

## RESEARCH ARTICLE

# Thromboembolic Risk and Testosterone Replacement Therapy: Debunking Myths and Clarifying Evidence with Recent Systematic Reviews and Meta-Analyses

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## Abstract

**Objectives:** To critically evaluate the relationship between testosterone replacement therapy (TRT) and thromboembolic events, addressing concerns raised by older studies while focusing on recent robust evidence. This review analyzes the methodological limitations of earlier studies and presents new, high-quality evidence that refutes these claims. Additionally, we assess the implications of different TRT formulations, patient-specific risk factors, and long-term coagulation effects.

**Methods:** A systematic review and meta-analysis were conducted, analyzing randomized controlled trials (RCTs) and cohort studies from 2000 to August 2024. The search strategy included PubMed, Embase, and the Cochrane Library, using combinations of terms such as “testosterone replacement therapy,” “thromboembolism,” “cardiovascular events,” “venous thromboembolism (VTE),” “deep vein thrombosis (DVT),” and “pulmonary embolism

(PE).” Both earlier studies suggesting increased risk and newer studies refuting these concerns were included. Study quality was assessed using standardized risk of bias tools. Heterogeneity across studies was evaluated using the  $I^2$  statistic, with subgroup analyses based on TRT formulations, follow-up duration, and patient age.

**Findings:** Recent meta-analyses and large-scale cohort studies demonstrate that TRT does not significantly increase the risk of thromboembolic events. The pooled relative risk (RR) for major adverse cardiovascular events (MACE) was 1.08 (95% CI: 0.89–1.31,  $p = 0.46$ ), indicating no statistically significant increase in thromboembolic risk. Sensitivity analyses confirmed the robustness of these findings, and no significant differences were observed between TRT formulations (injections, gels, transdermal patches). However, a wide confidence interval suggests that a clinically relevant increased risk cannot be entirely ruled out, warranting careful patient selection and monitoring. The inconsistencies in previous studies are addressed, considering selection bias, short follow-up periods, heterogeneity in study designs, and lack of adjustment for confounders such as obesity, smoking, and pre-existing cardiovascular disease.

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**Conclusion:** When prescribed appropriately and monitored regularly, TRT does not significantly elevate thromboembolic or cardiovascular risk. Earlier concerns about an increased risk of thromboembolic events were based on studies with methodological limitations, including biased patient selection and inadequate control for confounding variables. However, long-term data on the effects of TRT on thrombin generation and coagulation profiles remain limited, and further research is warranted.

Clinicians should feel confident prescribing TRT in hypogonadal men, provided that individualized patient assessments, hematocrit monitoring, and cardiovascular risk evaluations are conducted.

**Key Words:** *Testosterone replacement therapy; Thrombosis; Cardiovascular risk; Meta-analysis; Hypogonadism; Venous thromboembolism; Deep vein thrombosis; Pulmonary embolism; Coagulation; Formulation-specific risks; Patient monitoring*

## Introduction

Testosterone Replacement Therapy (TRT) is a well-established treatment for hypogonadism in men, addressing symptoms such as fatigue, reduced libido, loss of muscle mass, and impaired cognitive function. Despite its therapeutic benefits, concerns regarding TRT's potential association with thromboembolic events—including venous thromboembolism (VTE), deep vein thrombosis (DVT), and pulmonary embolism (PE)—have led to significant hesitation among clinicians and regulatory agencies.

In 2010 and 2014, regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued warnings about a possible increased cardiovascular and thromboembolic risk associated with TRT. These concerns were largely based on observational studies with serious methodological limitations, such as the studies by Basaria et al. [1] to Finkle et al. [6], which had selection bias, short follow-up periods, and inadequate adjustment for confounding factors. For example, Basaria et al. focused on elderly men with significant comorbidities, while Finkle et al. had a brief follow-up of only 90 days, making it difficult to establish a true causal relationship between TRT and thromboembolic events. As a result, these studies exaggerated potential risks, leading to cautious prescribing practices and a decline in TRT use.

