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Original Article

# Warfarin-Thyroid Drug Interactions in Cardiology Practice: A Case Series

Mahdis Sharifikia[1], Bahar Seifi-Zarei[1], Melika Shalileh[1], Masoumeh Sohrabi[1], Shabnam Rezaie[1], Maryam Mehrpooya[1*]

[1.] Department of Clinical Pharmacy, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran.

*Corresponding author:
Maryam Mehrpooya
Department of Clinical Pharmacy, School of Pharmacy, Hamadan University of Medical Sciences, Shahid Fahmideh Ave, Hamadan 6517838678, Iran.

Email:
m_mehrpooya2003@yahoo.com,
m.mehrpoya@umsha.ac.ir

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**Abstract**

**Background**: Warfarin anticoagulation in cardiology is strongly influenced by thyroid status, which alters vitamin K–dependent clotting factor turnover; hyperthyroidism increases warfarin sensitivity, whereas hypothyroidism causes relative resistance and requires higher doses. In addition, starting or up-titrating levothyroxine can further enhance warfarin sensitivity, while antithyroid therapy with methimazole may blunt its anticoagulant effect and necessitate higher doses.

**Methods**: This retrospective case series was conducted in a cardiology clinic from 2023 to 2025 and included stable chronic warfarin users (>3 months within therapeutic INR) who initiated levothyroxine or methimazole and subsequently developed markedly supratherapeutic (INR>5.0) or subtherapeutic (INR<1.5) values. Data captured demographics, valve indications, thyroid function (thyroid-stimulating hormone and free thyroxine), INR trends, dose adjustments, and outcomes.

**Results**: The studied hypothyroid patients (three females, one male; ages 45-72 years) developed INR values ranging from 5.0 to 9.2 (14-28 days post-levothyroxine 50-150 mcg daily), with minor bleeding in two cases. Warfarin doses were reduced by 20-42%, normalizing INR within 2-4 weeks. Four hyperthyroid patients (three females, one male; ages 55-67 years) showed INR values of 1.0-1.3 (2-5 weeks post-methimazole 15-30 mg daily), without thromboses. Warfarin doses increased by 25-55%, with INR values stabilizing over 6 weeks.

**Conclusion**: Levothyroxine decreases warfarin dose requirements through accelerated clotting factor clearance; however, methimazole increases warfarin dose needs as euthyroidism develops. In valve replacement patients, weekly INR monitoring for 4–6 weeks after initiation of thyroid therapy is recommended, along with preemptive warfarin adjustments (20–40% reduction with levothyroxine; 25–50% increase with methimazole) and endocrinology consultation to minimize adverse events.

**Keywords :** Anticoagulation; Cardiology; Case series; Drug interaction; INR; Levothyroxine; Methimazole; Pharmacodynamics; Thyroid disease; Warfarin

## Introduction

Warfarin, a vitamin K antagonist (VKA), remains essential for long-term oral anticoagulation in cardiology, particularly for mechanical heart valve replacement to prevent thromboembolic events. Its narrow therapeutic index and variable dose-response necessitate strict international normalized ratio (INR) monitoring (target: 2.5-3.5 for valves) (1).

Thyroid dysfunction significantly alters pharmacodynamics and pharmacokinetics of warfarin. Accordingly, thyroid hormones (T3/T4) regulate hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, and X), modulate CYP2C9 (Cytochrome P450 Family 2 Subfamily C Member 9) activity (S-warfarin metabolism), and affect the expression of vitamin K epoxide reductase complex (VKORC1), the target of warfarin (2). Hyperthyroidism accelerates factor catabolism and enhances warfarin sensitivity, increasing the risk of bleeding (3). Hypothyroidism impairs these processes, reducing warfarin potency with greater thrombotic potential (2). Corrective therapies, such as levothyroxine for hypothyroidism and methimazole for hyperthyroidism (e.g., Graves' disease), trigger INR instability during the transition to euthyroidism. Levothyroxine potentiates anticoagulation of warfarin, increasing the risk of supratherapeutic INR and hemorrhage, whereas methimazole attenuates warfarin effect, increasing the risk of subtherapeutic INR and thromboembolism[4-7].

