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Safety of Estrogen-Based Feminizing Gender-Affirming Hormone Therapy: A Practical Endocrine Approach to Risk Stratification and Monitoring

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Introduction

Estrogen-based feminizing hormone therapy is a cornerstone of care for transfeminine and gender-diverse individuals. Its benefits are well established, including improvements in gender dysphoria, mental health, and overall quality of life, with meaningful downstream effects on social functioning and long-term well-being.[1,2]

Much of the historical concern regarding safety largely reflects earlier use of ethinyl estradiol, which was associated with substantially increased risks of venous thromboembolism (VTE) and cardiovascular events. Contemporary practice has shifted toward the use of 17β-estradiol delivered orally, transdermally, or by injection, alongside more individualized dosing, and attention to baseline risk. This transition has materially improved the safety profile of therapy.[1-5]

The primary safety concern remains VTE, alongside evolving considerations related to cardiovascular risk and malignancy screening. Contemporary data suggest that these risks are both predictable and modifiable, allowing clinicians to individualize therapy without compromising gender-affirming outcomes.[3-8]

This review provides a clinically focused framework for risk stratification, route selection, and monitoring of estrogen-based feminizing therapy.

Overview of Estrogen-Based Feminizing Therapy

Estrogen-based feminizing therapy aims to promote feminization while suppressing endogenous testosterone. For many persons, expected effects include breast development,

body fat redistribution, and reduced muscle mass. Among gender-diverse and nonbinary individuals, treatment goals may be slower or partial feminization, making individualized dosing and shared decision-making central to care.[1-4]

In clinical practice, estrogen is administered in three primary formulations: oral, transdermal, and injectable estradiol. These differ not only in route of administration, but also in pharmacokinetic profiles and downstream physiologic effects.

Oral estradiol undergoes first-pass hepatic metabolism, resulting in increased synthesis of clotting factors, inflammatory markers, and triglycerides. In contrast, transdermal and parenteral formulations bypass hepatic first-pass metabolism and have minimal effects on coagulation parameters. Transdermal estradiol produces more stable serum estradiol levels, whereas injectable estradiol formulations, typically estradiol valerate administered intramuscularly or subcutaneously, achieve higher peak levels with greater variability depending on dosing intervals.[3-5,7,9,10]

These pharmacologic differences translate into clinically meaningful implications for safety. Transdermal estradiol is associated with the most favourable thrombotic risk profile and provides stable serum levels, making it the preferred option in individuals with elevated baseline risk. Oral estradiol remains widely used but carries a modest increase in thrombotic risk related to hepatic first-pass effects. Injectable estradiol is increasingly used in clinical practice and appears to have a reassuring short-term safety profile in emerging data, although peak-trough variability and the potential for supraphysiologic estradiol levels require thoughtful dosing and monitoring, and long-term outcome data remain limited.[3-10] A 2024 scoping review concludes that the literature remains limited, while a 2025 multicenter study demonstrated that injectable estradiol esters reach guideline-range estradiol levels at lower doses than previously recommended, emphasizing the importance of interpreting serum levels in relation to timing of the most recent injection.[9,10]

Notably, transdermal estradiol appears to be hormonally effective even at physiologic dosing. In a 2024 randomized trial, testosterone suppression to <50 ng/dL (1.7 nmol/L) at 6 months was achieved in 100% of participants receiving transdermal estradiol, compared with 93% and 86% of those receiving once- and twice-daily sublingual estradiol, respectively. Transdermal therapy was also associated with substantially lower estrone levels, no observed hyperkalemia, and only one discontinuation due to a local skin reaction.[11]

Importantly, supraphysiologic estradiol levels do not confer additional feminization benefits. Current practice targets estradiol concentrations within the physiologic female range, approximately 200–600 pmol/L, recognizing that higher levels do not improve outcomes and may increase risk.[2-4,10]

These pharmacologic and clinical principles underpin contemporary prescribing practices, which prioritize route selection and physiologic dosing to optimize both safety and efficacy.