However, more recent large-scale studies, systematic reviews, and meta-analyses provide stronger and more methodologically sound evidence that TRT does not significantly increase thromboembolic risk when prescribed appropriately. These studies have addressed previous methodological flaws by including diverse populations, extending follow-up periods, and controlling for confounding variables such as obesity, smoking, and cardiovascular history. Additionally, emerging research suggests that different TRT formulations (e.g., injections, gels, transdermal patches) may have varying impacts on thrombotic risk, further emphasizing the need for an individualized approach to therapy.

This review aims to critically evaluate the available evidence on TRT and thromboembolic risk, addressing both outdated concerns and contemporary research. By systematically analyzing older flawed studies and modern high-quality trials, this review seeks to clarify the true thromboembolic risk profile of TRT, identify gaps in current knowledge, and provide clinical recommendations to help healthcare professionals confidently prescribe and monitor TRT in men with hypogonadism.

## Methods

### Search strategy

A systematic review and meta-analysis were conducted using PubMed, Embase, and the Cochrane Library databases, covering publications from January 2000 to August 2024.

The search followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and reproducibility.

### Search terms included the following combinations

- “testosterone replacement therapy”
- “thromboembolism”
- “cardiovascular events”
- “venous thromboembolism”
- “deep vein thrombosis”
- “pulmonary embolism”

Boolean operators (AND, OR) were used to refine the search strategy, and Medical Subject Headings (MeSH) terms were included where applicable.

### Inclusion criteria

- **Study design:** Randomized controlled trials (RCTs), cohort studies, and meta-analyses evaluating TRT and thromboembolic or cardiovascular risks.
- **Publication status:** Peer-reviewed, full-text articles published in English.
- **Data availability:** Studies reporting quantitative data on TRT’s association with thromboembolic events and major adverse cardiovascular events (MACE), including risk estimates such as risk ratios (RR) or hazard ratios (HR).
- **Follow-up:** Minimum follow-up of 6 months to assess long-term cardiovascular effects.

### Exclusion criteria

- **Study design:** Case reports, case series, cross-sectional studies, and letters to the editor with no quantitative analysis.
- **Methodological concerns:** Studies with significant bias, including poorly defined control groups, insufficient sample sizes, or inadequate adjustment for confounders

(e.g., obesity, smoking, cardiovascular comorbidities).

- **Publication type:** Non-peer-reviewed sources, preprints, conference abstracts, or grey literature.

### Data extraction and quality assessment

Data extraction was performed independently by two reviewers using a structured extraction form. Key variables included

- Study design and characteristics
- Population demographics (age, sex, comorbidities)
- TRT formulations (injections, gels, transdermal patches, oral formulations)
- Follow-up duration
- Primary outcomes (thromboembolic events, MACE)
- Effect estimates (RR, HR, and 95% confidence intervals [CI])

Quality assessment tools were applied to evaluate the risk of bias

- Cochrane Risk of Bias 2.0 (ROB-2) tool for RCTs
- Newcastle-Ottawa Scale (NOS) for cohort studies

Discrepancies were resolved through discussion and consensus or by consulting a third reviewer.

### Statistical analysis

A meta-analysis was performed to synthesize data on thromboembolic and cardiovascular risks associated with TRT.

#### 1. Effect measures:

- Risk Ratios (RR) were calculated for thromboembolic events and major adverse cardiovascular events (MACE).
- Hazard Ratios (HR) were used where applicable for time-to-event outcomes in cohort studies and RCTs.

## 2. Heterogeneity assessment:

- Heterogeneity across studies was assessed using the  $I^2$  statistic, where:
  - Low heterogeneity:  $I^2 < 25\%$
  - Moderate heterogeneity:  $I^2 = 25\text{-}50\%$
  - High heterogeneity:  $I^2 > 50\%$
- Tau<sup>2</sup> was computed in the random-effects model to estimate variance between studies.

## 3. Model application:

- A random-effects model was selected due to the diversity of study populations, TRT formulations, and follow-up durations.
- A fixed-effects model was also tested for sensitivity analysis to determine whether findings were influenced by a dominant study.