Despite recognition in pharmacology references (e.g., Lexicomp and Micromedex) and guidelines from the American College of Cardiology/American Heart Association, these interactions remain underappreciated in busy cardiology practices, particularly among elderly patients with multiple comorbidities and polypharmacy. This retrospective case series reported eight consecutive valve replacement patients from a cardiology clinic during 2023-2025 who developed significant INR derangements after starting levothyroxine (n=4, supratherapeutic) or methimazole (n=4, subtherapeutic), despite prior stable chronic warfarin therapy. These cases highlight the clinical importance of intensified monitoring and multidisciplinary endocrinology-cardiology collaboration.

## Case Presentations

This single-center retrospective cohort study was conducted at the cardiology outpatient clinic of a tertiary teaching hospital in western Iran during 2023-2025. This study included adult patients (≥18 years) on chronic warfarin therapy for mechanical valve replacement with stable therapeutic INR values (2.5-3.5) for >3 months who initiated levothyroxine or methimazole for newly diagnosed hypothyroidism or hyperthyroidism, respectively, during the study period.

Inclusion criteria were documented INR derangement (supratherapeutic >5.0 or subtherapeutic <1.5) within 8 weeks of thyroid therapy initiation, with no confounding factors (e.g., new interacting drugs, dietary changes, illness, or poor compliance). Eight consecutive eligible cases were included (n=4 levothyroxine, n=4 methimazole).

Electronic medical records provided demographics (age and gender), clinical details (valve type and warfarin indication), thyroid function tests (thyroid-stimulating hormone [TSH] and free thyroxine [FT4] at baseline and follow-up), INR values (pre/post-thyroid therapy), warfarin dose adjustments, adverse events (bleeding per ISTH criteria; thrombotic events), and time to INR normalization. Descriptive statistics (mean and range) were used to summarize continuous variables, and categorical data were presented as frequencies. It should be mentioned that no inferential testing was performed due to case series design.

## Results

Eight patients (two males, six females; mean age=60 years, range=45-72 years) with mechanical valve replacements (five mitral, two combined mitral-aortic, and one aortic valve replacements) on stable chronic warfarin therapy experienced significant INR derangements after thyroid therapy initiation.

Group 1. Warfarin Toxicity Following Levothyroxine Initiation (n=4)

Table 1 summarizes the four cases of warfarin toxicity following levothyroxine initiation in mechanical valve patients with hypothyroidism.

### Case 1

The first case was a 45-year-old female with mechanical mitral valve replacement who had been receiving warfarin 5 mg/day for 2 years and had maintained a stable INR of 2.8–3.2 for 6 months. She was diagnosed with primary hypothyroidism (TSH=42 mU/L [0.4–4.0], FT4=0.45 ng/dL [0.8–1.8]). Levothyroxine 100 µg/day was initiated. On

day 14, the patient developed an INR of 6.8 with gum bleeding. Warfarin therapy was withheld for 2 days and subsequently resumed at 3.25 mg/day (35% reduction). The INR returned to the normal range (2.9) by week 4, and the TSH level normalized to 3.2 mU/L at 6 weeks.

**Table 1.** Warfarin Toxicity Post-Levothyroxine Initiation (n=4).

| Case | Age/ Sex | Valve Type | Warfarin Duration (Stable INR Duration) | Baseline Dose (INR) | TSH (mU/L) / FT4 (ng/dL) | Levothyroxine Dose | Peak INR (Day) | Adverse Event | Adjusted Dose (% Change) | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | 45/F | Mitral | 2 years (6 months) | 5 mg (2.8-3.2) | 42 / 0.45 | 100 mcg | 6.8 (14) | Gum bleeding | 3.25 mg (↓35%) | INR 2.9 wk4; TSH 3.2 wk6 |
| **2** | 52/F | Mitral | 6 years (12 months) | 6.55 mg (2.9) | 35 / 0.55 | 75 mcg | 5.5 (28) | None | 4 mg (↓41.7%) | INR 3.2 wk3; TSH 2.1 wk8 |
| **3** | 72/F | Mitral | 17 years (12 months) | 7.5 mg (3.1) | 38 / 0.4 | 50 mcg | 6.0 (28) | None | 6.25 mg (↓20%) | INR 2.8 wk4; TSH 1.8 wk6 |
| **4** | 65/M | Mitral-Aortic | 7 y (8 months) | 5 mg (3.2) | 48 / 0.35 | 150 mcg | 9.2 (21) | Epistaxis | 4 mg (↓20%) | INR 3.1 wk4; TSH 3.0 wk8 |

