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Glucagon-like Peptide-1 Medicines for Peripheral Arterial Disease in Type 2 Diabetes: Are They Ready for Prime Time?

Ronald M. Goldenberg, MD, FRCPC, FACE

Introduction

Comorbid peripheral arterial disease (PAD) affects approximately 12.5%–22% of individuals with type 2 diabetes (T2D), and is associated with an increased risk of major adverse limb events (MALE), such as revascularization procedures and lower extremity amputations, as well as heightened cardiovascular events and mortality.[1] Despite this elevated risk, few therapies have been proven to reduce the risk of MALE. Although statins, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and low dose rivaroxaban plus aspirin have been shown to reduce the risk of MALE in individuals with PAD, there remains an unmet need for disease-modifying agents to improve PAD outcomes in people with concomitant T2D and PAD.[1]

Current Diabetes Canada guidelines recommend glucagon-like peptide-1 (GLP-1) medicines for individuals with T2D and established cardiovascular disease (CVD), multiple risk factors, or chronic kidney disease (CKD) due to their proven cardiorenal benefits.[2] Emerging data has shown that GLP-1 medicines reduce the incidence of MALE in individuals with T2D. This review summarizes the totality of evidence for GLP-1 medicines and their impact on MALE, drawing from randomized controlled trials (RCTs) and observational studies.

Randomized Controlled Trials

Results from RCTs are considered the highest level of evidence for evaluating the effects of pharmacotherapies on clinical outcomes. The first indication that a GLP-1 medicine may reduce the risk of lower extremity amputation in individuals with T2D emerged from a post hoc exploratory analysis of the LEADER trial, demonstrating a significant 35% risk reduction in the composite outcome of diabetic foot ulcer plus amputation with liraglutide versus placebo.[3]

Similarly, in the SOUL cardiovascular outcomes trial comparing oral semaglutide versus placebo, a pre-specified secondary outcome of MALE, defined as hospitalization for acute or chronic limb ischemia, was reduced in semaglutide treated individuals (hazard ratio [HR] 0.71, 95% CI 0.53–0.96).[4] Furthermore, a meta-analysis by Goldenberg and Verma encompassing six RCTs comparing a GLP-1 medicine to placebo in individuals with T2D (**Figure 1A**) demonstrated a statistically significant reduction in MALE with low heterogeneity (HR 0.78, 95% CI 0.68–0.90; p=0.0005; I^2=3%).[5]

Two RCTs have studied the impact of GLP-1 medicines on MALE in individuals with T2D and comorbid PAD. A post hoc analysis of the EXSCEL trial demonstrated a non-statistically significant reduction in MALE with once-weekly exenatide (HR 0.83, 95% CI 0.66–1.04).[6] In the STRIDE trial, an exploratory MALE outcome did not show a statistically significant impact from semaglutide therapy; however, this outcome was limited by very low event rates, with only six events among 396 (1.5%) semaglutide treated individuals and five events among 396 (1.3%) placebo treated individuals.[7] Notably, an exploratory outcome reflecting PAD progression, defined as rescue treatment, MALE, or all-cause death, was reduced by 54% with semaglutide (HR 0.46, 95% CI 0.24–0.84). Giugliano et al. subsequently performed a meta-analysis of these two RCTs in individuals with T2D and PAD (**Figure 1A**) and demonstrated a non-significant reduction in MALE (HR 0.84, 95% CI 0.67–1.05; p=0.12; I^2 = 0%). The certainty of evidence was considered low, largely due to the limited number of available RCTs.[8]

Two RCTs have shown a beneficial effect of a GLP-1 medicine on walking distance in individuals with T2D and PAD.[7,9] The STARDUST trial demonstrated an improvement in the secondary outcome of 6-minute walking distance with liraglutide versus control (estimated treatment difference [ETD] 25.1 m, 95% CI 21.8–28.3; p<0.0001) alongside an increase in the primary outcome of peripheral perfusion, as measured by transcutaneous oxygen pressure.[9] Similarly, the STRIDE RCT reported a significantly greater maximum walking distance in the semaglutide group versus the placebo group (ETR 1.13, 95% CI 1.06–1.21; p=0.0004). A subsequent meta-analysis by Giugliano et al. pooling these two RCTs also demonstrated a significantly greater walking distance with the GLP-1 group versus the control group (ETR 1.10, 95% CI 1.05–1.15; p<0.001; I^2=5.8).[8] Interestingly, the improvements in walking distance observed in both STARDUST and STRIDE extended beyond the effects attributable to weight loss and glycemic control alone.