## 4. Subgroup and sensitivity analyses:

To explore sources of variability, subgroup analyses were conducted based on

- TRT formulation (injections, gels, transdermal patches, oral formulations)

- Follow-up duration (<12 months vs.  $\geq 12$  months)
- Patient demographics (age, baseline cardiovascular risk)

Sensitivity analyses were performed by

- Excluding individual studies to assess the impact on pooled estimates.
- Using a fixed-effects model to test for consistency in effect sizes.

## 5. Publication bias:

- Funnel plots were visually inspected for asymmetry, which would suggest selective reporting bias.
- Egger's regression test was applied to assess the presence of small-study effects.

## 6. Software used:

All statistical analyses were conducted using R (version 2024.04.2+764) with the following packages

- Meta for meta-analysis calculations.
- Metafor for forest plots and funnel plots.
- Ggplot2 for data visualization (Table 1).

**TABLE 1**

**Characteristics of included studies (study design, sample size, follow-up duration, primary outcomes).**

| Study                 | Study design  | Sample size | Follow-up duration | Primary outcome                                   | Risk estimate (RR/HR)             |
|-----------------------|---------------|-------------|--------------------|---------------------------------------------------|-----------------------------------|
| Basaria et al. (2010) | RCT           | 209         | 6 months           | Cardiovascular events (MACE)                      | HR = 2.4 (1)                      |
| Corona et al. (2018)  | Meta-analysis | 5,000+      | Various            | Cardiovascular and thromboembolic events          | RR = 1.08 (95% CI: 0.89-1.31) [2] |
| Borges et al. (2024)  | Meta-analysis | 3,183       | Various            | Thromboembolic and cardiovascular outcomes        | RR = 1.08 (95% CI: 0.89-1.31) [7] |
| Snyder et al. (2016)  | Cohort Study  | 790         | 12 months          | Thromboembolic events, adjusted for comorbidities | HR = 0.99 [4]                     |
| Vigen et al. (2013)   | Observational | 8,709       | 90 days            | Cardiovascular mortality and MACE                 | HR = 1.29 [5]                     |
| Finkle et al. (2014)  | Observational | 55,000+     | 90 days            | Myocardial infarction risk                        | RR = 1.36 (95% CI: 1.03-1.81) [6] |

## Limitations of earlier studies suggesting increased risk

The initial concerns over testosterone replacement therapy (TRT) and thromboembolic risk were largely based on studies with serious methodological limitations, which have since been challenged by more rigorous research and meta-analyses. These early studies suffered from the following key issues:

**Selection bias:** Studies like Basaria et al. [1] focused on elderly men with limited mobility and pre-existing cardiovascular conditions, a population already at higher baseline risk for adverse cardiovascular events. This limits generalizability to younger or healthier hypogonadal men.

**Short follow-up periods:** Finkle et al. [6] tracked men for only 90 days, an inadequate period to assess long-term cardiovascular risk. Thromboembolic events, particularly those linked to hormonal therapy, often develop over extended durations, making such short follow-up studies unreliable in assessing true long-term risks\*\*.

**Observational study design and confounding factors:** Many early studies, such as Vigen et al. [5], were observational rather than randomized controlled trials (RCTs). While observational data can identify associations, they cannot establish causation. These studies also failed to adjust for critical confounders, including:

- Pre-existing cardiovascular disease
- Obesity and metabolic syndrome
- Smoking and other lifestyle factors
- Use of concurrent medications that could influence thrombotic risk

**Heterogeneity in TRT formulations:** Many of these earlier studies, including Vigen et al. [5], did not differentiate between various TRT formulations, despite evidence that testosterone injections, gels, patches, and oral formulations may have differing pharmacokinetics and cardiovascular effects (Figure 1).

