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Effects of gender affirming hormone therapy with testosterone on coagulation and hematological parameters in transgender people assigned female at birth: A systematic review and meta-analysis

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ABSTRACT

Background: Hormone replacement therapy is associated with an increased thromboembolic risk. The effects of testosterone (T) on coagulation markers in people assigned female at birth (AFAB) under gender affirming hormone therapy (GAHT) are not well described.

Methods: Systematic review and meta-analysis on English-language articles retrieved from PubMed, Scopus and Cochrane Library up to April 2023 investigating T therapy in AFAB people. Coagulation parameters included international normalized ratio (INR), fibrinogen, activated partial thromboplastin clotting time (aPTT), plasminogen activator inhibitor-1 (PAI-1); hematological variables included hemoglobin (Hb) and hematocrit (HCT). We also reported the rate of thromboembolic events. Data were combined as mean differences (MD) with a 95 % confidence interval (CI) of pre- vs post-follow-up values, using random-effects models.

Results: We included 7 studies (6 prospective and 1 retrospective) providing information on 312 subjects (mean age: 23 to 30 years) who underwent GAHT with variable T preparation. T therapy was associated with a significant increase in INR values [MD: 0.02, 95 % confidence interval (CI): 0.01–0.03; $p = 0.0001$], with negligible heterogeneity ($I^2 = 4$ %). T therapy was associated with increased Hb (MD: 1.48 g/dL, 95%CI: 1.17 to 1.78; $I^2 = 9$ %) and HCT (4.39 %, 95%CI: 3.52 to 5.26; $I^2 = 23$ %) values. No effect on fibrinogen, aPTT and PAI-1 was found. None of the study reported thromboembolic events during the follow-up.

Conclusion: Therapy with T increased blood viscosity in AFAB men. A slight increase in INR values was also found, but the clinical relevance and mechanism(s) of this finding needs to be clarified.

1. Introduction

"Gender incongruence" (GI) is a diagnostic term used in the 11th Revision of the International Classification of Diseases (ICD-11) to describe a person's marked and persistent experience of incompatibility between gender identity and expected gender, based on sex assigned at birth [1,2]. Gender affirming hormone therapy (GAHT) is an elective treatment to mitigate such incongruence [3]. In trans women, also termed assigned male sex at birth (AMAB), hormonal treatment consists of estrogen administration, often in combination with antiandrogens, while in trans men, also termed assigned female sex at birth (AFAB), hormone treatment consists of testosterone (T), which is administered mainly in the form of gel or intramuscular injections. Hormone replacement therapy is a risk factor for venous thromboembolism (VTE), mainly when driven by estrogen dose and oral administration. The mechanisms of coagulation, especially from a pathophysiological point of view, with hypercoagulability and subsequent VTE have important differences in risk factors, absolute incidence, site of presentation, optimal management strategies, and prognosis between men and women [4–8]. In cisgender women, the use of oral contraceptives (depending on the dose of estrogen and type of progestin) [9] and hormonal replacement therapy for perimenopausal symptoms [10] represent a major risk factor for VTE, causing changes towards a pro-coagulant status: factors II, VII, VIII, IX, X, XI, protein C and fibrinogen increase; levels of antithrombin and protein S decrease and resistance to activated protein C (APCr) increases [11–14]. In contrast, available data on the effects of exogenous T on the coagulation profile of cisgender men are inconclusive. In a large case-crossover study, T therapy use was