Observational Studies

Observational studies represent a lower level of evidence than RCTs due to the potential for residual confounding, even when using propensity score methods or multivariate regression techniques. Despite this limitation, it is reassuring that there have been a large number of observational studies supporting a beneficial effect of GLP-1 medicines on MALE in people with T2D. Baviera et al. have reported the results from an observational analysis of two Italian cohorts, demonstrating that first-time users of GLP-1 medicines experienced significantly reduced rates of lower limb complications compared to users of other antihyperglycemic agents (AHAs) with relative risk reductions ranging from 31%–33%.[10] Observational studies comparing rates of MALE between GLP-1 medicines and sodium-glucose cotransporter-2 (SGLT2) inhibitors have shown conflicting results. While several studies have shown no significant differences between these two AHA classes,[11-14] others have demonstrated a reduction in the risk of MALE with GLP-1 medicines.[15–18]

These discrepant results are likely explained by different methodologies as well as variations in unmeasured confounders across the studies. In a meta-analysis of observational studies conducted in populations with T2D, Dutta et al reported a statistically significant 30% reduction (p=0.005, I^2=0%) in MALE (**Figure 1B**) and a 42% reduction (p<0.0001; I^2=0%) in amputations associated with GLP-1 therapy.[19]

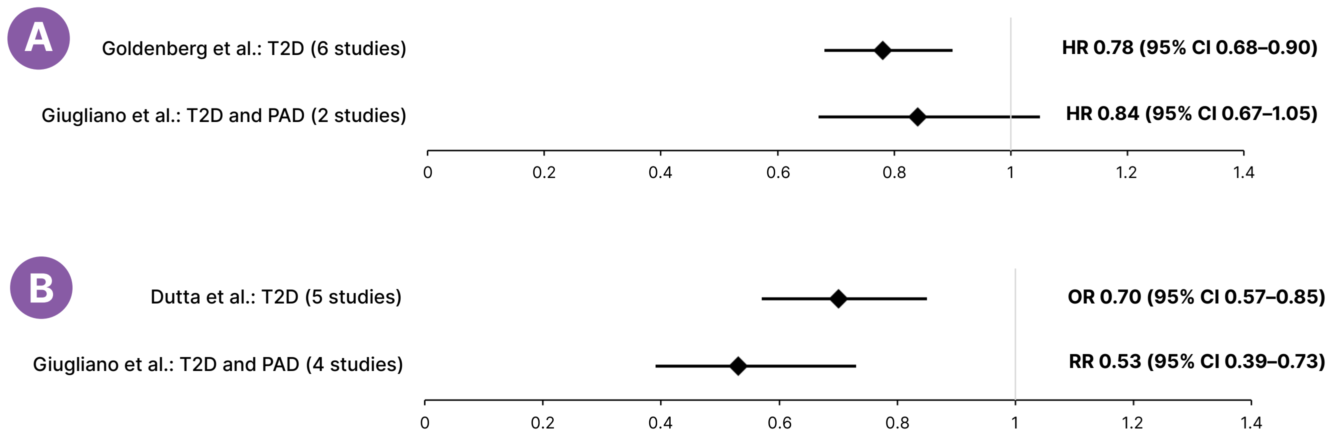

Figure 1. Summary of meta-analyses assessing the effects of GLP-1 medicines and MALE in people with T2D or T2D and PAD, based on **A)** RCTs, and **B)** observational studies; *courtesy of Ronald Goldenberg, MD, FRCPC, FACE*.

Abbreviations: GLP-1: glucagon-like peptide-1; **HR:** hazard ratio; **MALE:** major adverse limb events; **OR:** odds ratio; **PAD:** peripheral arterial disease; **RCTs:** randomized controlled trials; **RR:** risk ratio; **T2D:** type 2 diabetes.

Observational studies have also been performed in populations with T2D and comorbid PAD. The SMILE retrospective cohort study demonstrated a significant 33% reduction in MALE with semaglutide therapy compared to other AHAs (HR 0.77, 95% CI 0.61–0.97; p=0.029), along with a 50% reduction in lower extremity amputations (HR 0.50, 95% CI 0.30–0.83; p=0.008).[20]

Similarly, in a diabetes subgroup analysis of a retrospective observational study conducted in a PAD population, GLP-1 treated individuals experienced a 28% reduction in MALE compared to a control group not receiving GLP-1 therapy (HR 0.72, 95% CI 0.64–0.81; p<0.01).[21] In a retrospective cohort study in a population with T2D and foot ulcers, Lewis et al. reported a 55% reduction in amputation risk in semaglutide users compared to non-users (relative risk [RR] 0.45, 95% CI 0.37–0.55; p<0.001).[22] They also demonstrated reductions in other wound-related complications. In addition, a retrospective cohort study reported that tirzepatide was associated with a significant reduction in MALE (HR 0.44, 95% CI 0.33–0.59, p<0.001) compared to non-users in a population with diabetes and PAD. These findings support the concept that the benefits of GLP-1 medicines include GLP-1/GIP co-agonists in addition to GLP-1 receptor mono-agonists.[23] Consistent with this, other observational studies have shown similar benefits of GLP-1 medicines in populations with T2D and PAD.[24-26] Furthermore, a meta-analysis by Giugliano et al. of four observational studies in populations with T2D and PAD demonstrated a 47% reduction (p<0.001) in lower extremity amputations (**Figure 1B**).[8]

Mechanisms for Benefit on PAD Outcomes

The beneficial effects of GLP-1 medicines on glycemic control and body weight may indeed be a contributor to the clinical benefits observed in individuals with CVD or risk factors for CVD. However, the potential for vascular benefits of GLP-1 medicines that extend beyond improvements in glycemia or weight loss remains an ongoing area of research. Proposed mechanisms for improved vascular function include anti-inflammatory effects, reduced immune activation, improved endothelial function, as well as indirect effects on vascular regenerative progenitor cells.[27] In the STARDUST trial, liraglutide treatment was associated with significant improvements in markers of both inflammation and angiogenesis.[28]