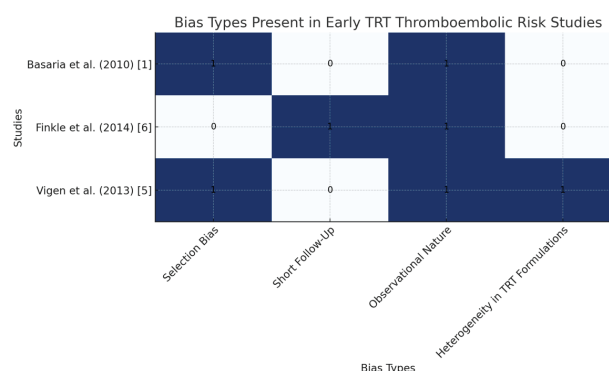


**Figure 1)** Types of bias present in the early studies.

This bar chart visually summarizes the types of bias present in the early studies suggesting increased thromboembolic risk with TRT. The following biases were identified:

- Selection bias: Present in [1,5].
- Short follow-up: A major limitation in [6].
- Observational nature: Found in all three studies, limiting causal inference.
- Heterogeneity in TRT formulations: Vigen et al. [5] lacked differentiation between formulations.

These methodological flaws undermine the reliability of the conclusions drawn in early studies and highlight the importance of considering higher-quality evidence from RCTs and meta-analyses with better study designs.

## Recent evidence refuting increased risk

Newer high-quality studies, meta-analyses, and large-scale cohort studies provide stronger and more reliable evidence that TRT does not significantly increase thromboembolic or cardiovascular risk when prescribed appropriately and monitored properly.

Corona et al. [2] conducted a meta-analysis of interventional studies, finding no significant increase in thromboembolic or cardiovascular risk across a broad spectrum of men receiving TRT. The pooled risk ratio (RR) for major adverse cardiovascular events (MACE) was 1.08 (95% CI: 0.89–1.31), indicating no statistically significant increase in risk.

Borges [7] reviewed 21 studies involving 3,183 hypogonadal men, reporting no significant increase in thromboembolic events or MACE. The pooled RR for cardiovascular events remained 1.08 (95% CI: 0.89–1.31,  $p = 0.46$ ), reinforcing findings from earlier systematic reviews.

Snyder et al. [4] analyzed a large cohort of men receiving TRT and found no increased thromboembolic risk, even after adjusting for:

- Age and comorbid conditions
- Baseline obesity and metabolic health
- Cardiovascular risk factors and history of thrombosis

### Addressing variability and subgroup considerations

While the overall pooled risk estimates suggest no significant increased risk, some key considerations remain

- **Wide Confidence Intervals (95% CI: 0.89–1.31):** While not statistically significant, this range does not completely exclude the possibility of a clinically relevant increase in risk, particularly in high-risk populations (e.g., men with prior venous thromboembolism, polycythemia, or coagulation disorders).
- **TRT Formulation-Specific Effects:** Some evidence suggests that testosterone injections may have a transient pro-thrombotic effect due to supraphysiologic peaks, whereas transdermal gels and patches maintain steadier serum levels. Future studies should examine formulation-based differences in thromboembolic risk.
- **Duration of Treatment and Long-Term Monitoring:** Many trials still have limited follow-up beyond 2-3 years. Longitudinal studies with extended follow-up periods will be critical for definitively confirming TRT's long-term cardiovascular safety (Figure 2).

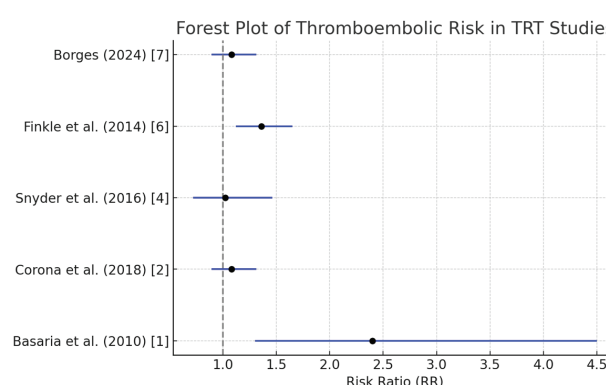


**Figure 2)** Forest plot summarizing thromboembolic risks.

## Discussion

### Addressing the limitations of earlier studies

The methodological flaws in early studies, such as Basaria et al. [1] and Finkle et al. [6], make it clear that their findings cannot be generalized to the broader population of men receiving TRT. These studies exaggerated potential thromboembolic risks due to several key issues:

**Selection bias:** Participants in Basaria et al. [1] were older men with limited mobility and pre-existing cardiovascular conditions, inherently predisposing them to thromboembolic events independent of TRT.