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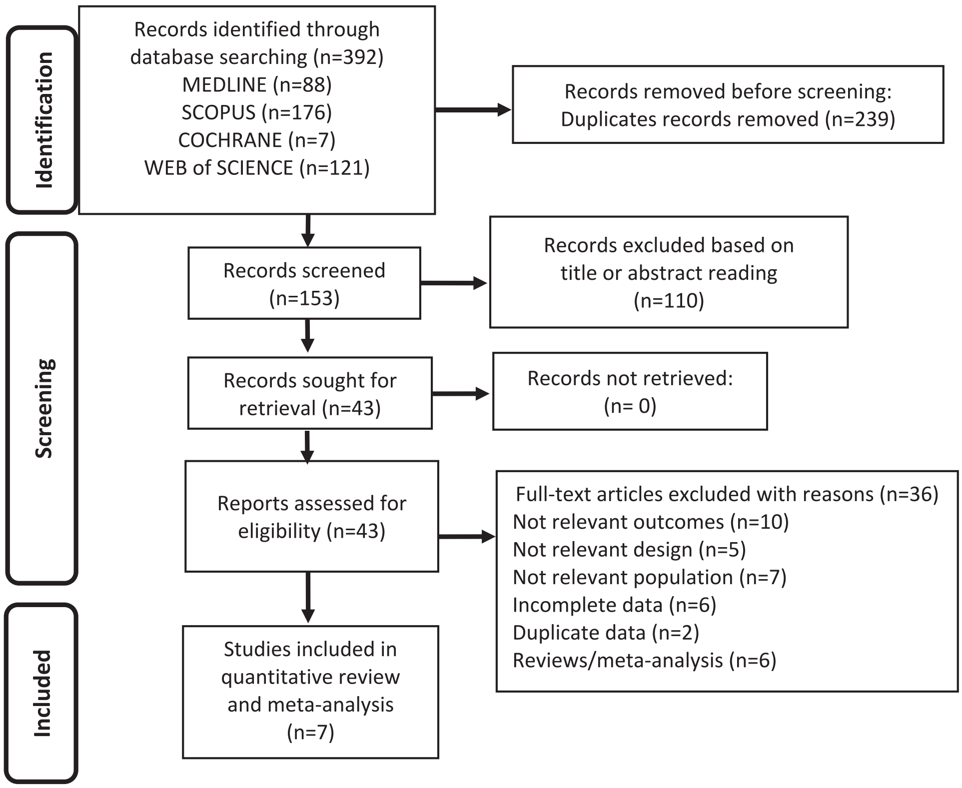

Fig. 1. Flowchart of the study selection process.

associated with a higher risk of VTE in men both with (odds ratio [OR]: 2.32, 95%CI: 1.97 to 2.74) and without (OR: 2.02, 95%CI: 1.47 to 2.77) hypogonadism in age-adjusted models [15]. This association was not confirmed in other studies [16,17]. In addition, T is typically used in men suffering from hypogonadism, where the underlying pathology may influence coagulation profiles [18]. The adverse effects of GAHT in people with GI are even less well defined, especially with regard to thrombotic risk. The few data available indicate a higher risk in AMAB and AFAB people receiving GAHT than in the general population, although apparently the effects of T on AFAB appears less relevant [19]. However, the pathophysiological mechanisms underlying this evidence are not fully elucidated. The results of studies of AMAB women taking estrogens, summarized in a recent meta-analysis [20], showed an increased rate of VTE, depending on age and duration of treatment, while the effects of exogenous T on coagulation mechanisms and thrombosis risk in trans men on GAHT appear more controversial. In a recent large cohort study, the risk of VTE in transgender males was not increased compared with cisgender women of the same age [16], and to date the effects of T on the coagulation system in AFAB trans males are largely unknown. On this basis, the aim of our study was to evaluate, through a meta-analytic approach, the effects of 12 months of T-based GAHT on coagulation parameters in AFAB men.

2. Materials and methods

The meta-analysis was conducted according to the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [21]; it also complies with the guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) [22]. Being a systematic review with meta-analysis, the study did not directly enroll human participants. The Declaration of Helsinki was adequately addressed, and no specific permissions were required for corresponding locations. The study protocol was registered in the international prospective registry for systematic reviews (PROSPERO) with registration number CRD42023409749.

2.1. Systematic search strategy

A systematic search was conducted in PubMed, Scopus, Cochrane Library and Web of Science to identify all relevant English-language studies published up to April 2023 without defining a start date for the search. Strategy search was performed using the following terms: (transgender OR FTM OR “female to male” OR “trans men” OR transmen OR AFAB) AND (testosterone OR “gender affirming hormone therapy” OR GAHT) AND (coagulation OR INR OR “international normalized ratio” OR fibrinogen OR PT OR APTT OR “prothrombin time” OR “activated partial thromboplastin time” OR platelets OR thromboembol* OR thrombosis OR “venous thromboembolism” OR VTE). If it was not clear from reading the abstract whether the study contained relevant data, the full text was retrieved. The identification of eligible studies was carried out by two independent authors (D.T., D.P.), and disagreements resolved by a third researcher (A.B.). References cited in all articles were also manually searched to identify possible additional studies.

