ORIGINAL RESEARCH

Radioactive Iodine-131 Therapy Reduced the Risk of MACEs and All-Cause Mortality in Elderly with Hyperthyroidism Combined with Type 2 Diabetes

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Aim: This study aimed to assess the efficacy of antithyroid drugs (ATDs) and radioactive iodine-131 (RAI) therapies in reducing the risk of major adverse cardiovascular events (MACEs) and all-cause mortality in patients with hyperthyroidism complicated with type 2 diabetes mellitus (T2DM).

Methods: Between January 2013 and December 2021, 540 subjects were included in the analysis. All participants were followed up for 9 years, with a median of 54 months (2451 person-years). The subjects were categorized into two groups: the ATDs group (n = 414) and the RAI group (n = 126). According to the free triiodothyronine (FT3) tertiles, the patients receiving RAI were further grouped as follows: low-level (≤ 4.70 pmol/L, n = 42), moderate-level (4.70–12.98 pmol/L, n = 42), and high-level (≥ 12.98 pmol/L, n = 42). The efficacy of ATDs and RAI therapies in reducing the risk of MACEs and all-cause mortality was assessed.

Results: Of the 540 participants, 163 experienced MACEs (30.19%), 25 (15.34%) of whom died. Multivariate Cox regression analyses revealed that RAI was associated with a 38.5% lower risk of MACEs (P = 0.016) and a 77.1% lower risk of all-cause mortality (P = 0.046). Stratified analyses indicated that RAI had a protective effect on MACEs in patients aged ≥ 60 years (P = 0.001, P for interaction = 0.031) and patients with a duration of diabetes mellitus ≥ 6 years (P = 0.013, P for interaction = 0.002). Kaplan–Meier analysis revealed a lower cumulative incidence of MACEs and all-cause mortality in the RAI group (log-rank, all P < 0.05). Moreover, the ROC curve suggested an optimal FT3 cut-off value of 5.4 pmol/mL for MACE (P < 0.001).

Conclusion: Our findings suggested that RAI therapy effectively reduced the risk of MACEs and all-cause mortality in elderly patients with hyperthyroidism combined with T2DM.

Keywords: hyperthyroidism, type 2 diabetes mellitus, radioactive iodine-131, major adverse cardiovascular events, all-cause mortality

Introduction

Hyperthyroidism and type 2 diabetes mellitus (T2DM) are frequently prevalent conditions with potential adverse clinical outcomes that affect society as a whole, both in developed and developing countries. The prevalence of hyperthyroidism is estimated to be approximately 0.2% to 2.5% in adults worldwide, with 2% for women and 0.5% for men.[1] Approximately 90% of the 537 million cases of diabetes worldwide are attributed to T2DM.[2] According to updated epidemiological findings, the prevalence of T2DM and hyperthyroidism in China is 12.8%[3] and 0.78%,[4] respectively. Despite the lack of consensus on the coexistence prevalence of the two diseases (ranging from 9.9 to 48%[5]), individuals with hyperthyroidism are undoubtedly at greater risk of T2DM and vice versa and are more susceptible to metabolic

dysregulation and adverse prognosis in clinical practice.[6] At present, from the perspective of clinical prognosis, which therapeutic strategy to adopt for hyperthyroidism complicated with T2DM is still controversial in routine clinical practice. Consequently, the topic covered in this study is crucial for providing practical insights into the establishment of appropriate treatment plans for patients with hyperthyroidism complicated with T2DM.

Thyroid hormones play a pivotal role in maintaining energy homeostasis and are characterized by a well-orchestrated metabolic pathway network to manage energy synthesis, storage, and expenditure.[7] Thyroid hormones play pleiotropic roles by controlling genes responsible for lipogenesis, lipolysis, differentiation, and thermogenesis in brown adipose tissue (BAT).[8–10] The excessive synthesis of thyroid hormones distinguishes hyperthyroidism. Overproduction of circulating thyroid hormones heightens β-adrenergic activity and directly activates thyroid hormone receptors on the myocardial cell membrane, the sinoatrial node, and the endothelial tissues of the coronary artery and the communication branch between the artery and vein, and the pathophysiological effects involve increased cardiac contractility and decreased systemic vascular resistance, resulting in increased cardiac output and cardiac enlargement, myocardial ischemia, atrial fibrillation (AF), and right heart failure (RHF).[11,12] The glucose-raising effects of thyroid hormones result from the impaired insulin secretory capacity of pancreatic B cells caused by an excess of thyroid hormones in patients with hyperthyroidism, which hastens the onset of T2DM and the progression of relevant complications as insulin reserves are depleted.[13–15] Thyrotoxicosis alters energy metabolism levels in patients with T2DM, which further worsens energy deficiency and promotes the occurrence of acute or chronic complications such as diabetic ketoacidosis, macrovascular and microvascular complications, and peripheral neuropathy.[16,17] A growing body of evidence has elucidated the relationship between hyperthyroidism and adverse cardiovascular outcomes, such as AF, RHF, acute myocardial infarction (AMI), stroke, and all-cause mortality.[18–20]

Antithyroid drugs (ATDs), radioactive iodine-131 (RAI), minimally invasive operation, or near-total thyroidectomy are all options for treating hyperthyroidism due to their specific indication profiles, efficacy, and safety.[21] Despite the lack of clear and persuasive evidence, ATDs seem to be the preferred therapeutic approach in daily clinical practice around the world, including in China, because of their convenience and some concerns about hypothyroidism induced by RAI.[22–24] In recent years, the United States has also shown a similar trend, particularly in primary treatment for hyperthyroidism, even though RAI has historically been preferred.[25,26] A network meta-analysis conducted on 8 studies with 1402 participants with hyperthyroidism from 5 continents confirmed the relatively high relapse rate of ATDs in comparison to RAI, along with an adverse effect of ATDs involving cutaneous allergy, agranulocytosis and hepatotoxicity in 692 of 5136 (13%) patients from an additional 31 cohort studies.[27] A 12-year longitudinal cohort study with 114 062 patients with newly diagnosed hyperthyroidism based on the Taiwan National Health Insurance Research Database demonstrated that compared with ATDs, RAI was associated with a 55% lower risk of major adverse cardiovascular events (MACEs) (HR = 0.45; 95% CI, 0.22–0.93; P = 0.03).[28] A retrospective cohort study of 2793 hyperthyroidism patients who received RAI at Tampere University Hospital between 1965 and 2002 with a median age of 9 years showed that the risk of cerebrovascular mortality increased following RAI treatment, while the development of hypothyroidism significantly reduced mortality.[29] Boelaert's team observed increased all-cause mortality caused by complications of the circulatory system in patients with hyperthyroidism receiving ATDs, while patients receiving RAI who experienced hypothyroidism had risks comparable to those of the general population.[30] In contrast to that of typical hyperthyroidism, the prognosis of T2DM patients with long-term atherosclerotic cardiovascular disease (ASCVD) is highly complicated. Dyslipidemia caused by hypothyroidism in hyperthyroidism patients receiving RAI results from nonalcoholic fatty liver disease (NAFLD) and the development of hepatic insulin resistance, which leads to hyperthyroidism occurrence and the progression of cardiovascular complications in T2DM patients.[31] In short, to date, evidence-based therapeutic strategies for hyperthyroidism combined with T2DM based on long-term adverse clinical prognoses are lacking.