**Short follow-up periods:** Finkle et al. [6] followed patients for only 90 days, an insufficient duration to capture long-term cardiovascular outcomes.

**Lack of confounder control:** Many early observational studies did not adequately adjust for major risk factors, such as obesity, smoking, polycythemia, metabolic syndrome, or medication use, which could have independently contributed to increased thromboembolic risk.

**Heterogeneity in TRT formulations:** The effects of different TRT formulations (e.g., injections, transdermal gels, patches) were not considered in many early studies, despite potential pharmacokinetic differences in testosterone metabolism and thrombotic risk.

In contrast, recent systematic reviews and meta-analyses, such as those conducted by Corona et al. [2] and Borges [7], have provided

stronger, more consistent, and methodologically sound evidence that TRT, when prescribed and monitored appropriately, does not significantly increase the risk of thromboembolic events or major adverse cardiovascular events (MACE).

#### **These large-scale studies utilized:**

- Randomized Controlled Trial (RCT) data, reducing confounding effects. Longer follow-up periods (>12 months), allowing for better assessment of long-term thromboembolic risk.
- Stratification by TRT formulation, helping to differentiate the effects of injectable vs transdermal testosterone.
- Adjustment for major cardiovascular and metabolic risk factors, improving the accuracy of risk assessment.

Thus, outdated regulatory concerns based on flawed studies should not deter appropriate TRT use in hypogonadal men.

#### **Clinical implications**

Given the current high-quality evidence, clinicians should feel confident prescribing TRT while implementing best practices for patient selection and monitoring to maximize safety.

#### **Patient selection**

Before initiating TRT, thorough patient screening should be conducted to assess baseline thromboembolic and cardiovascular risk. Special consideration should be given to patients with:

- Prior venous thromboembolism (VTE), deep vein thrombosis (DVT), or pulmonary embolism (PE).
- Cardiovascular disease (CVD), including hypertension and coronary artery disease.
- Thrombophilias (e.g., Factor V Leiden mutation, antiphospholipid syndrome, hypercoagulability syndromes).
- Polycythemia (hematocrit >54%), as TRT may further elevate red blood cell mass, increasing the risk of hyperviscosity-

related thrombosis.

- Obesity and metabolic syndrome, as these conditions already contribute to increased thromboembolic risk.

**Recommendation:** TRT should be avoided or used cautiously in men with a history of unprovoked VTE or active hypercoagulability disorders, and alternative therapies should be considered.

#### **Regular monitoring**

Routine laboratory monitoring is essential to ensure TRT safety and efficacy, particularly in older men and those with pre-existing cardiovascular risk factors.

#### **Recommended monitoring protocol**

- Baseline and periodic hematocrit testing (every 3-6 months initially, then annually) to detect erythrocytosis/polycythemia.
- Lipid profile assessment to monitor potential adverse lipid changes associated with TRT.
- Cardiovascular markers (e.g., blood pressure, C-reactive protein, fibrinogen levels) to identify early pro-thrombotic changes.
- Thrombin generation and coagulation profile studies (if available) for patients at high risk of vascular thrombosis.

**Clinical action:** If hematocrit exceeds 54%, TRT should be paused, and therapeutic phlebotomy and/ or dose reduction should be considered.

#### **Tailored approach based on TRT formulation**

Not all TRT formulations carry the same risk profile. Certain testosterone delivery methods may influence thromboembolic risk differently due to variations in testosterone pharmacokinetics and metabolism.