**Case 2**

Case 2 involved a 72-year-old female with mechanical mitral valve replacement who had been receiving warfarin therapy for 17 years and had a stable INR of 3.1 for 12 months. She had been taking warfarin 7.5 mg daily. She was diagnosed with overt hypothyroidism (TSH=38 mU/L [0.4–4.0], FT4=0.4 ng/dL (0.8–1.8). Levothyroxine 50 µg/day was initiated. On day 28, her INR increased to 6.0 with no bleeding. The warfarin dose was reduced to 6.25 mg daily (20% reduction), and the INR decreased to 2.8 by week 4. The TSH level was 1.8 mU/L at 6 weeks.

**Case 3**

This case was a 52-year-old female with mechanical mitral valve replacement who had been on warfarin 6.5 mg/day for 6 years and had maintained a stable INR of 2.9 for 12 months. She was diagnosed with overt hypothyroidism (TSH=35 mU/L (0.4–4.0), FT4=0.55 ng/dL (0.8–1.8). Levothyroxine 75 µg/day was initiated. On day 28, her INR increased to 5.5 without any symptoms. The warfarin dose was reduced to 4 mg/day (38% reduction), and the INR decreased to 3.2 by week 3. The TSH level was 2.1 mU/L at 8 weeks.

**Case 4**

Case 4 involved a 65-year-old male with mechanical mitral-aortic valve replacement who had been receiving warfarin 5 mg/day for 7 years with a stable INR of 3.2 for 8 months. He was diagnosed with post-thyroidectomy hypothyroidism (TSH=48 mU/L [0.4–4.0], FT4=0.35 ng/dL (0.8–1.8). Levothyroxine 150 µg/day was initiated. On day 21, the INR increased to 9.2 with epistaxis. The warfarin dose was reduced to 4 mg/day (20% reduction), and the INR was reduced to 3.1 by week 4. The TSH was 3.0 mU/L at 8 weeks.

Group 2. Subtherapeutic International Normalized Ratio Post-Methimazole Initiation (n=4).

Table 2 summarizes the four cases of subtherapeutic INR following methimazole initiation in mechanical valve patients with hyperthyroidism.

**Case 1**

The first case was a 55-year-old female with combined mechanical mitral-aortic valve replacement who had been receiving warfarin 3.25 mg/day for 3 years and had a stable INR of 2.9 for 10 months. She was diagnosed with Graves' disease (TSH<0.01 mU/L, FT4=4.1 ng/dL). Methimazole 20 mg/day was initiated. At week 3, her INR was 1.2, and the warfarin dose was increased to 5 mg/day (54% rise). The INR decreased to 2.8 by week 6. The TSH was 1.2 mU/L.

**Table 2.** Subtherapeutic INR Post-Methimazole Initiation (n=4)

| Case | Age/Sex | Valve Type | Warfarin Duration (Stable INR Duration) | Baseline Dose (INR) | TSH (mU/L) / FT4 (ng/dL) | Methimazole Dose | Nadir INR (Week) | Adjusted Dose (% Change) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| **1** | 55/F | Mitral-Aortic | 3 years (10 months) | 3.25 mg (2.9) | <0.01 / 4.1 | 20 mg | 1.2 (3) | 5 mg (↑54%) | INR 2.8 wk6; TSH 1.2 |
| **2** | 60/F | Mitral | 5 years (9 months) | 5 mg (3.0) | <0.01 / 3.7 | 15 mg | 1.1 (4) | 6.5 mg (↑30%) | INR 3.2 wk6; TSH 0.8 |
| **3** | 64/F | Aortic | 6 years (12 months) | 6.25 mg (2.7) | <0.01 / 3.9 | 30 mg | 1.3 (5) | 8.75 mg (↑40%) | INR 2.6 wk5; TSH 2.0 |
| **4** | 67/M | Aortic | 9 years (6 months) | 10 mg (3.4) | 0.02 / 3.5 | 20 mg | 1.0 (4) | 12.5 mg (↑25%) | INR 3.0 wk6; TSH 1.5 |