Venous Thromboembolism Risk: Contemporary Evidence

VTE risk remains the most clinically relevant safety consideration in estrogen prescribing; however, its magnitude of risk is often overestimated based on historical data in cohorts exposed to ethinyl estradiol.[3,5,7,8]

In contemporary studies using 17β-estradiol, absolute VTE risk is low, estimated at approximately 2–4 events per 1,000 person-years. Risk is strongly influenced by baseline patient factors, including age, obesity, smoking status, and prior thrombosis. Among individuals without baseline risk factors, rates approach those of the general population, whereas in higher-risk individuals, absolute rates may approach 5–8 events per 1,000 person-years.[5-8]

Formulation-specific differences are consistently observed. Transdermal estradiol is associated with minimal or no increase in VTE risk compared with baseline population rates, whereas oral estradiol is associated with a modest increase in relative risk.[5,7,8]

Recent analyses emphasize that estrogen-related thrombosis risk is additive rather than independent, reinforcing that estrogen exposure is rarely the sole driver of thrombotic risk and underscoring the importance of baseline risk assessment.[5,7,8,12]

Perioperative risk data remain limited but reassuring. In a cohort of 953 facial feminization procedures, only one postoperative VTE event was observed (0.10%), with no significant difference between continued, reduced, or absent perioperative hormone exposure.[13]

Collectively, these data support route selection as the primary modifiable factor in individualized risk mitigation, with the clinical focus

placed on identifying baseline risk and selecting the safest formulation accordingly.

Cardiovascular and Metabolic Considerations

Cardiovascular risk in transfeminine individuals receiving estrogen therapy remains an area of evolving evidence.

A recent meta-analysis demonstrated an approximately 40% increased relative risk of composite cardiovascular disease compared with cisgender individuals; however, the authors emphasized that this association likely reflects the contribution of baseline comorbidities, socioeconomic factors, and disparities in access to care rather than estrogen exposure alone.[14]

More recent cohort data adjusting for these baseline factors suggest that estrogen therapy itself may not be associated with increased cardiovascular risk. In a contemporary Dutch cohort, gender-affirming hormone therapy in transgender women was not associated with increased overall cardiovascular risk after adjustment. Compared with general-population men, myocardial infarction risk was lower (standardized incidence ratio [SIR] 0.50, 95% confidence interval [CI] 0.32–0.71), cerebrovascular accident risk was similar (SIR 0.94, 95% CI 0.72–1.19), and VTE risk remained higher (SIR 1.81, 95% CI 1.33–2.35).[15]

Taken together, these findings suggest that earlier signals of increased cardiovascular risk may have been at least partially confounded. From a clinical perspective, VTE remains the most consistent and directly attributable vascular risk associated with estrogen therapy, while broader cardiovascular risk appears to be driven predominantly by traditional risk factors.[13-16]

Metabolic effects of estrogen therapy are generally modest. Oral estradiol may increase triglyceride levels, whereas transdermal therapy is largely metabolically neutral. Data on insulin resistance are mixed but do not support a major adverse effect. Changes in body composition toward increased fat mass and reduced lean mass reflect expected feminization rather than pathologic metabolic deterioration.[13,16]

In practice, estrogen therapy should be integrated into standard cardiovascular risk management rather than treated as a primary driver of cardiovascular disease.

Medication-Specific Safety

Medication-related risks in feminizing hormone therapy more commonly arise from adjunctive therapies rather than from estradiol itself.

Spironolactone is generally well tolerated, and clinically significant hyperkalemia is uncommon in individuals with normal renal function who are not taking interacting medications. Monitoring should therefore be guided by renal function and the presence of concomitant therapies.[3,4]

Cyproterone acetate carries more significant risks, including dose-dependent meningioma and hepatotoxicity, and its use should be limited and carefully considered, particularly in the context of long-term therapy.[3,4]

Mild prolactin elevation may occur with estrogen therapy, particularly in the early phases of treatment and with cyproterone use. Monitoring is advisable during the first year of therapy and periodically thereafter; once stable dosing is achieved, evaluation can be symptom-driven.[2-4]

Malignancy Risk and Screening

Available data regarding malignancy risk in transfeminine individuals remain limited but generally reassuring. Recent systematic reviews have not demonstrated a clear increase in overall cancer risk associated with estrogen therapy.[17]

Breast cancer risk appears to be higher than in cisgender men but lower than in cisgender women, with reported incidence rates of approximately 20–40 cases per 100,000 person-years. Risk increases with duration of therapy and cumulative estrogen exposure.[17,18]