Conclusions

PAD and MALE are highly prevalent complications in individuals with T2D. Evidence from secondary outcomes of MALE in RCTs, meta-analyses of RCTs, and observational studies demonstrates that GLP-1 medicines are associated with reductions in MALE among populations with T2D, including those with comorbid PAD. Current clinical guidelines prioritize GLP-1 medicines for cardiorenal protection in individuals with T2D and either established CVD, multiple risk factors, or CKD. With the current evidence for GLP-1 medicines and their benefits on PAD outcomes, these agents should be considered an important component of our therapeutic armamentarium for reducing MALE in people with T2D.

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

Jagoda Kissock, MD

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]

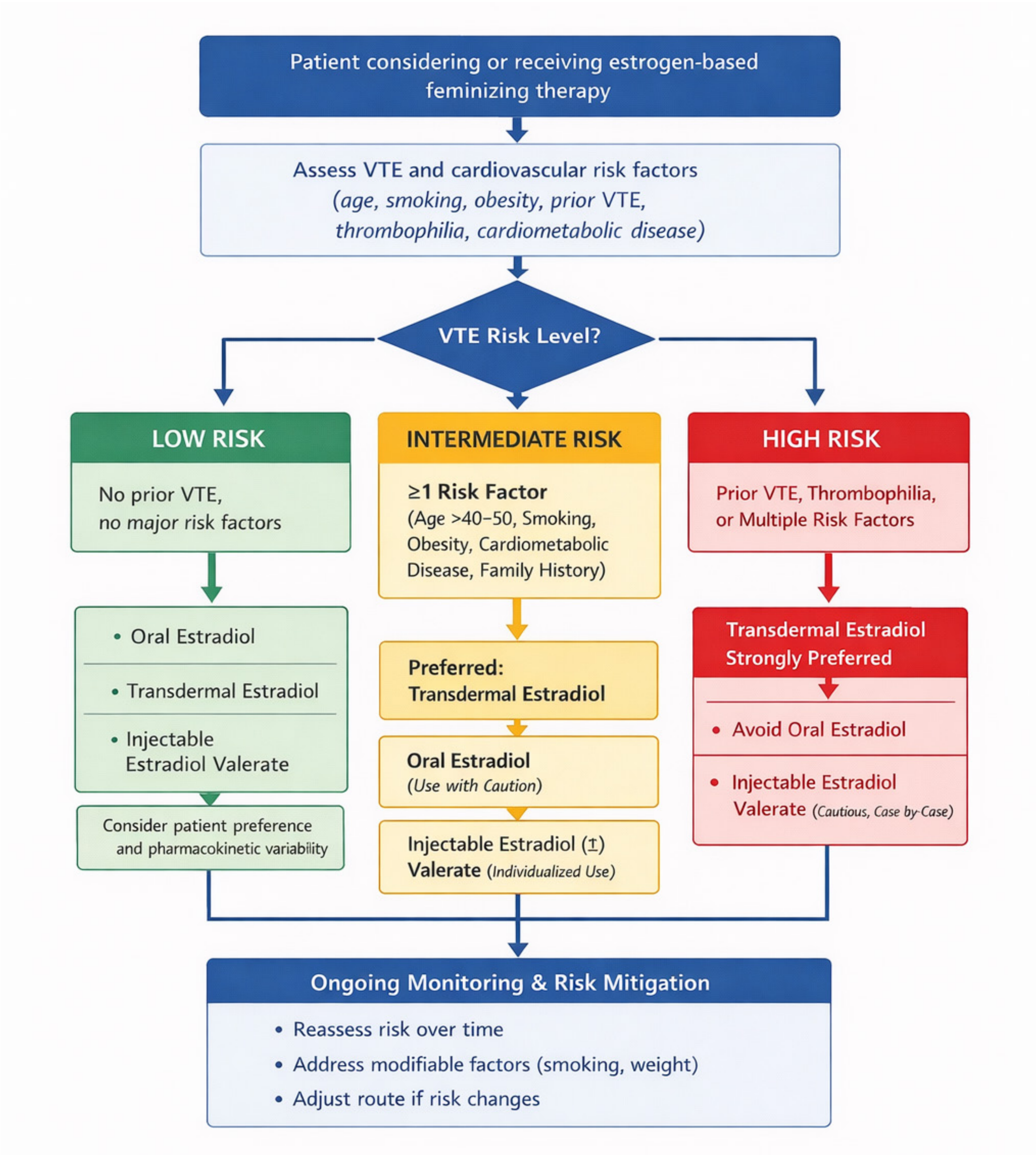

Figure 1. Estrogen Selection and Venous Thromboembolism Risk Stratification Algorithm; *courtesy of Jagoda Kissock, MD.*

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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Anabolic Androgenic Steroids: No Longer on the Fringes of Endocrinology

Adam Millar, MD, MScCH, FRCPC

In this review, "Anabolic Androgenic Steroids," or "AAS" is used as the preferred term to indicate the use of exogenous androgens in supraphysiologic doses for the purpose of muscle growth or image enhancement. This definition does not include the use of physiologic doses of testosterone prescribed for the treatment of male hypogonadism. Although there is disagreement regarding the accuracy of this terminology, AAS continues to be one of the most common designations used in the literature today.