As noted above, the choice of therapeutic strategy for hyperthyroidism complicated with T2DM remains largely controversial in routine clinical practice. The association between RAI and adverse clinical outcomes in patients with T2DM combined with hyperthyroidism has not been well studied. The present study was designed to investigate the relationships between RAI and the risk of MACEs and all-cause mortality in hyperthyroidism patients with T2DM for the first time.

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Methods

Study Design

This study is an ambispective longitudinal cohort study. A total of 832 participants with hyperthyroidism combined with diabetes were recruited for this study from the People's Hospital of Guangxi Zhuang Autonomous Region and Heping Hospital Affiliated with Changzhi Medical College between January 2013 and December 2021. Ultimately, after a median follow-up of 54 months (2451 person-years), 540 patients were included in the current analysis. The subjects were categorized into two groups: ATDs (n = 414) and RAI (n = 126). Patients receiving RAI were further grouped according to tertiles of free triiodothyronine (FT3): low-level (≤ 4.70 pmol/L, n = 42), moderate-level (4.70–12.98 pmol/L, n = 42), and high-level (≥ 12.98 pmol/L, n = 42). The associations between the RAI and the risk of MACEs and all-cause mortality were evaluated by multivariate Cox regression analysis, stratified analysis, Kaplan–Meier survival analysis, and receiver operating characteristic (ROC) analysis. The inclusion criteria were as follows: (1) had a diagnosis of T2DM or hyperthyroidism based on the World Health Organization (WHO) 1999 or 2012 criteria, respectively;[32,33] (2) had hyperthyroidism combined with diabetes; and (3) received normative antihyperthyroidism or antidiabetes therapies. Participants with one of the following conditions were excluded: (1) non-T2DM; (2) iodine-induced hyperthyroidism, subacute thyroiditis with thyrotoxicosis, or Hashimoto's thyroiditis with thyrotoxicosis; (3) thyroidectomy; (4) severe cardiac, hepatic, or renal disease before a diagnosis of hyperthyroidism; (5) pregnancy; (6) malignant tumors; or (7) incomplete clinical information, loss to follow-up, or a follow-up time of less than one year. All patients agreed to participate in this study and signed a written informed consent and a nondisclosure agreement (NDA) to safeguard their privacy during the data analysis. The Ethics Committees of the People's Hospital of Guangxi Zhuang Autonomous Region and Changzhi Medical College Affiliated Heping Hospital approved the study, which complied with the guidelines of the Declaration of Helsinki.

Data Collection

Demography, anthropometry, laboratory biochemical parameters, medical imaging data, and therapeutic regimen information were collected from the inpatient medical records of the People's Hospital of Guangxi Zhuang Autonomous Region and Heping Hospital Affiliated with Changzhi Medical College. All participants were followed up by trained professional staff every 6 months for 9 years for a median of 54 months (2451 person-years) through outpatient visits, medical records retrievals, and home telephone interviews.

Specific Definitions

The relevant definitions in this study were as follows: (1) The levels of serum FT3, free thyroxine (FT4), and thyroid-stimulating hormone (TSH) were measured by electrochemiluminescence. The reference range of serum FT3 was 3.19–9.15 pmol/l, and the reference range of serum FT4 was 9.11–25.47 pmol/L. The reference range of serum TSH is 0.3–5.91 μIU/mL. (2) Standardized ATD treatment regimens lasting at least 1 year. (3) End-point events were defined as compound end-point events of MACE, consisting of nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, heart failure, and all-cause death, obtained by trained professional medical staff through in-person outpatient interviews and family fixed-line telephone visits. (4) The follow-up time was defined as the time from the first treatment of hyperthyroidism complicated with T2DM to the occurrence of MACE or the end of follow-up. In this study, over a median follow-up of 54 months (2451 person-years), the deadline for follow-up was December 2022, and the longest follow-up time was 15 years.

Statistical Analysis

PASS 11.0 software (https://www.ncss.com/download/pass/updates/pass11/) was used to determine the sample size to ensure that the case scale met a high testing power of more than 90%. Data analysis was performed using GraphPad Prism 9.3 (GraphPad Software, San Diego, CA) and the SPSS 27.0 statistical software package (IBM Corp., Armonk, NY, USA). Statistical significance was defined as P < 0.05.

The mean ± standard deviation (SD) was used to express continuous variables with a normal distribution, and group comparisons were tested using analysis of variance. The median (interquartile ranges) was used to express variables with nonnormal distributions, and group comparisons were conducted using the Kruskal–Wallis H-test. Categorical variables are represented as frequencies and were compared between groups using the chi-squared test.

The risk factors for endpoint events were initially identified using univariate Cox regression analysis. Factors that showed a P value lower than 0.1 in the univariate analysis were included in the multivariate Cox regression analysis. Multicollinearity between variables was detected using tolerance and variance inflation factors. Collinearity could be observed when the tolerance was less than 0.1 or the variance inflation factor was greater than 10. The tolerance in this study was more than 0.1, and the variance inflation factor was less than 10, suggesting no multicollinearity between variables. Four multivariate regression models were built and used to adjust for potential confounding factors for the endpoint events gradually. Model I was adjusted for gender. Model II was additionally adjusted for age with Model I. Model III was gradually adjusted for FT3, CVD, and the duration of diabetes with Model II. Model IV was further adjusted for the duration of hyperthyroidism with Model III. The forest plots for subgroup analyses were constructed using the R language software package version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Kaplan-Meier survival curve analysis and Log rank tests were used to evaluate the cumulative incidence of MACE and all-cause mortality. ROC analysis was used to assess the diagnostic efficiency of the ideal FT3 cutoff value for MACEs.

Results
Baseline Data

The recruitment strategy for participants is depicted in Figure 1. A total of 832 patients with hyperthyroidism combined with diabetes were recruited for this study from the People's Hospital of Guangxi Zhuang Autonomous Region and the Heping Hospital Affiliated with Changzhi Medical College between January 2013 and December 2021. Ultimately, a total of 540 participants with hyperthyroidism combined with T2DM were included in the current analysis. All participants were followed up by trained professional staff every 6 months for 9 years with a median of 54 months (2451 person-years) through outpatient visits, medical records retrievals, and home telephone interviews. The baseline characteristics are displayed in Table 1. The primary baseline characteristics of the participants included 325 females (60.2%), a median age of 60.07±12.35 years, a median BMI of 23.36 (21.03–26.03) kg/m^2, a duration of hyperthyroidism of 5.00 (2.00–10.00) years, and a duration of T2DM of 6.00 (3.00–11.00) years. The subjects were categorized into two groups: ATDs (n = 414, 76.7%) and RAI (n = 126, 23.3%). Patients receiving RAI were further grouped according to tertiles of free triiodothyronine (FT3): low-level (≤ 4.70 pmol/L, n = 42), moderate-level (4.70–12.98 pmol/L, n = 42), and high-level (≥ 12.98 pmol/L, n = 42). Sex, age, body mass index (BMI), history of smoking, CVD, fasting blood glucose (FBG), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), FT3, FT4, TSH, and duration of T2DM were not significantly different between the ATDs and RAI groups (all P > 0.05). In contrast, the HbA1c level and duration of hyperthyroidism were significantly different (all P < 0.05). Additionally, among the different FT3 level groups, gender, history of smoking, CVD, HbA1c, triglyceride (TG), duration of hyperthyroidism, duration of T2DM, duration of T2DM, and death were not significantly different (all P > 0.05). However, age, BMI, FBG, TC, LDL-C, HDL-C, FT4, TSH, and MACEs were significant (all P < 0.05).