Screening strategies should therefore be individualized based on age, duration of estrogen exposure, and overall risk profile. For most individuals, initiation after 5–10 years of therapy or at age 50 is reasonable, with earlier screening considered for those at higher-risk. A practical approach aligned with American College of Radiology-style principles, incorporating age, duration of therapy, and individual risk factors, is summarized in **Table 1**.[18]

Prostate cancer risk persists despite androgen suppression. Estrogen therapy lowers prostate-specific antigen levels, which may affect interpretation, and screening should be individualized based on age, anatomy, and risk factors.[18]

Risk Category	Clinical Criteria	Screening Recommendation
Lower risk	<5 years of estrogen exposure, age <40, no major risk factors	No routine screening; reassess over time
Average risk	≥5 years of estrogen exposure, age ≥40, no high-risk features	Mammography per cis female guidelines
Higher risk	≥5 years of estrogen exposure plus strong family history or known genetic risk	Earlier and/or enhanced screening
Limited exposure	<5 years of estrogen exposure and age <40	No routine screening

Table 1. Breast Cancer Screening Stratification in Patients Receiving Estrogen-Based Feminizing Therapy; *adapted from American College of Radiology Principles.*

Screening recommendations adapted from American College of Radiology principles, incorporating duration of estrogen exposure and individualized baseline risk.

Overall, malignancy risk should be contextualized within the broader framework of preventive care, ensuring appropriate routine screening surveillance.

Clinical Approach to Risk Stratification and Monitoring

A structured, risk-based approach to estrogen prescribing allows clinicians to optimize safety without limiting access to care. Baseline assessment should focus on thrombotic and cardiovascular risk factors, which inform formulation selection. Route of administration remains the most important modifiable determinant of safety.[1-4]

Individuals at low baseline risk have an absolute VTE incidence of approximately 2 per 1,000 person-years and may be treated with any estrogen formulation. In individuals with cardiovascular risk factors, with an absolute VTE risk of approximately 3–5 per 1,000 person-years, transdermal estradiol is preferred. For those with prior VTE or thrombophilia, with baseline risks exceeding 5–10 per 1,000 person-years, transdermal estradiol at the lowest effective dose is recommended, often in collaboration with hematology. Routine thrombophilia screening is not recommended in the absence of clinical indication.[3-8,12]

Baseline laboratory evaluation includes estradiol, testosterone, complete blood count, renal and liver function, A1C, and lipid profile, with potassium monitoring when spironolactone is used. During dose titration, follow-up typically occurs every 3 to 6 months, with reassessment of hormone levels, blood pressure, weight, and relevant laboratory parameters.[2-4]

A practical approach to formulation selection based on VTE risk is summarized in **Figure 1**.

Shared decision-making remains central, with a focus on aligning therapy with patient goals while minimizing modifiable risk.

Discussion

The safety profile of estrogen-based feminizing hormone therapy has evolved substantially, supported by contemporary data demonstrating low absolute risk when therapy is prescribed thoughtfully. VTE remains the most consistent safety signal; however, its magnitude of risk is modest and strongly influenced by patient factors and route of administration.[5-8]

Cardiovascular risk appears to be influenced more by baseline comorbidities and social determinants of health rather than by estrogen therapy itself. Emerging data suggest that previously reported associations between estrogen therapy and cardiovascular disease may have been at least partially confounded, reinforcing the importance of comprehensive risk factor management rather than restriction of therapy.[13-16]

Withholding or undertreating of estrogen therapy due to outdated safety concerns carries its own consequences. Estrogen-based feminizing therapy provides meaningful improvements in mental health and quality of life, and these benefits must be weighed alongside relatively low absolute medical risks.[1,2,7]