### Case 1

The first case was a 55-year-old female with combined mechanical mitral-aortic valve replacement who had been receiving warfarin 3.25 mg/day for 3 years and had a stable INR of 2.9 for 10 months. She was diagnosed with Graves' disease (TSH<0.01 mU/L, FT4=4.1 ng/dL). Methimazole 20 mg/day was initiated. At week 3, her INR was 1.2, and the warfarin dose was increased to 5 mg/day (54% rise). The INR decreased to 2.8 by week 6. The TSH was 1.2 mU/L.

### Case 2

Case 2 involved a 60-year-old female with mechanical mitral valve replacement who had been on warfarin 5 mg/day for 5 years and had a stable INR of 3.0 for 9 months. She was diagnosed with Graves' disease (TSH<0.01 mU/L, FT4=3.7 ng/dL). Methimazole 15 mg/day was initiated. At week 4, the INR was decreased to 1.1. The warfarin dose was increased to 6.5 mg/day (30% rise), and the INR reached 3.2 by week 6. The TSH was 0.8 mU/L.

### Case 3

Case 3 was a 64-year-old female with mechanical aortic valve replacement. She had been receiving warfarin 6.25 mg/day for 6 years and had a stable INR of 2.7 for 12 months. She was diagnosed with Graves' disease (TSH<0.01 mU/L, FT4=3.9 ng/dL). Methimazole 30 mg daily was initiated, and INR decreased to 1.3 by week 5. The warfarin dose was increased to 8.75 mg/daily (40% rise), and INR reached 2.6 by week 5. The TSH was 2.0 mU/L.

### Case 4

This case involved a 67-year-old male with mechanical aortic valve replacement who had been receiving warfarin 10 mg/day for 9 years. He had a stable INR of 3.4 for 6 months. He was diagnosed with Graves' disease (TSH=0.02 mU/L, FT4=3.5 ng/dL). Methimazole 20 mg daily was initiated, and INR decreased to 1.0 by week 4. The warfarin dose increased to 12.5 mg/day (25% rise). The INR reached 3.0 by week 6, and the TSH was 1.5 mU/L.

## Discussion

Thyroid hormones exert profound effects on hemostasis and drug metabolism, explaining the bidirectional warfarin interactions observed in this series. Levothyroxine initiation in hypothyroid patients restores euthyroidism, upregulating hepatic cytochrome P450 enzymes (particularly CYP2C9, responsible for S-warfarin clearance) and accelerating catabolism of vitamin K-dependent clotting factors (II, VII, IX, and X) through enhanced receptor-mediated degradation (2,7-9). This potentiates the anticoagulant effect of warfarin, typically manifesting as supratherapeutic INR within 2-4 weeks, precisely matching our Group 1 cases(10). Minor bleeding episodes (epistaxis, hematuria) in two patients underscore the hemorrhagic risk, though rapid intervention prevented major events.

Conversely, methimazole in hyperthyroid patients inhibits thyroid hormone synthesis, gradually normalizing FT4/FT3 levels over 2-6 weeks.

Heightened warfarin sensitivity of hyperthyroidism—driven by increased clotting factor turnover and altered VKORC1 expression—wanes as euthyroidism ensues, diminishes hypoprothrombinemic response, and yields subtherapeutic INR, as seen in Group 2 (INR=1.0-1.3 at 2-5 weeks) (3,4,11). Dose increases of 25-54% restored therapeutic INR levels without thromboses, consistent with the predictable temporal shift associated with the thyroid axis recovery.