Cox Regression Analyses for Assessing the Risk Factors for Endpoint Events

The Cox regression analysis of risk factors for endpoint events is shown in Table 2. The risk factors for endpoint events were initially identified using univariate Cox regression analysis. Afterward, the variables with P < 0.1 in the univariate analysis were included in the multivariate Cox regression analysis. Multicollinearity between variables was detected using tolerance and variance inflation factors. A tolerance less than 0.1 or a variance inflation factor greater than 10 indicates collinearity. The tolerance in this study was more than 0.1, and the variance inflation factor was less than 10, suggesting no multicollinearity between variables. Four multivariate regression models were built and used to adjust for potential confounding factors for the endpoint events gradually. Model I was adjusted for gender. Model II was additionally adjusted for age with Model I. Model III was gradually adjusted for FT3, CVD, and the duration of diabetes
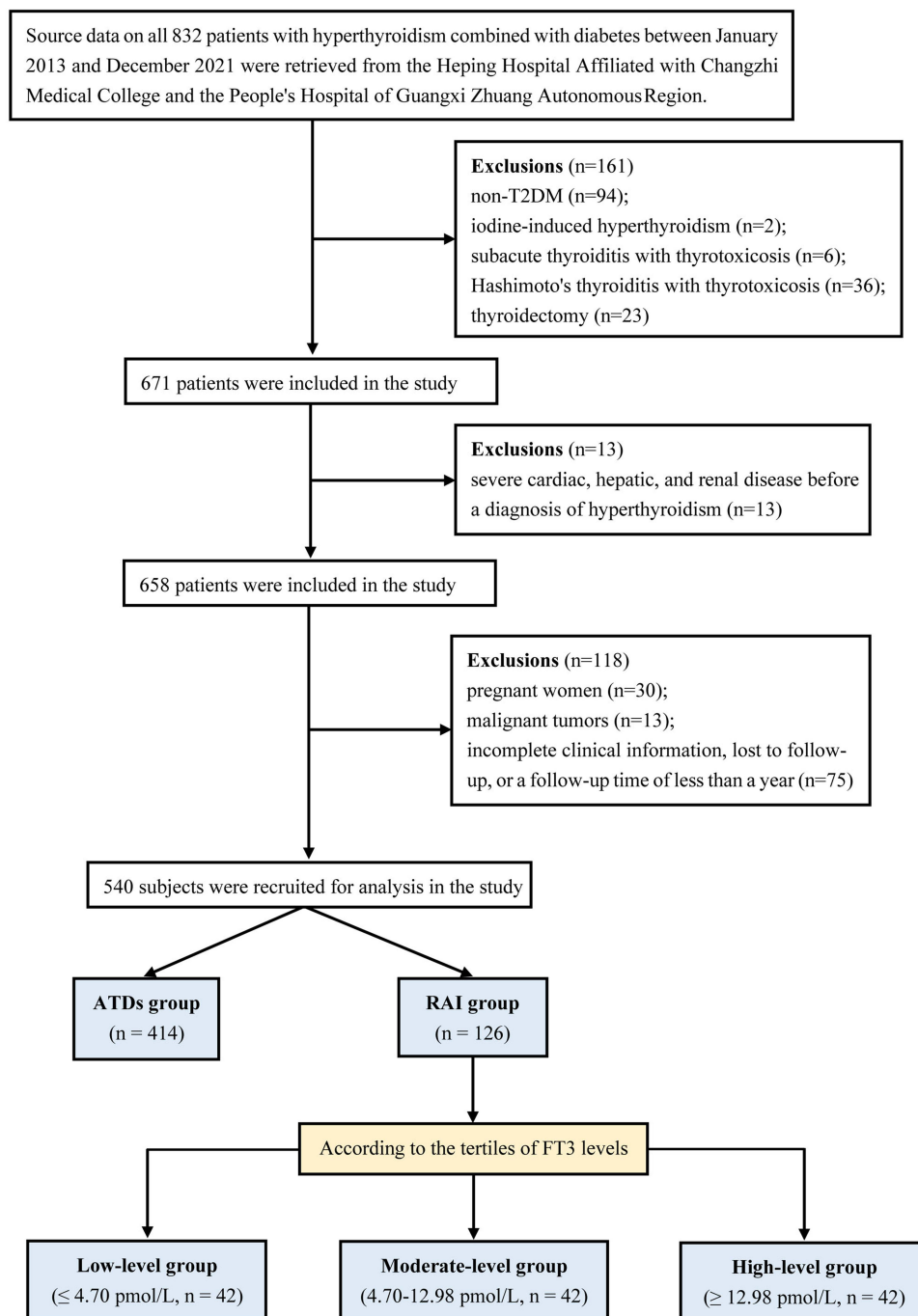
Figure 1 Flow chart for selecting participants. Data on all 832 patients with hyperthyroidism combined with diabetes between January 2013 and December 2021 were retrieved from the Heping Hospital Affiliated with Changzhi Medical College and the People's Hospital of Guangxi Zhuang Autonomous Region. Finally, a total of 540 participants with hyperthyroidism combined with T2DM were analyzed over a median follow-up of 54 months (2451 person-years). The subjects were categorized into two groups: ATDs (n = 414) and RAI (n = 126). According to free triiodothyronine (FT3) tertiles, the patients receiving RAI were further grouped into low-level (≤ 4.70 pmol/L, n = 42), moderate-level (4.70–12.98 pmol/L, n = 42), and high-level (≥ 12.98 pmol/L, n = 42) groups.

with Model II. Model IV was further adjusted for the duration of hyperthyroidism with Model III. Multivariate Cox regression analyses revealed that when the HR of ATDs was 1, the RAI was associated with a 38.5% lower risk of MACEs (HR = 0.615, 95% CI = 0.414–0.914, P = 0.016) in Model III and a 77.1% lower risk of all-cause mortality (HR = 0.229, 95% CI = 0.054–0.974, P = 0.046) in Model I in patients with hyperthyroidism combined with T2DM. Multivariate Cox regression analyses revealed the efficacy of RAI treatment in patients with hyperthyroidism combined with T2DM.