2.2. Inclusion and exclusion criteria

The selection of articles for inclusion was carried out in several stages. In the identification phase, database queries identified potentially eligible studies that could be included in the meta-analysis. After removal of repeated articles (same article found in more than one database), in the second phase, papers of possible interest were screened by reading the title and abstract. In the third phase, the remaining articles were assessed in full text for eligibility. The eligibility inclusion criteria used for the study were: (1) Observational studies, both prospective and retrospective, as well as longitudinal intervention studies, enrolling AFAB people aged 18 years or older receiving T-based GAHT; (2) availability of mean ± standard deviation (SD) values or data for its calculation for coagulation/hematological parameters: *International*

Table 1
Main characteristics of the included studies.

Author	Year	Country	Study design	N	Age* (years)	Testosterone preparation	Follow-up (months)	Primary endpoint(s)				TE events (number)
								INR	aPTT (sec)	Fibrinogen (g/l)	PAI-1 (ng/ml)	
Aranda	2019	Spain	Prospective	20	27 ± 8	TU, TG	Up to 12				Pre: 23.5 ± 9.4 Post: 23.1 ± 6.9	NR
Gava (a)	2018	Italy	Retrospective	25	30 ± 5	TU	Up to 60	Pre: 1.03 ± 0.07 Post: 1.05 ± 0.07	Pre: 1.05 ± 0.1 Post: 1.06 ± 0.09			0
Gava (b)	2018	Italy	Retrospective	25	30 ± 7	TE	Up to 60	Pre: 1.02 ± 0.03 Post: 1.05 ± 0.04	Pre: 1.06 ± 0.15 Post: 1 ± 0.13			0
Giltay	1999	Netherlands	Prospective	15	26 ± 6	TP	Up to 12				Pre: 28.8 ± 19.5 Post: 24.3 ± 13.3	NR
Mueller	2007	Germany	Prospective	28	30 ± 9	TU	12	Pre: 1.01 ± 0.03 Post: 1.02 ± 0.03		Pre: 2.71 ± 0.27 Post: 2.74 ± 0.36		0
Pelusi (a)	2014	Italy	Prospective	15	31 ± 5	TED	12	Pre: 1.01 ± 0.05 Post: 1.05 ± 0.06	Pre: 1.01 ± 0.14 Post: 0.99 ± 0.14	Pre: 3.01 ± 0.5 Post: 3.17 ± 0.6		0
Pelusi (b)	2014	Italy	Prospective	15	28 ± 4	TG	12	Pre: 1.04 ± 0.07 Post: 1.05 ± 0.08	Pre: 0.98 ± 0.15 Post: 1.04 ± 0.14	Pre: 2.88 ± 0.6 Post: 3.09 ± 0.75		0
Pelusi (c)	2014	Italy	Prospective	15	29 ± 4	TU	12	Pre: 1.05 ± 0.04 Post: 1.09 ± 0.06	Pre: 1.08 ± 0.12 Post: 1.08 ± 0.12	Pre: 2.85 ± 0.5 Post: 2.69 ± 0.6		0
Scheres	2020	Netherlands	Prospective	100	27 ± 10	MTE, TG	12			Pre: 3.2 ± 0.92 Post: 3.18 ± 0.88		0
Schutte	2022	Netherlands	Prospective	47	23 ± 5	TG	Up to 12			Pre: 3.5 ± 0.5 Post: 3.2 ± 0.6	Pre: 22.7 ± 3.83 Post: 21 ± 6.1	NR

Abbreviations. aPTT: activated partial thromboplastin time; INR: *international normalized ratio;* MTE: mixed testosterone esters; NR: not reported; PAI-1: *plasminogen* activator *inhibitor*-1; TE: testosterone enanthate; TED: testosterone enanthate depot; TE: thromboembolic; TG: testosterone gel; TP: testosterone propionate; TU: testosterone undecanoate.

* Age is expressed as mean ± SD.

Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT), fibrinogen, *Plasminogen Activator Inhibitor*-1 (PAI-1), hemoglobin (Hb) and hematocrit (HCT). Exclusion criteria were: (1) not relevant study design (non-experimental descriptive studies, studies carried out in populations other than that of interest, studies in which endpoints other than those under analysis were evaluated); (2) studies with incomplete or inaccurate data were excluded. Two independent reviewers (D.T., A. B.) assessed the full text of all selected studies to establish eligibility, and any disagreements were resolved through an open discussion involving a third reviewer (D.P.). The PRISMA flow-chart [23] was used to schematize the steps of article inclusion.