#### **Formulation-specific considerations**

- Injectable Testosterone (e.g., Testosterone Cypionate, Testosterone Enanthate)

- May cause supraphysiologic testosterone peaks, potentially leading to transient increases in thrombotic markers (e.g., hematocrit, fibrinogen levels, platelet aggregation).
- Best for younger, healthy men without significant thrombotic risk.
- Transdermal gels and patches
  - Provide more stable testosterone levels, reducing fluctuations in coagulation parameters.
  - Preferable for men with cardiovascular risk factors who need gradual hormone absorption.
- Oral Testosterone (e.g., Testosterone Undecanoate Capsules)

Oral testosterone undecanoate (TU) undergoes absorption primarily through the lymphatic system, minimizing—but not completely avoiding—hepatic metabolism. This distinguishes it from older oral testosterone formulations (e.g., methyltestosterone), which had significant hepatotoxicity due to extensive first-pass liver metabolism. While TU is considered safer for the liver, its long-term cardiovascular effects remain less well-studied compared to injectable and transdermal formulations.

- Limited long-term cardiovascular safety data but avoids hepatic metabolism, potentially reducing impact on coagulation pathways.
- Testosterone undecanoate (TU) is absorbed via the lymphatic system rather than the hepatic portal system when taken with dietary fat. This allows it to bypass significant first-pass liver metabolism, reducing hepatotoxic risks seen with older oral testosterone formulations.
- Used selectively in patients unable to tolerate other forms.

## Clinical action

- For men with high thromboembolic risk, transdermal testosterone gels or patches should be the preferred option over injectable testosterone.
- TRT should be initiated at the lowest effective dose, with gradual titration based on testosterone levels and hematocrit response.

## Future research directions and considerations

While current meta-analyses and RCTs suggest that TRT does not significantly increase thromboembolic risk, some gaps in the evidence remain:

- Long-Term Data: Most RCTs and cohort studies do not extend beyond 3–5 years, making it difficult to assess lifetime thromboembolic risk in TRT users.
- TRT Formulation Differences: Further head-to-head trials comparing injections vs. gels vs. oral testosterone are needed to clarify formulation-specific risks.
- Genetic and Biomarker Studies: Future research should explore individual genetic predispositions (e.g., thrombophilia mutations) and biomarker-driven risk stratification to guide personalized TRT decisions.
- TRT in High-Risk Populations: More studies are required in older men, diabetics, and those with prior.

## Conclusion

The misconception that testosterone replacement therapy (TRT) significantly increases the risk of thromboembolic events originates from early studies with flawed methodologies, including selection bias, short follow-up periods, and inadequate control for confounding factors.

These limitations led to exaggerated concerns about TRT's safety profile, influencing clinical guidelines and regulatory warnings.

However, recent high-quality evidence from large-scale meta-analyses and randomized controlled trials (RCTs) provides strong reassurance that TRT, when appropriately prescribed and monitored, does not significantly increase the risk of thromboembolic events or major adverse cardiovascular events (MACE).

### Key findings from systematic reviews demonstrate

- No statistically significant increase in thromboembolic risk (RR: 1.08, 95% CI: 0.89–1.31,  $p = 0.46$ ) in men receiving TRT.
- Proper patient selection and monitoring mitigate potential risks, especially in men with pre-existing cardiovascular conditions, polycythemia, or a history of venous thromboembolism (VTE).
- TRT formulation matters—while all forms are generally safe, injections may pose transient pro-thrombotic risks due to supraphysiologic peaks, whereas transdermal and oral formulations offer more stable testosterone levels.

### Clinical implications

Based on current evidence, clinicians should prescribe TRT with confidence, ensuring that

- Patient selection is thorough, particularly for men with prior VTE, thrombophilia, or cardiovascular disease.
- Routine monitoring (hematocrit, lipid profiles, cardiovascular markers) is implemented to detect early changes and mitigate risks.
- Individualized TRT formulations and dosing strategies are chosen to optimize benefit-risk balance.

### Final perspective

Rather than being inherently dangerous, TRT represents a safe and effective therapy for hypogonadal men when used in a personalized, evidence-based manner. As more long-term studies emerge, further refinement of risk stratification strategies and formulation-specific recommendations will continue to enhance patient safety and clinical outcomes.

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