Table 1 Baseline Characteristics of Subjects

Characteristics	All Subjects (n=540)	ATD Group (n=414)	RAI group (n=126)					P values
			RAI Patients (n=126)	Low-Level FT3 (≤4.70) (n=42)	Moderate-Level FT3 (4.71–12.97) (n=42)	High-Level FT3 (≥12.98) (n=42)	P values	
Gender, n (%)							0.592	0.703
Female	325 (60.2)	251 (77.2)	74 (22.8)	26 (61.90%)	22 (52.38%)	26 (61.90%)		
Male	215 (39.8)	163 (75.8)	52 (24.2)	16 (38.10%)	20 (47.62%)	16 (38.10%)		
Age, years	60.07 ± 12.345	60.29 ± 12.825	59.33 ± 10.630	62.76±9.36	59.12±10.43	56.10±11.20	0.015*	0.395
BMI, kg/m^2	23.36 (21.03–26.03)	23.36 (20.93–26.00)	23.39 (21.60–26.04)	23.87 (22.62–26.99)	24.32 (21.42–25.71)	22.76 (20.81–24.74)	0.042*	0.236
History of smoking, n (%)							0.712	0.085
Yes	85 (15.7)	59 (69.4)	26 (30.6)	9 (21.43%)	10 (23.81%)	7 (16.67%)		
No	455 (84.3)	355 (78.0)	100 (22.0)	33 (78.57%)	32 (76.19%)	35 (83.33%)		
CVD, n (%)							0.754	0.098
Yes	117 (21.7)	83 (70.9)	34 (29.1)	13 (30.95%)	11 (26.19%)	10 (23.81%)		
No	423 (78.3)	331 (78.3)	92 (21.7)	29 (69.05%)	31 (73.81%)	32 (76.19%)		
FBG, mmol/L	6.87 (5.60–9.06)	6.83 (5.53–8.96)	7.10 (5.81–9.43)	6.36 (5.21–7.17)	7.38 (5.65–9.70)	7.95 (6.58–10.08)	0.008*	0.277
HbA1c, %	7.30 (6.50–9.10)	7.20 (6.40–8.80)	8.00 (6.70–9.60)	7.20 (6.62–8.78)	8.30 (6.58–9.67)	8.00 (6.93–9.57)	0.630	0.024*
TC, mmol/L	3.99 (3.13–4.98)	3.99 (3.27–4.87)	3.92 (2.89–5.14)	5.11 (4.07–6.25)	3.96 (2.87–4.65)	2.99 (2.37–3.76)	<0.001*	0.691
TG, mmol/L	1.20 (0.86–1.78)	1.21 (0.86–1.77)	1.20 (0.87–1.96)	1.22 (0.84–2.40)	1.12 (0.73–1.61)	1.24 (1.00–1.94)	0.233	0.980
LDL-C, mmol/L	2.36 (1.85–3.12)	2.36 (1.90–3.11)	2.28 (1.50–3.13)	2.78 (1.67–3.68)	2.26 (1.70–3.12)	1.86 (1.32–2.54)	0.004*	0.273
HDL-C, mmol/L	1.03 (0.86–1.29)	1.03 (0.87–1.28)	1.01 (0.82–1.35)	1.21 (0.92–1.45)	1.08 (0.85–1.40)	0.92 (0.74–1.07)	0.002*	0.693
FT3, pmol/L	6.69 (4.72–12.79)	6.73 (4.80–11.88)	6.14 (4.22–16.70)	N/A	N/A	N/A	N/A	0.896
FT4, pmol/L	22.15 (12.68–41.49)	21.69 (13.50–39.57)	25.16 (10.69–44.11)	9.98 (7.71–12.34)	26.57 (14.48–36.43)	48.38 (43.15–59.52)	<0.001*	0.795
TSH, μIU/mL	0.02 (0.01–0.37)	0.02 (0.01–0.20)	0.02 (0.01–4.95)	7.11 (1.44–18.91)	0.01 (0.01–1.00)	0.01 (0.01–0.01)	<0.001*	0.052
Duration of hyperthyroidism, years	5.00 (2.00–10.00)	4.00 (1.00–9.00)	6.00 (3.00–11.00)	10.00 (5.00–13.50)	6.00 (3.25–12.75)	6.00 (3.00–7.00)	0.110	0.000*
Duration of diabetes, years	6.00 (3.00–11.00)	6.00 (2.00–11.00)	6.00 (3.00–12.00)	9.50 (4.00–12.00)	5.00 (2.00–8.75)	7.00 (3.25–13.00)	0.066	0.360
Death, n (%)							0.602	0.063
Yes	25 (4.6)	23 (92.0)	2 (8.0)	1 (2.38%)	1 (2.38%)	0 (0.00%)		
No	515 (95.4)	391 (75.9)	124 (24.1)	41 (97.62%)	41 (97.62%)	42 (100.00%)		
MACEs, n (%)							0.008*	0.119
Yes	163 (30.2)	132 (81.0)	31 (19.0)	17 (40.48%)	9 (21.43%)	5 (11.90%)		
No	377 (69.8)	282 (74.8)	95 (25.2)	25 (59.52%)	33 (78.57%)	37 (88.10%)		

Notes: Mean ± standard deviation (SD) and median (interquartile range, IQR) for continuous variables. Percentages (%) for categorical variables. *P < 0.05.
Abbreviations: ATD, antithyroid drug; RAI, radioactive iodine-131; BMI, body mass index; CVD, cardiovascular disease; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; MACEs, major adverse cardiovascular events.

Table 2 Univariate and Multivariate Cox Proportional Hazards Models for Evaluating the Relationship Between Antithyroid Therapeutics and Adverse Clinical Outcomes in Patients with Hyperthyroidism and T2DM

Adjustment Strategy	MACEs		All-Cause Mortality	
	HR (95% CI)	P values	HR (95% CI)	P values
Adjust for non				
ATDs	Ref		Ref	
RAI	0.628 (0.424–0.930)	0.020*	0.229 (0.054–0.973)	0.046*
Model I				
ATDs	Ref		Ref	
RAI	0.629 (0.425–0.930)	0.020*	0.229 (0.054–0.974)	0.046*
Model II				
ATDs	Ref		Ref	
RAI	0.652 (0.440–0.967)	0.033*	0.249 (0.058–1.063)	0.060
Model III				
ATDs	Ref		Ref	
RAI	0.615 (0.414–0.914)	0.016*	0.260 (0.060–1.119)	0.070
Model IV				
ATDs	Ref		Ref	
RAI	0.682 (0.457–1.018)	0.061	0.291 (0.067–1.252)	0.097

Notes: With the ATD schemes as a reference, the HR of ATDs is set to 1. Model I: adjusted for sex. Model II: adjusted for age in Model I. Model III: adjusted for Model II, FT3, CVD, and duration of diabetes. Model IV: The duration of hyperthyroidism was adjusted for in Model III. *$P < 0.05$.
Abbreviations: T2DM, type 2 diabetes mellitus; MACEs, major adverse cardiovascular events; HR, hazard ratio; CI, confidence interval; ATDs, antithyroid drugs; RAI, radioactive iodine-131; FT3, free triiodothyronine; CVD, cardiovascular disease.

Stratified Analysis for Subgroups

The forest plots (Figure 2) display the subgroup analysis based on stratified factors: age, sex, CVD, FT3, duration of diabetes mellitus, and duration of hyperthyroidism. Stratified analysis indicated that RAI had a protective effect on MACEs in patients aged ≥ 60 years (HR = 0.445, 95% CI = 0.272–0.730, P = 0.001, P for interaction = 0.031), patients with a duration of diabetes mellitus ≥ 6 years (HR = 0.493, 95% CI = 0.283–0.861, P = 0.013, P for interaction = 0.002), and patients with hyperthyroidism status, including FT3 levels (P for interaction = 0.006) and duration of hyperthyroidism (P for interaction = 0.005). Stratified analysis indicated that although RAI was the best therapeutic option for patients with hyperthyroidism combined with T2DM, specific indication profiles, efficacy, and safety still need to be investigated.