2.3. Quality assessment

The methodological quality of the included studies was assessed using the Effective Public Health Practice Project Quality assessment

Table 2
Quality assessment of included studies by Effective Public Health Practice Project Quality assessment tool (EPHPP).

Study	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Global rating
Aranda 2019	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Gava 2018	Moderate	Strong	Strong	Weak	Strong	Strong	Moderate
Giltay 1999	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Mueller 2007	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Pelusi 2014	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Scheres 2020	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate
Schutte 2022	Moderate	Moderate	Strong	Weak	Strong	Strong	Moderate

tool (EPHPP) [24]. This assessment tool, used for intervention studies such as randomized controlled trials and case-control studies, has been validated for use in systematic reviews as well [25]. The tool evaluates six domains: selection bias, study design, confounding factors, study blindness, data collection method and loss to follow-up. The quality of each domain can be assessed as strong (strong), moderate (moderate) or weak (weak), and in the overall judgement the quality can be assessed as 'strong', if no weak score was assigned, 'moderate', if only a weak judgement was assigned to one of the domains, and finally, 'weak', if two or more weak judgements were assigned to several domains. The assessment was performed independently by two reviewers (A.B., D.P.), with a third reviewer involved to resolve any discrepancies in judgement (D.T.).

2.4. Data extraction

Data were extracted from the studies selected by two independent reviewers (A.B., D.T.). The primary outcome evaluated was the mean pre- vs. post-treatment difference in coagulation parameters (INR, aPTT, fibrinogen, PAI-1) assessed basally and after one year of T-based GRHT in AFAB subjects, while changes in Hb and HCT of the same subjects were evaluated as secondary outcomes. Additional information extracted was: first author, year of publication, country/geographical region, study design, sample size, mean age of the study population, T formulations and duration of follow-up in months. Data were combined as mean differences (MD) with a 95 % confidence interval (CI) using random-effects models.

2.5. Statistical analysis

The mean difference between the pre/post-follow-up values for each end point was used as effect estimates. Despite the absence of heterogeneity, DerSimonian and Laird's random-effects model was used to generate a more conservative estimate of the overall effect [26]. The Cochran's Chi-square test (Cochran's Q) and the I^2 test were used to analyze statistical heterogeneity between the results of the different studies: an $I^2 \geq 50$ % and/or a *P*-value <0.05 indicated significant heterogeneity [27]. Publication bias was identified both graphically using funnel plots and numerically by performing Egger's test [28]. Data analysis was performed using the "metafor" package of the statistical software R (version 3.6.3, 2020; The R Foundation for Statistical Computing, Vienna, Austria) and the Review Manager (RevMan) of the Cochrane Library (version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

3. Results

3.1. Selection of studies

The electronic search yielded a total of 304 articles. After the removal of duplicates, 153 articles were obtained, of which 110 were excluded, because they were deemed irrelevant based on title and/or abstract reading. Thus, as shown in Fig. 1, a total of 43 articles were identified, of which 7 met the inclusion criteria [18,29–34]. Details of the main characteristics of the articles included in the quantitative analysis are shown in Table 1.

3.2. Quality of included studies

The quality assessment, based on the EPHPP, is presented in Table 2. All studies included received moderate quality scores, mainly due to the absence of double-blind randomization procedures.

3.3. Summary of results

Overall, the studies included, both prospective ($n = 6$) [18,29,31–34] and retrospective ($n = 1$) [30], gave information about a total sample of 312 AFAB people undergoing therapy with various T formulations over a time frame of 12 months. Mean age ranged from 23 to 30 years. All studies were performed in Europe.

Subjects were treated with mixed T esters in 1 study [18], T enanthate/depot in 2 studies [30,33], T gel in 3 studies [18,29,33], T propionate in 1 study [31], and T undecanoate in 4 studies [29,30,32,33]. Regarding the primary outcomes, the pooled estimate indicated that T therapy was associated with a significant increase in INR values (MD: 0.02, 95%CI: 0.01 to 0.03; $p = 0.0001$) (Fig. 2A), in the substantial absence of heterogeneity ($I^2 = 4$ %; $p = 0.39$). On the contrary, none of the other primary outcomes studied appeared to change significantly at the end of the follow-up, including aPTT (Fig. 2B) plasma concentration of fibrinogen (Fig. 2C) and PAI-1 (Fig. 2D). Finally, as expected with regard to secondary outcomes, T therapy produced significant increases in Hb values of about 1.5 g (Fig. 2E) and HCT values of almost 4.5 percentage points (Fig. 2F).