Background/Prevalence

Public awareness of AAS has historically focused on athletes seeking a competitive advantage over their peers.[1] More recently, this pattern has shifted, with the majority of AAS use occurring among recreational users whose motivations differ from those of athletes.[2,3] While these substances were once available only through black market sources, they are now widely available via social media, internet websites, and direct mailing of substances to consumers, despite laws prohibiting their use in many countries.[4] As recreational AAS use has increased, so too have referrals to endocrinologists for issues ranging from infertility and adverse drug effects to assistance with discontinuing AAS use altogether. Previously, some physicians have been reluctant

Drug name (Trade name)	Route
17β Ester Derivatives	
Testosterone propionate	IM
Testosterone enanthate	IM
Testosterone cypionate	IM
Testosterone undecanoate	IM/PO
Boldenone undecylenate (Equipoise®)	IM
17α Alkyl Derivatives	
Metandienone (Dianabol®)	PO
Methyltestosterone (Android®)	PO
Oxandrolone (Anavar®)	PO
Oxymetholone (Anadrol®)	PO
Stanozolol (Winstrol®)	PO/IM
19-Nortestosterone Derivatives	
Nandrolone decanoate (Deca-Durabolin®)	IM
Trenbolone acetate (Parabolan®)	PO, IM, pellets

Table 1. Commonly Used Anabolic Androgenic Steroids listed by name and route; *adapted from Grant et al., 2024*[4]; *Solanki et al., 2023.*[9]

Abbreviations: IM: intramuscular; **PO:** oral.

to accept such referrals due to a lack of expertise in this area or ethical concerns related to AAS use.[3,5] However, the emergence of commercial testosterone clinics, the ease of purchasing medications online, the growing availability of guidance from internet forums,[4,5] and artificial intelligence tools have led many physicians to realize that AAS management can no longer be exclusively confined to specialized clinics.

AAS use is increasing, with lifetime prevalence estimates ranging from 1% to 5% in Western countries,[6] and a 1.6% lifetime prevalence of AAS use among sampled adolescents and young adults in a Canadian cohort.[7]

Substances obtained through underground sources are notoriously variable in quality and purity and may be contaminated with other unlabelled substances, or in some cases, may not contain the intended product at all.[2] In the HAARLEM study, only 47% of sampled AAS products contained the substance listed on the product label; additionally, 68% of samples contained undeclared AAS, and 49% contained a higher number of AAS compounds than indicated.[8]

Pharmacology/Patterns of Use

AAS are not one specific compound, rather; they encompass a heterogeneous group of substances that share structural similarities to testosterone. These substances can be broadly divided into 17-beta-ester derivatives, 17α-alkylated derivatives, and 19-nortestosterone derivatives[4,9] (see **Table 1**). Differences in their effects on body tissues arise in part based on whether they undergo further conversion by aromatization or 5-alpha reduction.[10] AAS are frequently used in combination with other hormonal or non-hormonal substances, and are administered over variable timeframes, often in fluctuating doses throughout their cycles of use.[1] These multiple variables complicate efforts to attribute adverse events to any single androgenic agent.[1]

Specific terminology is employed to describe patterns of AAS use. "Cycles" refer to discrete periods during which AAS are used typically followed by a period of discontinuation until a new cycle begins. "Stacking" refers to the concurrent use of additional steroidal or non-steroidal agents on top of a testosterone ester "core"[8] regimen (see **Table 2**). "Pyramiding" involves the stepwise escalation of AAS doses to a peak level, which is then tapered back down.[4] Another commonly used regimen is "blasting and cruising," in which AAS doses are increased and then tapered back down to a lower, but still supratherapeutic, maintenance dose. Note that this approach does not involve a recovery period during which AAS use is temporarily discontinued.[4]

Among people who use AAS, there is also widespread use of supplements, nutraceuticals, and "testosterone boosters" that have not undergone proper safety or quality testing.[1] Although these products are often perceived as safe and accurately labelled, research shows that many contain doses inconsistent with what is stated on the label or include undeclared ingredients.[11] In one study, undeclared doping substances were identified in 25 of the 66 sports nutrition supplements that were analyzed.[11]

Type of Substance	Examples
Non-steroidal drugs with anabolic effects	IGF-1, GH, GHRH, insulin
Drugs that counteract the effects of AAS	Aromatase inhibitors, SERMs, gonadotropins
Drugs for weight loss, fat reduction, or water loss	Diuretics, L-thyroxine, GLP-1 agonists, beta-2 adrenergic agonists
Fertility preservation drugs	Gonadotropins, clomiphene citrate
Drugs to prevent AAS detection	Diuretics, estrogens, probenecid

Table 2. Substances Often "Stacked" with AAS; *adapted from Pope et al., 2014.*[1]

Abbreviations: AAS: anabolic androgenic steroids; **GLP-1:** glucagon-like peptide-1; **GH:** growth hormone; **GHRH:** growth hormone releasing hormone; **hCG:** human chorionic gonadotropin; **IGF-1:** insulin-like growth factor-1; **LH:** luteinizing hormone; **SERMs:** selective estrogen receptor modulators

Clinical Recognition/Diagnosis

Although the prevalence of AAS use has increased, clinical presentations likely represent only the "tip of the iceberg." Many individuals who use AAS avoid physician involvement for several reasons, such as a perceived lack of medical expertise regarding these substances, a desire to avoid being chastised for their use, and a belief that their use does not pose significant health risks.[3] Improving physician education in this area may therefore improve patient confidence in disclosing their AAS use.

