpoints on the basis of combined hs-cTnT and T3

Endpoints	**Total (N=250)**	**Normal hs-cTnT /T3 (N=150)**	**Normal hs-cTnT /low T3 (N=30)**	**High hs-cTnT /normal T3 (N=37)**	**High hs-cTnT /low T3 (N=33)**	**P-value**
Primary endpoint						
Overall events, *n* (%)	17 (6.8)	3 (2.0)	1 (3.3)	6 (16.2)	7 (21.2)	<0.001
Components of overall events						
Sudden cardiac death, *n* (%)	4 (1.6)	0 (0.0)	0 (0.0)	3 (8.1)	1 (3.0)	0.004
Ischemic stroke, *n* (%)	5 (2.0)	2 (1.3)	0 (0.0)	1 (2.7)	2 (6.1)	0.281
Newly developed AF, *n* (%)	5 (2.0)	1 (0.7)	1 (3.3)	2 (5.4)	1 (3.0)	0.261
Thrombosis, *n* (%)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)	0.004
Pericardial effusion, *n* (%)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0.086

hs-cTnT denotes high-sensitivity cardiac troponin T; T3, Triiodothyronine; AF, atrial fibrillation.
Cut-off level of hs-cTnT and T3; 0.014 ng/mL and 60 ng/dL, respectively.

Table 3. Univariate and multivariate Cox proportional hazard model determining the significant and independent predictors for overall event, respectively

Factor	Univariate HR (95% CI), P value	Multivariate HR (95% CI), P value
Combined hs-cTnT and T3		
Normal hs-cTnT/low T3	1.56 (0.16-14.99), 0.701	1.65 (0.17-16.00), 0.664
High hs-cTnT/normal T3	8.45 (2.11-33.80), 0.003	6.03 (1.40-26.07), 0.016
High hs-cTnT/low T3	15.81 (4.07-61.34), <0.001	11.72 (2.83-48.57), 0.001
eGFR < 60 ml/min/1.73 m^2	2.92 (1.11-7.68), <0.030	1.62 (0.58-4.54), 0.360
LVH	3.90 (1.44-10.56), 0.007	2.27 (0.78-6.65), 0.135

hs-cTnT denotes high-sensitivity cardiac troponin T; T3, Triiodothyronine; LVH, left ventricular hypertrophy; eGFR, estimated glomerular filtration rate.

Cut-off level of hs-cTnT and T3; 0.014 ng/mL and 60 ng/dL, respectively.

Acknowledgements

새로운 배움과 학위를 취득하며 무언가를 이루었다는 성취감에 마음이 뿌듯하며 이 모든 것을 이루는데 밑거름이 되게 하신 모든 분들께 감사의 말을 전하고자 합니다.

좋은 연구 테마를 주시고 물심양면으로 격려와 조언으로 학위의 꿈을 주신 최동현 교수님께 머리 숙여 감사를 드립니다.

항상 격려와 조언을 아끼지 않으신 내과 김동민 교수님, 신병철 교수님, 박근호 교수님, 송희상 교수님께 깊은 감사를 드립니다.

항상 기도해 주시고 염려해 주신 부모님께 한없는 감사를 드립니다.

박사학위를 가진 의사로서 이웃과 환자들에게 봉사하고, 더욱 더 매진하여 세상의 빛과 소금이 되어 하나님께 영광을 돌리는 의사가 되고자 노력 하겠습니다.