3.4. Publication bias

Although the asymmetry of the results of the INR studies at the funnel plot could suggest a possible publication bias (Fig. 3), the degree of asymmetry was not significant at the Egger's test ($p = 0.3$).

4. Discussion

This is the first systematic literature review with meta-analysis on the effects of 12 months of masculinizing T therapy on coagulation and blood parameters in a population of AFAB adults, showed an increased blood viscosity in subjects taking T along with a statistically significant lengthening of INR values.

In recent years, an increasing number of gender incongruity studies have investigated cardiovascular thrombo-embolic risk related to GAHT [35–38]. A recent retrospective study [19] compared the risk of cardiovascular events between cis- and trans-gender subjects. The study population included all subjects aged 10 years and older in Sweden linked to the Swedish national health registries (2006–16). Two comparison groups without GI or GAHT were matched (1:10) by age, county of residence, and assigned male and female sex at birth, respectively. Among the 1779 transgender individuals (48 % AMAB, 52 % AFAB), 18 developed a cardiovascular (CV) event, most of which were conduction disorders, however. The CV event incidence for AFAB individuals with GI was 3.7 per 1000 person-years (95 % CI: 1.4 to 10.0), while AMAB individuals with GI had a CV event incidence of 7.1 per 1000 person-

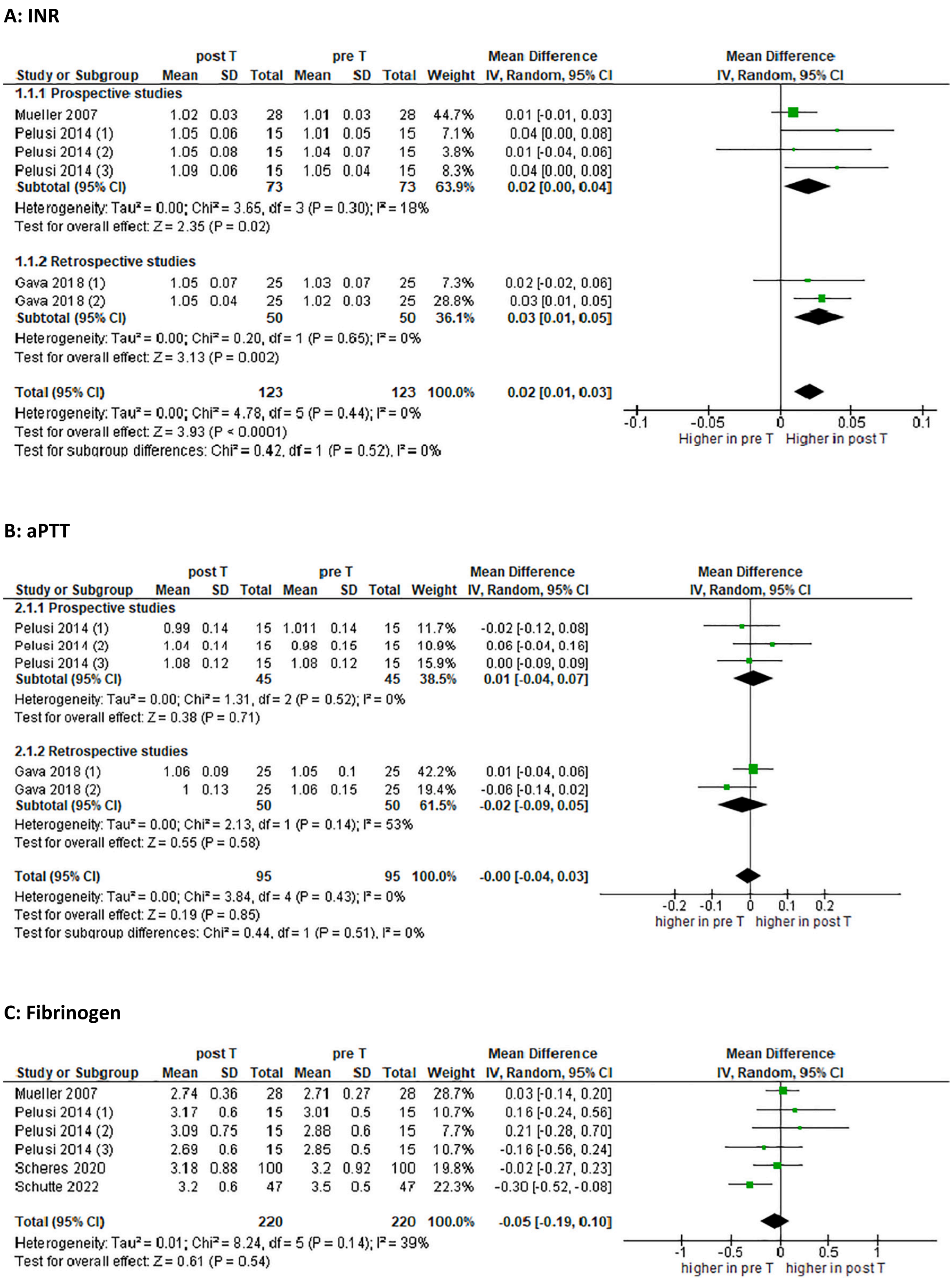

Fig. 2. Forest plot of the effects of testosterone therapy on coagulation parameters. Diamonds indicate the overall effect estimates (and diamond width the 95 % CI); squares indicate the weight of individual studies in the pooled estimate. CI, confidence interval; IV, inverse variance.

years (95 % CI: 4.2 to 12.0). The risk of cardiovascular disease (CVD) was 2.4 times higher in AMAB individuals [hazard ratio (HR): 2.4, 95 % CI: 1.3 to 4.2] than in cisgender women and 1.7 times higher than in cisgender men (HR: 1.7, 95 % CI: 1.0 to 2.9). Indeed, in both trans populations there was evidence of increased CV risk, in AFABs the risk and severity of such events was still lower, despite the well-known prothrombotic effects brought about by the increase in hematocrit percentage and mean hemoglobin concentration [39,40].

A study by Nota et al. [37] on 3875 transgender people showed a two-fold increase in myocardial infarction among AFAB transgender people compared to cis women, but not compared to cis men, versus a two-fold increase in stroke risk and a five-fold increase in VTE risk for