Patients who seek medical attention while using AAS may do so for health monitoring or because of concerns about adverse events.[5] However, presentations are often subtle. Some patients may report concerns of inadequate muscle development despite having a muscular physique, suggesting a subtype of body dysmorphic disorder termed "muscle dysmorphia".[12] Others may report no longer "seeing the same gains" at the gym, or prolonged recovery times following exercise. Physical features that may also suggest AAS use can include testicular atrophy, gynecomastia (or related surgical scars), truncal acne, or truncal striae.[2,6]

Measurement of testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels is commonly used in in the evaluation of AAS use and can produce different laboratory patterns based on the substances that are being used[13] (see **Table 3**). Elevated testosterone levels are not always observed on laboratory testing, as some androgens are not detected by testosterone assays, resulting in paradoxically low testosterone levels despite physical findings that suggest the opposite to be true.[13] LH and FSH levels can be low/suppressed; however, in patients using aromatase inhibitors or clomiphene, levels of LH and FSH may instead be elevated, accompanied by high testosterone levels.[6] Additional laboratory findings that may suggest AAS use include low sex hormone-binding globulin levels, elevated hemoglobin/hematocrit, reduced thyroxine-binding globulin, and low high-density lipoprotein (HDL) levels.[4,6]

Potential Adverse Effects

Adverse effects from AAS use are commonly reported by users. In a Canadian study of 2,774 young men, 75% reported experiencing at least one AAS-related adverse event.[7] Most concerning, however, is the evidence suggesting a threefold increase in mortality among AAS users.[4] The adverse events outlined below represent a selection of potential adverse effects, and are not intended to be an exhaustive list.

Hormone/Substance	Testosterone	LH	FSH
Testosterone	↑	↓	↓
Non-testosterone Androgen	↓	↓	↓
Testosterone Precursor (e.g. androstenedione)	↑	↓	↓
hCG	↑	↓	↓
Aromatase Inhibitor	↑	↑	↑
Clomiphene	↑	↑	↑

Table 3. Hormones/Substances and Their Effects on Testosterone, LH and FSH serum levels; *adapted from Anawalt, 2024.*[13]

Abbreviations: FSH: follicle-stimulating hormone; **hCG:** human chorionic gonadotropin; **LH:** luteinizing hormone

Gynecomastia

Gynecomastia, or breast tissue growth, has been reported in men during both AAS use and in the recovery phases following AAS use, with prevalence rates estimated as high as 52%.[4] It is most commonly attributed to conversion of supraphysiologic androgen doses to estrogens and is therefore more commonly observed with aromatizable substances.[14] In an effort to self-manage the acute phase of breast tissue growth, men often use selective estrogen receptor modulators (SERMs) such as tamoxifen or aromatase inhibitors.[4,10] Others use cabergoline or bromocriptine to treat gynecomastia, under a misguided belief that prolactin elevation is the sole cause of their breast growth.[10] However, once breast growth has progressed to the fibrotic/chronic stage of growth, surgical intervention is often required.[14]

Acne Vulgaris

Acne is a common manifestation of AAS use, with prevalence rates of 50% or higher.[4,8] It results from androgen-dependent sebum production, and suggests AAS use when located in a truncal pattern in adult men.[2] Patients may experience improvement with targeted therapies such as isotretinoin, and a subset of AAS users report incorporating low doses of this medication into their AAS cycles.[10]

Androgenic Alopecia

Androgenic alopecia is another reported adverse effect of AAS use and is often linked to increased production of dihydrotestosterone, via the 5-alpha reductase pathway.[10] In the HAARLEM study, 12% of participants reported alopecia by the end of their AAS cycles. To counteract this effect, some users add 5-alpha reductase inhibitors, such as finasteride and dutasteride, to their AAS cycles.[14] However, the effectiveness of these medications on high dose androgen users remains unclear, especially when substances are used that cannot undergo 5-alpha reduction.[10]

Hepatotoxicity

Hepatotoxicity, contrary to popular belief, is not a common complication associated with standard testosterone replacement therapy. The risk, however, is well-recognized with 17α-alkylated oral androgens and selective androgen receptor modulators.[2] Hepatic injury associated with 17α-alkylated androgens is thought to result from their increased oral bioavailability and diminished hepatic degradation.[4] These agents can cause elevations in aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase and gamma-glutamyl transferase, and can present with jaundice or pruritus.[10] In rare cases, their use has been linked to serious hepatic complications, including peliosis hepatis, hepatocellular carcinoma, and liver adenomas.[10]