Kaplan-Meier Survival Curve Analysis for the Cumulative Incidence of Endpoint Events

During the follow-up period, 163 out of 540 participants experienced MACEs (30.19%), of which 25 (15.34%) died. The Kaplan-Meier survival curve analyses were used to evaluate the cumulative incidence of endpoint events between the two groups (ATDs vs RAI or low-level FT3 vs high-level FT3). The analysis results demonstrated that compared with the ATDs group, the RAI group had a lower cumulative incidence of MACE (Figure 3) and all-cause mortality (Figure 4) (log-rank, all P < 0.05). Moreover, in patients receiving RAI, the same dose of iodine had different effects on the endpoints at different baseline FT3 levels; the greater the baseline FT3 level, the greater the iodine intake ability, and the lower the cumulative incidence of MACEs (log-rank, P = 0.021) (Figure 5). Kaplan-Meier survival curve analysis revealed that the RAI treatment strategy was the first-line therapy for patients with hyperthyroidism combined with T2DM.
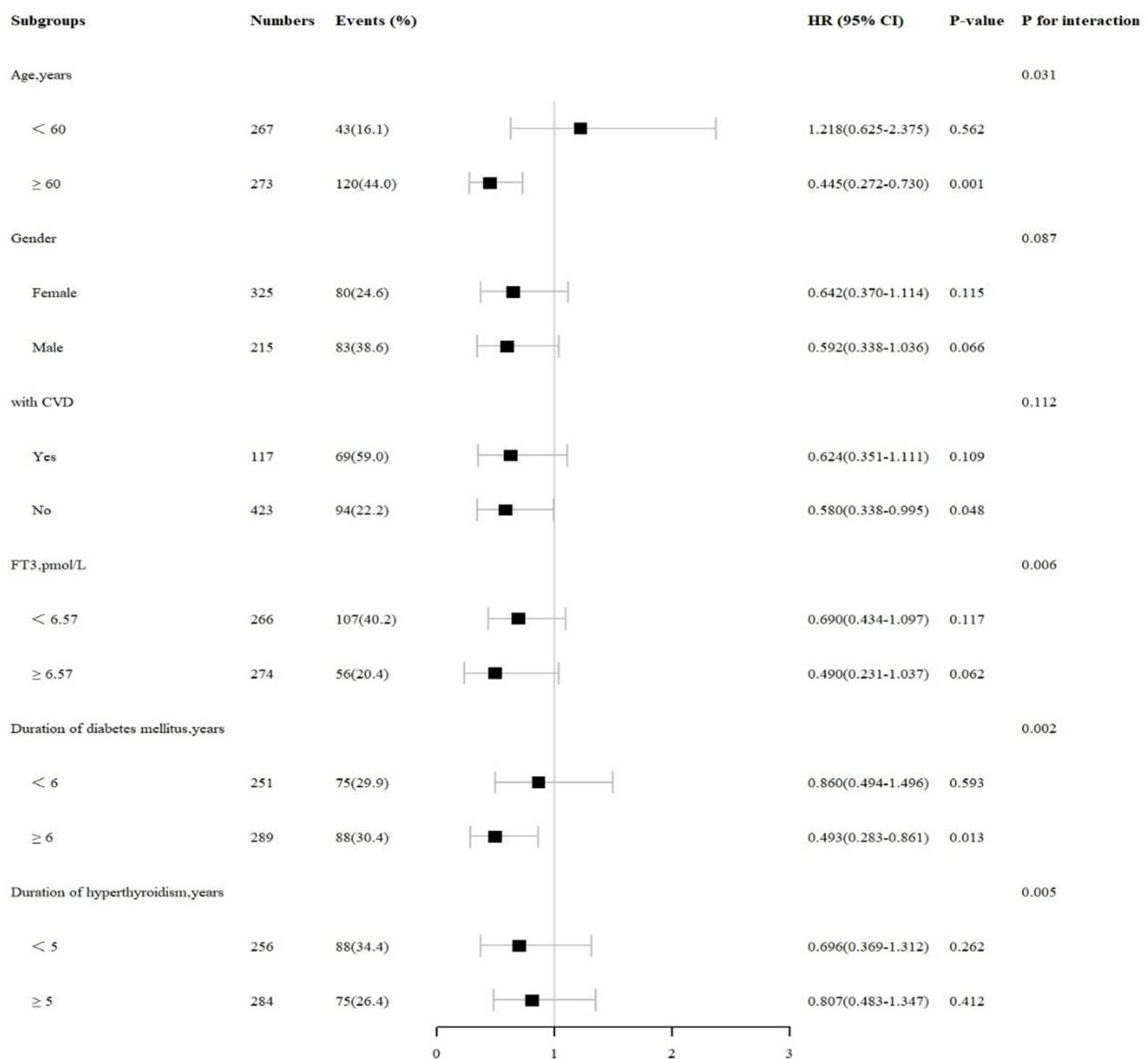
Subgroups	Numbers	Events (%)		HR (95% CI)	P-value	P for interaction
Age,years						0.031
< 60	267	43(16.1)		1.218(0.625-2.375)	0.562	
≥ 60	273	120(44.0)		0.445(0.272-0.730)	0.001	
Gender						0.087
Female	325	80(24.6)		0.642(0.370-1.114)	0.115	
Male	215	83(38.6)		0.592(0.338-1.036)	0.066	
with CVD						0.112
Yes	117	69(59.0)		0.624(0.351-1.111)	0.109	
No	423	94(22.2)		0.580(0.338-0.995)	0.048	
FT3,pmol/L						0.006
< 6.57	266	107(40.2)		0.690(0.434-1.097)	0.117	
≥ 6.57	274	56(20.4)		0.490(0.231-1.037)	0.062	
Duration of diabetes mellitus,years						0.002
< 6	251	75(29.9)		0.860(0.494-1.496)	0.593	
≥ 6	289	88(30.4)		0.493(0.283-0.861)	0.013	
Duration of hyperthyroidism,years						0.005
< 5	256	88(34.4)		0.696(0.369-1.312)	0.262	
≥ 5	284	75(26.4)		0.807(0.483-1.347)	0.412	

Figure 2 Forest plots for stratification analyses in subgroups. Stratified analysis indicated that RAI had a protective effect on MACEs in patients aged ≥ 60 years (HR = 0.445, 95% CI = 0.272–0.730, P = 0.001, P for interaction = 0.031), patients with a duration of diabetes mellitus ≥ 6 years (HR = 0.493, 95% CI = 0.283–0.861, P = 0.013, P for interaction = 0.002), and patients with hyperthyroidism status, including FT3 levels (P for interaction = 0.006) and duration of hyperthyroidism (P for interaction = 0.005).