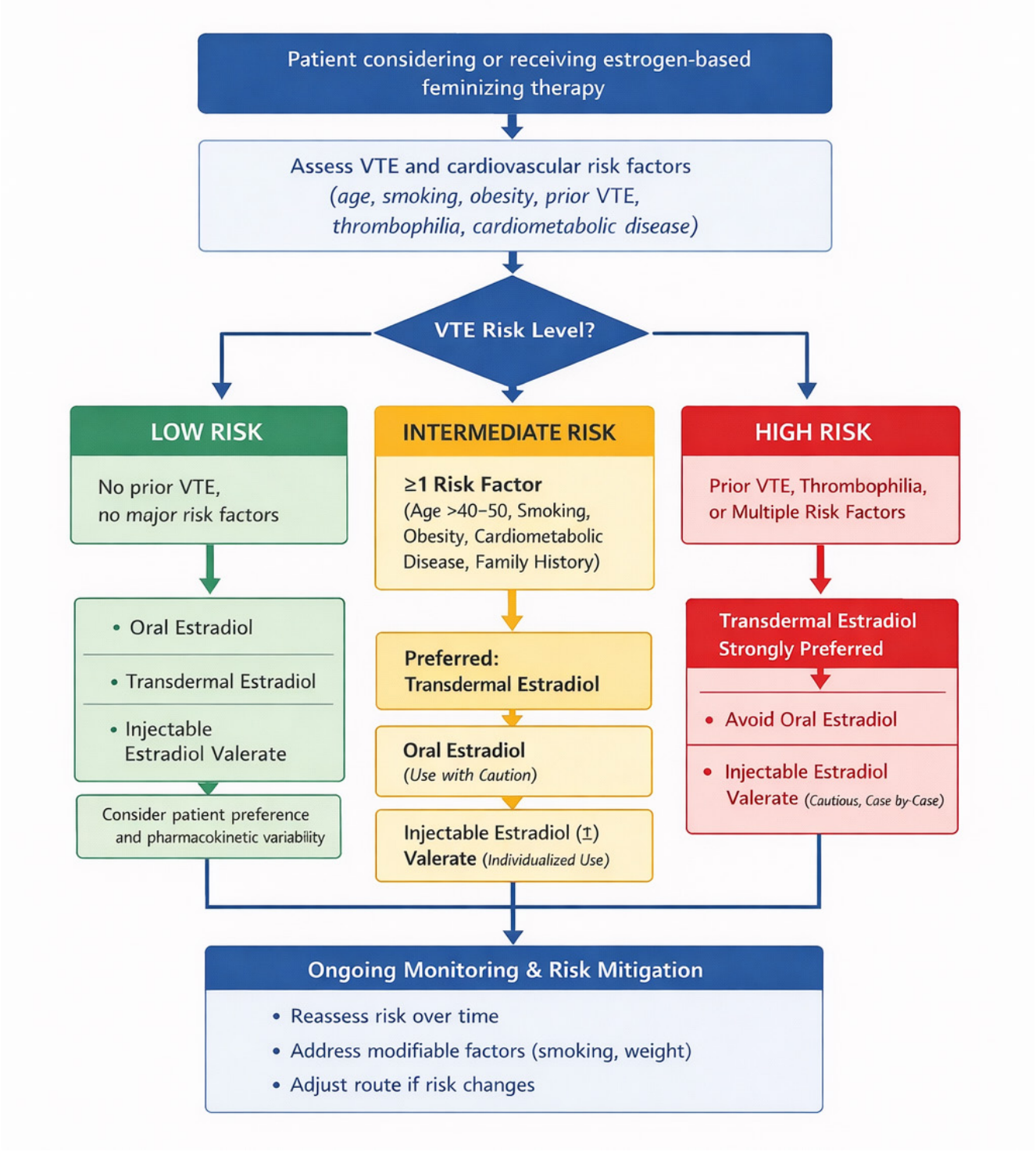

Figure 1. Estrogen Selection and Venous Thromboembolism Risk Stratification Algorithm; *courtesy of Jagoda Kissock, MD.*

Clinical algorithm outlining venous thromboembolism (VTE) risk stratification and estrogen route selection in transfeminine individuals and gender-diverse persons receiving estrogen-based feminizing therapy. Transdermal estradiol is preferred in moderate- to high-risk individuals. Injectable estradiol valerate is increasingly used in practice; however, long-term safety data remain limited, and variability in serum levels should be considered.

Several important gaps in the evidence base remain, including limited long-term data for injectable estradiol and sparse data in older individuals and those with significant comorbidities. These areas represent important priorities for future research.[9,10,17]

Conclusion

Estrogen-based feminizing hormone therapy is both safe and essential when prescribed using a structured, risk-based approach. Safety is driven primarily by route of administration and baseline patient factors. The role of the clinician is to individualize therapy, minimize modifiable risks, and support patients in achieving their gender-affirming goals while maintaining overall health.[1-4]

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