Cardiovascular Effects

AAS use is associated with a range of adverse effects on the cardiovascular system, with a 2-3-fold increase in cardiovascular disease among users.[4] AAS use has been linked to left ventricular hypertrophy, hypertension, dyslipidemia, abnormal cardiac remodelling, fibrosis, prothrombotic states, premature atherosclerosis, and arrhythmias.[4,6,15]

Cumulative androgen exposure–defined as the number of years that a user has been exposed to supraphysiologic doses of androgens and conceptually akin to pack-years in smokers—has been associated with an increased risk of cardiovascular disease.[5] Clinically, dyslipidemia manifests as elevated low-density lipoprotein (LDL) levels and reduced HDL levels,[6] with more pronounced lipid disturbances observed with 17α-alkylated androgens.[10] Sustained stimulation of androgen receptors (AR) in multiple cardiac tissues is thought to lead to the diverse adverse effects. Left ventricular hypertrophy results from chronic stimulation of AR in cardiac myocytes, while overstimulation of AR in vascular endothelial and smooth muscle cells results in vasoconstriction.[15] Accordingly, the presence of unexplained premature coronary artery disease, left ventricular hypertrophy, or arrhythmias in young patients should prompt physicians to consider possible AAS use as the underlying etiology.[15]

Mental Health

The relationship between mental health and AAS use is complex and difficult to unravel. It remains unclear whether mental health conditions predispose individuals to AAS use, or whether AAS use contributes to mental health conditions. Most likely, this relationship is bidirectional.[4] Muscle dysmorphia, a subtype of body dysmorphic disorder, is associated with a perceived inability to gain muscle or achieve one's desired physique, despite physical evidence to the contrary.[12] This perception may lead individuals to either seek medical evaluation for consideration of testosterone therapy (to treat presumed hypogonadism), or to self-treat with AAS.

AAS use has been implicated in the development of de novo mental health conditions, including mood disorders, anxiety, manic episodes, psychosis, and increased aggression.[1,6] AAS users are also at risk of developing drug dependence and addiction, with studies showing AAS dependence rates of approximately 30%.[1] A Canadian study has shown that one in five adolescents and young adults who used AAS experienced moderate-severe dependence.[17] As a result, androgen dependence is now recognized in the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders.[2] Of greatest concern, however, is the increased risk of suicidal ideation and suicide-related death, both of which occur more often in AAS users compared to non-users.[4]

Infertility

Infertility is one of the most common reasons for AAS users to seek medical attention.[6] Exogenous androgens and estrogens suppress gonadotropin-releasing hormone, thereby reducing production of the gonadotropins, LH, and FSH. This suppression results in decreased production of intratesticular testosterone by Leydig cells, impaired Sertoli cell function, and disruption of spermatogenesis.[9,16] Long-term suppression of spermatogenesis results in testicular atrophy, as two-thirds of testicular volume is comprised of the seminiferous tubules.[4]

Contraception studies show an average time span of 6–24 months for sperm concentrations to normalize after testosterone discontinuation.[16] In AAS users, however, recovery can take over 24 months, owing to higher androgen doses and the concurrent "stacking" of other substances that can further inhibit spermatogenesis.[16] It has therefore been proposed that, in the absence of a recovery in spermatogenesis by 24 months following AAS cessation, initiation of gonadotropin therapy may be reasonable.[14,16]

Management

Although several studies have assessed the prevalence of AAS use and associated adverse events, considerably less research has focused on the management of patients using AAS, or on the associated health concerns that can arise following discontinuation of these substances.[17]

Approaches to caring for patients who use AAS vary widely, with some clinicians declining to engage with such patients altogether, while others advocate for a harm-reduction approach in addition to supported cessation attempts.[5,6,18] While some state that prescribing androgens to people who use AAS "colludes with and perpetuates the androgen use,"[2] others are more accepting of a harm-reduction approach that "acknowledges the reality of continued use and seeks to promote health and patient engagement."[5] **Table 4** illustrates components of a harm-reduction approach to AAS use.[5,18]

At present, there are no established medical guidelines for the management of AAS use or recovery. Consequently, there remains a lack of consensus among physicians. In one endocrine conference survey conducted at an endocrinology conference, 84% of respondents reported engaging in watchful waiting after AAS cessation, while the remaining participants actively

Components of a Harm-reduction Approach to AAS Abuse
Reducing the dose of AAS and associated drugs/supplements
Reducing the absolute number of substances overall
Preferential use of AAS with lower known toxicity (e.g., avoidance of 17α-alkylated androgens)
Shortening the duration of cycles, and discouraging "blast and cruise" cycles that eliminate drug-free intervals
Avoidance of needle sharing
Ensuring that cardiovascular risk factors are being monitored/managed
Ongoing encouragement/assistance with AAS cessation
Offering psychiatric/psychologic support to manage withdrawal symptoms and reduce relapse risk

Table 4. Components of a harm-reduction approach to AAS abuse; *adapted from Smit et al., 2026*[5]*; Bonnecaze et al., 2021.*[18]

Abbreviations: AAS: anabolic androgenic steroids

prescribed hormonal therapies for symptom management.[19] When asked about their confidence in managing hypogonadism following AAS use, only 20% of respondents stated that they felt confident or extremely confident in doing so.[19]