ROC Analysis Evaluating the Predictive Value of FT3 for MACEs in the RAI Group

The outcome of the ROC curve analysis in the RAI group is shown in Figure 6. ROC analysis was conducted to evaluate the diagnostic efficacy of the optimal cut-off value for FT3 for predicting MACEs in patients with hyperthyroidism combined with T2DM and to provide clinical practice with appropriate guidance information. The ROC curve suggested an optimal FT3 cut-off value of 5.4 pmol/mL for MACE (P < 0.001), with an area under the curve (AUC) of 0.7, a sensitivity of 71.0%, and a specificity of 65.3%. ROC curve analysis confirmed that timely RAI therapy was essential in patients with hyperthyroidism combined with T2DM.

Discussion

With aging, economic development, and fast-paced lifestyles, the global epidemic of diabetes mellitus and hyperthyroidism has caused serious public health issues. Significantly, the incidence of hyperthyroidism complicated with T2DM
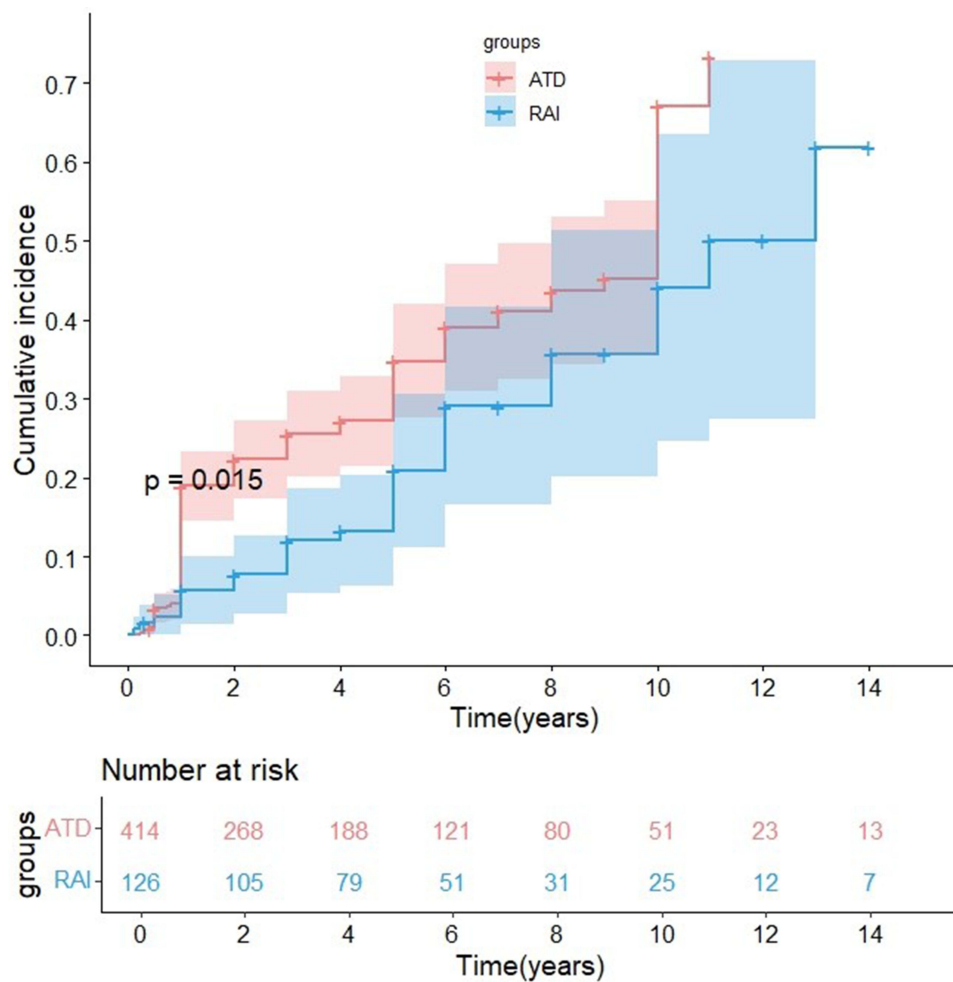
Figure 3 Survival analysis for the cumulative incidence of MACEs by ATDs and RAI. Kaplan-Meier survival analysis revealed that compared with the ATDs group, the RAI group had a lower cumulative incidence of MACEs (log-rank, P = 0.015).

is becoming increasingly severe. Currently, evidence-based therapeutic strategies for hyperthyroidism combined with T2DM based on long-term adverse clinical prognoses are lacking. Therefore, exploring the optimal therapeutic plan for hyperthyroidism patients with T2DM is particularly urgent. For the first time, the present study aimed to determine the associations between RAI and MACE and all-cause mortality in elderly patients with hyperthyroidism combined with T2DM through the follow-up of clinically adverse clinical outcomes for nearly 10 years based on a retrospective cohort. This study proposes the optimal therapeutic path for hyperthyroidism complicated with T2DM, which has essential guiding value for solving the puzzles encountered in current clinical practice.

For the first time, in this study, the following results were obtained in elderly individuals with hyperthyroidism combined with T2DM. First, compared with ATDs, RAI was associated with a 38.5% lower risk of MACEs and a 77.1% lower risk of all-cause mortality. Second, RAI had a protective effect on MACEs in patients aged $\geq$ 60 years, with an FT3 level $\geq$ 5.4 pmol/L, and with a duration of diabetes mellitus $\geq$ 6 years. Third, FT3 levels were independently associated with the risk of MACEs in an inversely J-shaped dose–response pattern in patients receiving RAI. The same dose of iodine had different effects on the endpoints at different baseline FT3 levels; the greater the baseline FT3 level was, the greater the iodine intake, and the lower the cumulative incidence of MACE. These results indicate that from the standpoint of adverse clinical outcomes, RAI should be the first choice for patients with hyperthyroidism combined with T2DM.
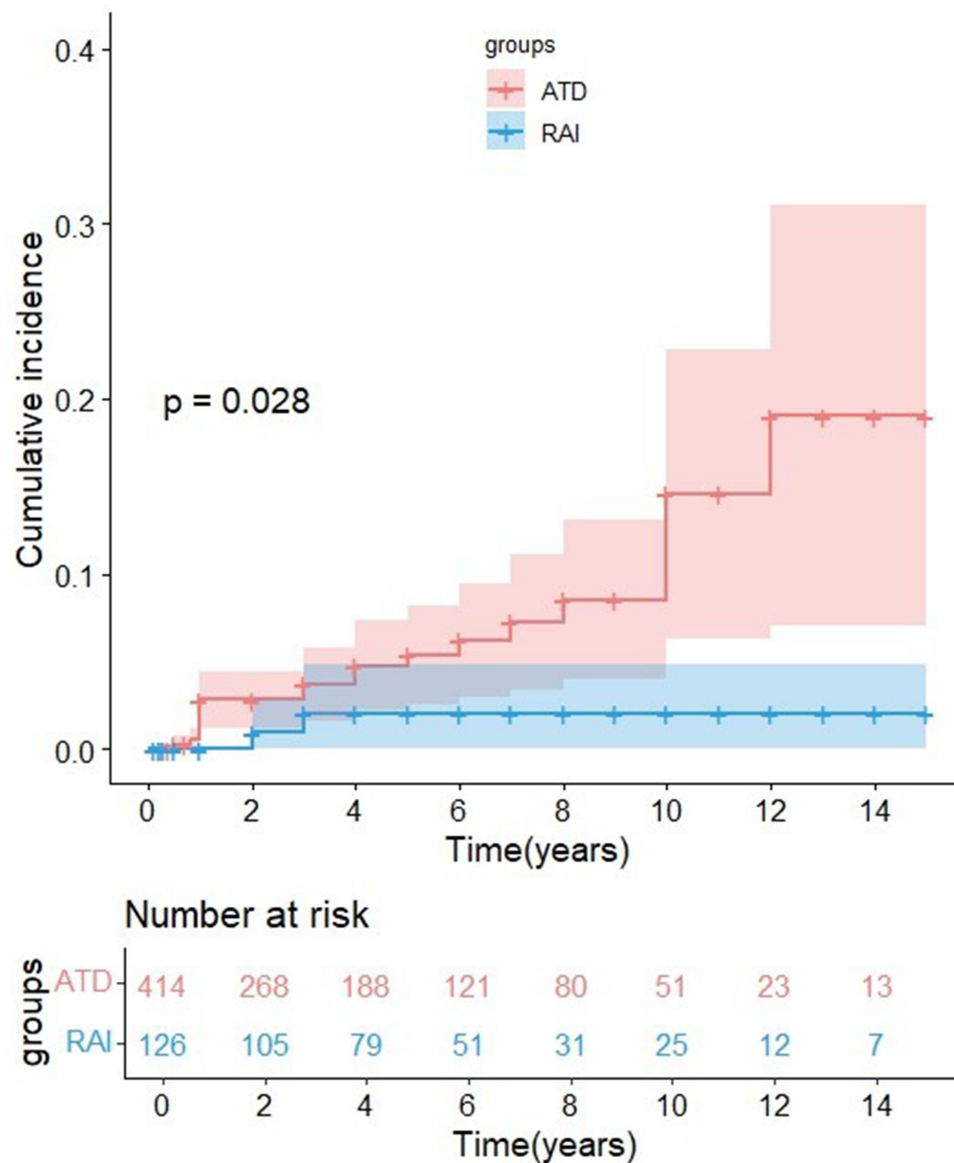
Figure 4 Survival analysis for the cumulative incidence of all-cause mortality by ATDs and RAI. Kaplan-Meier survival analysis indicated that compared with ATDs, the RAI had a lower cumulative incidence of all-cause mortality (log-rank, P = 0.028).