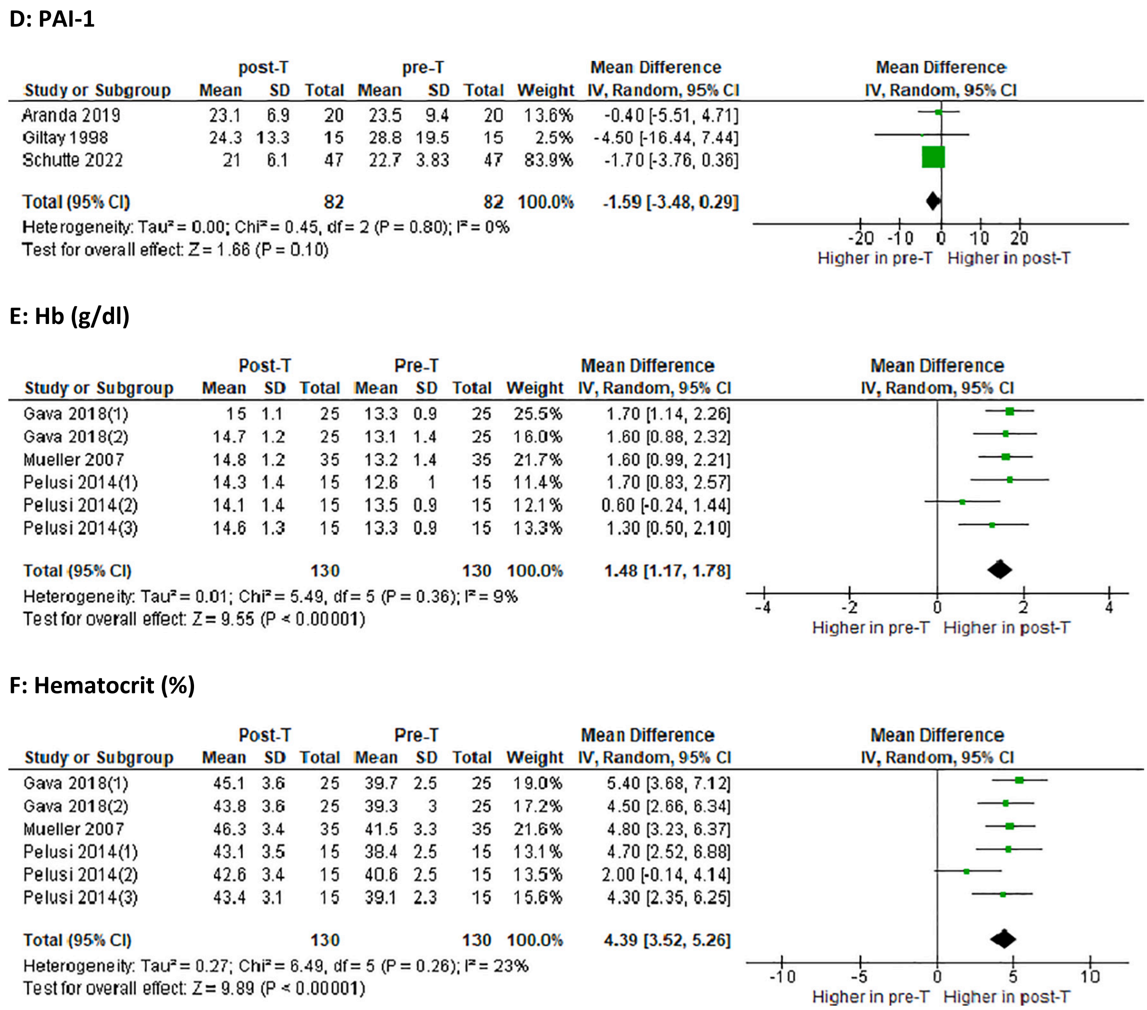

Fig. 2. (*continued*).

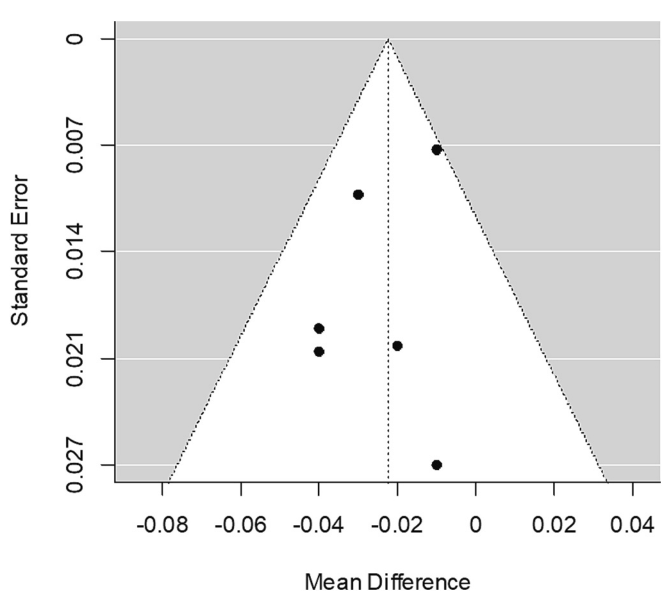

Fig. 3. Assessment of publication bias. Funnel plot and Egger's test for INR papers ($p = 0.3$).

AMAB transgender people compared to cis men and cis women. In a cross-sectional study of 50 transgender men on T therapy for an average of 10 years, no subjects experienced myocardial infarction, stroke, or deep vein thrombosis [41]. This latter evidence appears consistent with findings from the studies selected for our meta-analysis in which, where reported, no thromboembolic CV events were registered throughout the follow-up period.

In a case-control study, 138 transgender men on T therapy for an average of 7.4 years showed low CV morbidity: the prevalence of myocardial infarction was higher than in cisgender women, but there was no difference compared with cisgender men. After adjustment for CV risk factors, however, the study showed that transgender men still had a higher risk of myocardial infarction than both cisgender populations. Similar data emerged from a Dutch study of 1358 transgender men who used T, followed up for an average of 8 years: authors found three times as many heart attacks as cisgender women, with no differences compared to cisgender men and no differences in stroke occurrence compared to cisgender women or men [37].

In contrast to the findings in AMAB patients, in which the role of estrogen as pro-thrombotic factors is now extensively demonstrated [20,38,42,43], the role played by T, in both cis and trans men, is still controversial.

The here reported elongation of INR induced by T-based GAHT, while statistically significant, is likely to be of little clinical significance, given the small extent. Nevertheless, this effect is of interest in driving research into the still controversial and understudied possible pathophysiological mechanisms by which exogenous testosterone administration may affect the coagulation cascade.