Patients often ask for post-cycle treatment (PCT), which may include use of human chorionic gonadotropin, SERMs and/or aromatase inhibitors.[13] Several recovery algorithms have been proposed, including an algorithm described by Rahnema et al.,[14] and another termed the "Scally Protocol", which is a popular discussion topic on online forums.[4] Although PCT is often requested, there is no high quality medical evidence demonstrating that it either hastens recovery of testicular function or produces better long-term outcomes.[4,10] In fact, participants in the HAARLEM study had similar serum testosterone levels 3 months after AAS cessation regardless of whether PCT was employed.[10]

There is also a lack of consensus regarding which laboratory tests and imaging studies should be completed in current and former AAS users. One review characterized physicians' overall diagnostic evaluations of these patients to be "inconsistent and at times inadequate."[3] A reasonable approach could include measuring total testosterone along with either free or bioavailable testosterone levels (given the suppressive effects of AAS on sex hormone-binding globulin) as well as LH and FSH levels to observe for recovery of the hypothalamic-pituitary-gonadal axis. Additional testing should include hemoglobin and hematocrit, especially if the patient has a history of erythrocytosis associated with their AAS use. In patients who have used 17α-alkylated AAS, assessment of liver enzymes and liver function tests are advised,[5] although the evidence supporting routine hepatic ultrasounds remains uncertain. Some authors also advise evaluation of a lipid profile, electrolytes, calcium, glucose, creatinine, and blood urea nitrogen.[18] If there is suspicion that a patient is employing a "cutting phase" in their AAS cycles, during which they are stacking multiple substances to lose weight, measurement of insulin-like growth factor-1 and thyroid testing should also be considered.[13] Finally, prostate-specific antigen testing should be considered on an individualized basis.[3,18]

Recommendations for cardiac monitoring vary widely across studies, with one author suggesting echocardiograms be ordered on an individualized basis.[10]

Many AAS users experience difficulty with prolonged cessation of AAS. One study reported unsuccessful cessation attempts in 60% of respondents.[3] This highlights the need for a multidisciplinary approach that includes addiction services and behavioural health specialists to support recovery and reduce the risk of relapse.[3]

Conclusions/Future Goals

Despite recent progress, this field remains fragmented by barriers to both knowledge and trust. These challenges range from clinical discomfort and a lack of public health recognition to the more profound erosion of the physician-patient relationship. Without mutual trust, patients are less likely to disclose AAS use, making it difficult to establish the shared goals that are central to an effective therapeutic partnership.

Addressing the growing concerns surrounding the use of AAS will require a coordinated strategy that includes further research, improved education for both physicians and the public, and the development of public health policies aimed at mitigating harm and supporting patient care.

Public education campaigns should be directed toward populations at highest risk for AAS use, alongside more stringent restrictions on online sales and improved enforcement and quality control within the supplement industry.

There is also a need for more effective strategies to address the role of internet-based misinformation and the growing influence of large language model artificial intelligence programs in this field. Further research is needed to better understand the links between social media and body image issues in men, including the development of body dysmorphia.

Research that focuses on the management of AAS use and on effective strategies to support patients during their recovery is essential. Equally important is recognition of the need for close collaboration between physicians and mental health care providers throughout this process. Improving physician education about AAS use and addressing physician discomfort in this area will improve the likelihood of patients being willing to disclose use, thereby leading to better outcomes in the long-term.

Physicians need to be educated and willing to engage with patients navigating AAS use and recovery. Although these discussions may be uncomfortable, AAS use remains a growing public health concern that is unlikely to resolve in the immediate future and requires thoughtful, sustained clinical engagement.

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To Hold or Not to Hold? Periprocedural Management of Glucagon-like Peptide-1 Receptor-based Agonists (GLP-1ra) in Patients with Diabetes and Obesity

Tayyab S. Khan, MD

Glucagon-like peptide-1 receptor-based agonists have transformed the care of patients with diabetes and obesity. However, case reports that have associated their use with retained gastric contents and pulmonary aspiration have raised concerns regarding their safe use in patients undergoing procedures involving deep sedation, general anesthesia, or upper endoscopy. Here we present the evidence underlying these concerns and provide an evidence-informed framework for the periprocedural management of these agents. Further research is needed to better characterize these risks and provide mitigation strategies for individuals taking them in the perioperative period.

Introduction

Glucagon-like peptide-1 receptor (GLP-1r)-based agonists (GLP-1ra) were initially developed for the treatment of diabetes and obesity, but have since emerged as treatment options for a broader range of conditions, including obstructive sleep apnea, metabolic dysfunction associated steatotic liver disease, heart failure, chronic kidney disease, and even cardiovascular risk reduction in patients with obesity or diabetes.[1] Due to their myriad beneficial

Non GLP-1R-based agonists that can delay gastric emptying	• Opioid analgesics • Anticholinergic agents • Tricyclic antidepressants • Calcium channel blockers • Progesterone • Octreotide • Proton pump inhibitors • Interferon alpha • L-DOPA • Sucralfate • Aluminum hydroxide antacids • β-adrenergic receptor agonists • Glucagon

Figure 1. Non GLP-1ra medications that can delay gastric emptying.[11]

Abbreviations: GLP-1ra: Glucagon-like peptide-1 receptor-based agonists; **L-DOPA:** 3,4-dihydroxy-L-phenylalanine

effects, we have seen a surge in the prescription patterns for these medications,[2] one that is likely to continue with easier access and the growing number of indications for their use.