Findings of the present study are consistent with those of prior reports that highlight the marked impact of thyroid status on warfarin response in patients with structural heart disease and valve populations. Several case reports and small series in the literature described dramatic INR elevations in hyperthyroid patients on warfarin, particularly in the setting of thyroid storm or uncontrolled Graves' disease, with INR values frequently exceeding 8–10 and associated major bleeding (e.g., gastrointestinal or intracranial hemorrhage) (3,5,12,13). In these reports, the mechanism is attributed to increased turnover of vitamin K–dependent clotting factors and enhanced sensitivity to a given warfarin dose, where warfarin requirements decrease substantially during the hyperthyroid phase. As antithyroid therapy is introduced and thyroid function normalizes, the same patients often require progressive warfarin dose escalation to maintain INR within the therapeutic range (4,14). This mirrors the pattern observed in our methimazole group, where subtherapeutic INR values of 1.0–1.3 necessitated 25–54% dose increases.

However, most previously published cases involve single patients or small heterogeneous cohorts (e.g., non-valvular atrial fibrillation, venous thromboembolism, or mixed cardiac indications). The present case series adds to this body of evidence by providing four consecutive mechanical valve patients with overt hyperthyroidism who were treated with methimazole, all of whom showed a consistent decrease in INR after antithyroid initiation and required systematic warfarin dose titration. The uniformity of this response in a high-thrombotic-risk mechanical valve population strengthens the external validity of earlier observations that were largely limited to isolated cases.

On the hypothyroid side, levothyroxine-associated INR elevation has been recognized in pharmacology references and scattered case reports, but detailed data in mechanical valve patients remain sparse (6, 7). The levothyroxine group in the present study, which exhibited peak INR values of 5.5–9.2, extends this literature by quantifying the magnitude of dose reduction (20–42%) needed in chronically anticoagulated valve patients with long-standing stable INR values before thyroid replacement. This supports the concept that normalization of thyroid function in hypothyroidism effectively mimics a shift towards a more hypermetabolic coagulation state, unmasking an increased response to warfarin as hepatic synthesis and clearance of clotting factors accelerate (8,15). It is noteworthy that while earlier reports often emphasize either the theoretical mechanism or single dramatic cases, our data provide practical ranges and time frames for clinicians, indicating significant INR changes within a few weeks of starting thyroid therapy and adjustment magnitudes large enough to be clinically meaningful in mechanical valve patients.

**Management Recommendations**

Weekly INR monitoring for 4-6 weeks post-thyroid therapy initiation, followed by biweekly monitoring until INR stabilization, is essential. Following the initiation of levothyroxine, the warfarin dose should be reduced by at least 20% preemptively and be adjusted further according to INR response. Conversely, following the initiation of methimazole, the warfarin dose should be increased by at least 25% as FT4 normalizes, titrating based on serial INR measurements. Patient education regarding bleeding symptoms (bruising, epistaxis, and hematuria) and thrombotic signs (dyspnea and leg swelling) is critical, with low-molecular-weight heparin bridging considered during adjustments for high-thrombotic-risk mechanical valve patients.

**Limitations**

This single-center retrospective case series (n=8) has key limitations. The small sample size limits statistical power and generalizability beyond Iranian mechanical valve patients. Moreover, there were no control groups, though confounders were minimized by strict inclusion criteria. CYP2C9/VKORC1

genotyping was absent; 5 mg tablet splitting introduced minor dosing variability. The short-term follow-up (6-8 weeks) captured acute interactions but missed long-term outcomes. Consistent bidirectional INR patterns across cases maintain clinical relevance despite constraints.

## Conclusion

Warfarin-thyroid interactions remain clinically relevant in mechanical valve patients despite direct oral anticoagulants alternatives. This Iranian case series demonstrated predictable INR instability following levothyroxine (supratherapeutic, requiring ≥20% dose reduction) or methimazole initiation (subtherapeutic, requiring ≥25% dose increase). Weekly INR monitoring for 4-6 weeks, preemptive adjustments, patient education, and endocrinology collaboration optimize safety. These findings underscore proactive anticoagulation management when correcting thyroid dysfunction in high-risk cardiology patients.

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## Availability of data and materials

All data supporting the findings of this case series are fully provided within the article.

## Consent for publication

No individual patient consent was required. All data are fully de-identified (no names/identifiers)

## Conflict of interest

The authors declare that they have no conflict of interest regarding the present study.

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