Hyperthyroidism, which manifests as elevated serum thyroid hormone levels, is commonly known as Graves' disease. It is caused by antibodies interacting with the specific TSH receptor on thyroid follicular cells.[34] Thyroid dysfunction strongly affects the pathophysiology of the cardiovascular system.[12] Excessive thyroid hormone in circulation leads to increased abnormal activity of the sinoatrial node, a weakened threshold of atrial activity, and a shortened atrial repolarization period, which can cause sinus tachycardia, pulmonary hypertension (PAH), and right ventricular dysfunction.[12,35] Elevated FT3 levels increase heart rate, cardiac contractility, and venous tension, which eventually leads to an increase in cardiac preload and output.[12] Hyperthyroidism has been identified as an independent risk factor for ASCVD and serious adverse cardiovascular events such as myocardial infarction, AF, HF, and stroke.[36] In most regions other than the United States, such as Europe and East Asia, the first-line treatment for hyperthyroidism is ATDs from the thionamide family. ATD treatment is typically maintained for approximately two years. The approximately 50% rate of hyperthyroidism relapse after ATDs withdrawal constitutes a significant limitation of this therapeutic in clinical practice.[37] Compared with ATDs, individualized RAI has a lower recurrence of hyperthyroidism, longer-term lower FT3 levels, and a lower MACE risk.[28] This is consistent with our findings in this study. Although RAI is an effective and
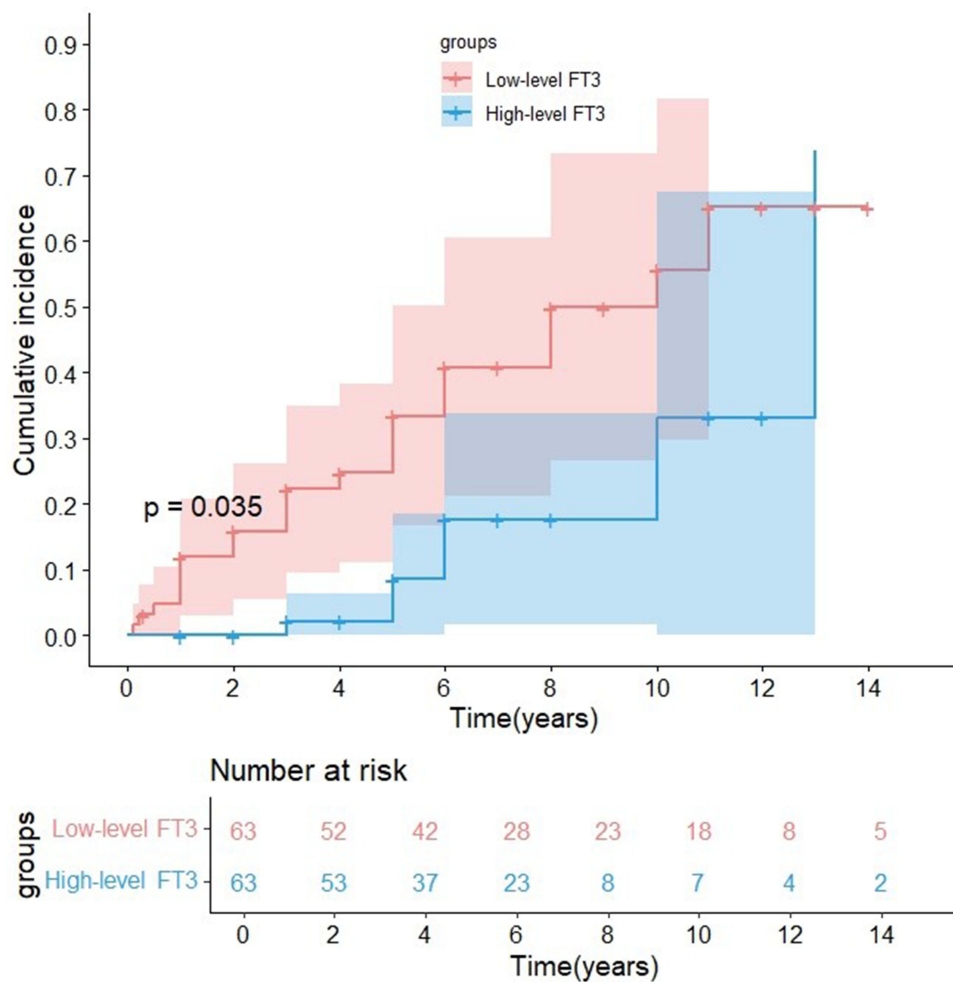
Figure 5 Survival analysis for the cumulative incidence of MACE by FT3 level. In patients receiving RAI, the Kaplan–Meier survival curve showed that the greater the FT3 concentration was, the lower the cumulative incidence of MACE (log-rank, P = 0.021).

preferred strategy in the United States, hypothyroidism, commonly caused by RAI, has caused great concern among doctors and patients, making it challenging to treat patients with hyperthyroidism in clinical settings. Undeniably, low FT3 caused by RAI heralds deteriorates hospital outcomes in patients with acute HF.[38] However, the evidence-based literature on the short-term and long-term adverse cardiovascular outcomes of RAI therapy is still limited, especially for patients with hyperthyroidism combined with T2DM.