Administration of physiological doses of T to elderly men with hypogonadism does not induce any significant changes in the coagulation system in terms of tissue factor (TF)-induced thrombin generation [44], whereas reduced thrombin generation, and thus a potential anticoagulant effect of T replacement therapy (TRT), has been reported in men with hypogonadism due to Klinefelter syndrome [45]. A very recent case-control study by Bøgehave et al. analyzed in detail the effect of TRT at physiologic doses on the capacity of TF and coagulation contact activation pathways and related coagulation factors and inhibitors in men with hypogonadism secondary to chronic opioid treatment, showing that TRT affects the coagulation system in an anti-coagulant sense through suppression of the TF pathway, significant reduction in functional levels of coagulation factors and inhibitors (factor II, VII and X) and an increase in free protein S [46]. On the other hand, more extreme doses of androgens, which can be observed during abuse of anabolic androgenic steroids for cosmetic or doping purposes, induced a pro-coagulant effect related to TF-induced thrombin generation [47]. In contrast, GAHT in transgender men, performed in accordance with the mode of administration and dosages recommended by current guidelines, does not appear to be associated with a pro-coagulant state, as confirmed by the present meta-analysis. To date, only very few studies have investigated the effects of GAHT on coagulation factors in AFABs. In a study by Scheres et al. [18] on 100 trans men on therapy, the pro-coagulant changes observed in addition to the expected increase in HCT and Hb were an average increase in factor IX, while those in anti-coagulant direction were an average increase in APC ratio and a decrease in factor II and factor XI. Protein S was found to be increased, while fibrinogen and protein C levels apparently did not change. In that study, however, there is a lack of correlation between the changes in the mean concentration of coagulation factors and the values of the main laboratory parameters of clinical interest, which were not investigated. The data obtained from our study, which show a statistically significant prolongation of INR duration, would seem to indicate a greater involvement of the extrinsic coagulation pathway, particularly factor VII, the behavior of which was not investigated in the study by Scheres et al. In fact, the other outcomes investigated in our meta-analysis, such as aPTT and fibrinogen, indicators mainly of the intrinsic and common coagulation pathways, are not significantly changed by T-based affirmation therapy. Our hypothesis about the involvement of the extrinsic pathway would be supported by the studies by Alhawiti and Alqahtani, who showed in a mouse model that chronic administration of a supraphysiological dose of T propionate for 12 weeks produced relevant effects on the hemostatic system by decreasing fibrinolysis and causing hypo-coagulation, significantly prolonging (16.8 %) bleeding time values in treated rats compared with control rats [48].

The same authors also studied the effect of T deficiency and replacement on platelet function and aggregation, coagulation, and fibrinolysis in healthy orchiectomized rats. Following testicular removal, enhancement of platelet aggregation and coagulation and inhibition of fibrinolysis were observed. These rats showed increased adenosine diphosphate-induced aggregation ratio, decreased bleeding time, clotting time, prothrombin and aPTT, and their sera showed increased levels of thromboxane B2 and fibrinogen. At the same time, their plasma showed increased levels of TPA-1 and decreased levels of tissue plasminogen activator. At the molecular level, there was an increase in mRNA and protein levels of PAI-1, protein levels of von Willebrand factor and a decrease in mRNA and protein levels of tPA, while the liver showed an increase in protein levels of prothrombin and, indeed, factor VII. Thus, in this model, T administration significantly reversed all hematologic and molecular changes brought about by orchiectomy, normalizing prothrombin and factor VII concentrations [49].

This meta-analysis has some limitations, the main one of which is undoubtedly the relatively small sample size and the observational design of the included studies, lacking control groups and double-blind randomization procedures, resulting in an overall moderate quality score. In such a scenario, it is impossible to determine whether some of the observed effects are related to T therapy or to other unmeasured events occurring during the follow-up. It cannot be ruled out that additional studies, especially from European databases, would have been identified by including EMBASE among the search tools, which unfortunately was not available to our team. The strengths of our meta-analysis, on the other hand, are the rigorous selection of the studies to be included in the quantitative synthesis. This resulted in negligible heterogeneity values.

5. Conclusions

Our meta-analysis suggests that T-based GAHT in AFAB people is associated with some expected pro-coagulant effects, such as increased HCT and Hb values, but also with potentially protective changes on thromboembolic risk, such as prolonged INR. Further prospective studies on large case series will be needed to confirm these data and possibly provide a possible pathophysiologic interpretation.

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CRediT authorship contribution statement

Daniele Pastori: Writing – review & editing, Validation, Supervision, Methodology. **Arcangelo Barbonetti:** Writing – review & editing, Validation, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2024.02.029.

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