The coexistence of hyperthyroidism and T2DM is increasingly common in the daily clinical practice of endocrinology and metabolism.[39] According to reports from multiple countries, the prevalence of thyroid disease among individuals with T2DM is between 4% and 20%.[40] The relationship between hyperthyroidism and T2DM lies in the complex interaction of biochemical, genetic, and hormonal dysfunctions.[41] Thyroid hormones directly and indirectly regulate insulin secretion, liver glucose output, and peripheral tissue glucose treatment.[42] An increased concentration of glucose transporter 2 in the plasma membrane of hepatocytes can increase hepatic glucose output with the help of thyroid hormone.[43] In addition, excessive thyroid hormone can increase catecholamine-induced gluconeogenesis in the liver.[44] Hyperthyroidism can cause hyperglycemia through increased intestinal glucose absorption.[45] In addition, diabetes affects thyroid function by controlling TSH release at the hypothalamus level and influencing T4-T3 transformation in peripheral tissues.[46] The vicious cycle of the hyperthyroidism-T2DM axis further amplifies the adverse effects on cardiovascular outcomes, and elevated FT3 levels play a crucial role in patients with hyperthyroidism complicated with T2DM.[47] It is particularly urgent to relieve the pathological influence of FT3 on the cardiovascular system as soon as possible. In light of this, we can speculate that compared with ATDs, RAI, which acts quickly
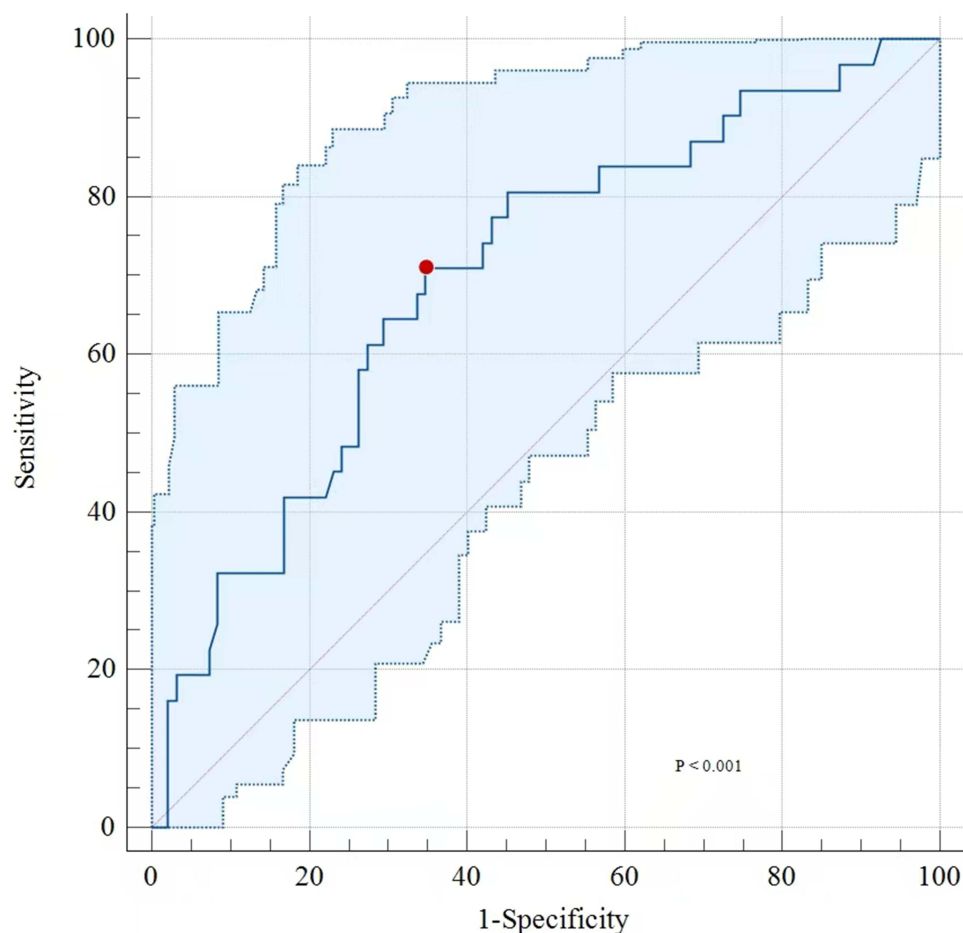
Figure 6 ROC analysis evaluating the predictive value of FT3 for MACEs in the RAI group. The ROC curve suggested an optimal FT3 cut-off value of 5.4 pmol/mL for MACE (P < 0.001) (the red dot position), with an area under the curve (AUC) of 0.7, a sensitivity of 71.0%, and a specificity of 65.3%, respectively.

and maintains a low FT3 level for a long time, benefits the cardiovascular system. In the present study, we verified and further supported this inference: in the RAI group, the higher the baseline FT3 level was, the lower the cumulative incidence of MACE. Thyrotoxicosis and hypothyroidism are both significant risk factors for adverse cardiovascular outcomes in patients with hyperthyroidism combined with T2DM. Using levothyroxine as a replacement for RAI-induced hypothyroidism can prevent hyperlipidemia and the adverse effects of hypothyroidism on diabetic ASCVD.[48]

Limitations

The present data are limited by the small-scale retrospective nature of the study. In addition, this was a retrospective study that did not allow for much modification of the protocol because of the necessity of depending on existing data. Furthermore, The duration of the study was not long enough because patients treated with RAI in the last two years of the study did not have much time to be observed". As we are currently working on, all subjects in this cohort will require continued follow-up to refine the conclusions drawn from this study. Conducting well-designed, large-scale, multicenter, and randomized double-blind prospective longitudinal cohort studies is necessary to determine the optimal treatment for hyperthyroidism complicated with T2DM, which should be on the agenda of clinical researchers and healthcare providers for thyroid and cardiovascular diseases.

Conclusions

The present study demonstrated that compared with ATDs, RAI was associated with a 38.5% lower risk of MACEs and a 77.1% lower risk of all-cause mortality, especially in individuals aged ≥ 60 years, those with an FT3 level ≥ 5.4 pmol/L,

and those with a duration of diabetes mellitus ≥ 6 years. Our findings suggested that radioactive iodine-131 therapy reduced the risk of MACEs and all-cause mortality in elderly patients with hyperthyroidism combined with type 2 diabetes. Therefore, in routine clinical practice, paying more attention to hyperthyroidism combined with T2DM and starting the RAI treatment plan in time may help reduce the risk of MACE and all-cause mortality.

Ethics Statement

All patients agreed to participate in this study and provided written informed consent. The principles of the Declaration of Helsinki were followed. The ethics committees of the People's Hospital of Guangxi Zhuang Autonomous Region (as the center's ethics unit, approval number: Ethics-KY-IIT-2023-60) and the Heping Hospital Affiliated with Changzhi Medical College approved the study.

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Disclosure

No conflicts of interest were reported by the authors in this study.

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