GLP-1ra have been associated with a delay in gastric emptying (GE), an effect that has been correlated with their antihyperglycemic and weight lowering effects.[3,4] This delay in GE, along with reports of retained gastric contents (RGC) and the risk of pulmonary aspiration, has raised concerns regarding their safety during the perioperative period. Recently, several international groups have provided guidance on the use of these agents prior to elective surgery. Considerable divergence exists within current guidance regarding perioperative treatment with these agents. Some groups have suggested withholding these agents in all patients for varying amounts of time, ranging from three drug half-lives,[5] to one day for daily and one week for weekly GLP-1ra.[6] Others advocate taking an individualized approach, withholding them in some patients deemed at higher risk for aspiration for one day for daily and one week for weekly GLP-1ra.[7] In contrast, several recommendations advise against withholding these agents prior to surgery.[8-10] Our own recommendations similarly support using a personalized approach to decisions regarding withholding these agents prior to surgery.[11] Here, we review the background underlying the risk of aspiration with the use of GLP-1ra in patients undergoing elective procedures involving deep sedation, general anesthesia, or upper endoscopy, and use this evidence to formulate recommendations for their use in this patient population.

GLP-1ra and Delayed Gastric Emptying

GE has been associated with diabetes, even without the use of GLP-1ra. Risk factors for its development include type 1 diabetes,[12] longstanding duration (>10 years) of diabetes,[13] poor glycemic control (HbA1c >9%),[14] and obesity.[15] GE delay has also been associated with other commonly prescribed medications, including opioid agonists, proton pump inhibitors, calcium channel blockers, tricyclic antidepressants, and non-prescription substances such as alcohol, tobacco, and nicotine (**Figure 1**).[16] Several symptom groups have been inconsistently associated with delayed GE, including early satiety, nausea, vomiting, dyspepsia, and bloating. While their absence does not exclude delayed GE, their presence often necessitates further investigations, treatments, and precautionary measures to avoid complications.

GLP-1ra affect the gastrointestinal motor neuron system by acting on receptors located on the myenteric neurons, leading to inhibition of peristalsis and delayed GE.[17] In a meta-analysis, this effect was associated with a 36-minute delay in GE for solids but not liquids; however, a high level of heterogeneity (I^2=79%) was observed among studies involving solids.[18] The degree of GE varies within the drug class, with more pronounced effects observed with short-acting agents (lixisenatide, exenatide) versus long-acting

GLP-1ra (liraglutide, dulaglutide, semaglutide).[19] Tirzepatide, a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) co-agonist, has been shown to delay GE similar to that observed with GLP-1ra dulaglutide.[20] In a randomized, open label, head to head comparison, lixisenatide delayed GE to a greater extent compared to liraglutide.[21] Tachyphylaxis has been associated with longer acting, but not short-acting GLP-1ra. In studies examining the gastric emptying of solids in participants treated with liraglutide, GES time increased by 5 weeks of treatment, and decreased by 16 weeks, although it remained prolonged compared to baseline.[22] Similar results were reported in another trial with liraglutide, whereby liraglutide delayed GES at 5 weeks by a median of 70 minutes compared to placebo. While there was improvement in this parameter by 16 weeks, median GES time remained increased in those taking liraglutide by a median of 30 minutes compared to those taking placebo.[23] However, in half of these individuals who experienced GE delay at 5 weeks, it had normalized by 16 weeks, suggesting its reversibility in a subset of individuals taking liraglutide.[23] To our knowledge, data regarding the time to resolution of delayed GE upon discontinuing GLP-1ra are currently lacking.

GLP-1ra and Retained Gastric Contents

While there is evidence of a delay in GE with GLP-1ra which could be partially reversible with long-acting agents, it remains important to examine whether this delay leads to an increased risk of RGC. Multiple observational studies have demonstrated an increase in RGC on upper gastrointestinal endoscopy in individuals taking GLP-1ra compared to controls.[24-38] Evidence regarding whether holding GLP-1ra in accordance with multisociety guidance,[7] one day for daily agents and one week for weekly GLP-1ra, is mixed. Some studies suggest that withholding these agents protects against RGC with a reduction in this risk if these agents are withheld,[26] whereas others have demonstrated no difference in GLP-1ra cessation between those with and without RGC.[27] Potential mitigation strategies have also been explored that could be protective in reducing the risk of RGC, including use of a liquid diet on the day prior to same-day colonoscopy. In a case series of 57 individuals undergoing sleeve gastrectomy, no participant who adhered to a liquid diet for 24 hours prior to surgery experienced RGC.[35]

Contrary to this, a recent retrospective analysis reported a higher likelihood of RGC among patients taking GLP-1ra compared to those not taking these agents.[17] Among patients who underwent same-day colonoscopy, 86.4% were found to have RGC while only 13.6% did not. However, several limitations should be considered, including the retrospective nature of the study, the small number of patients who underwent same-day colonoscopy (n=22) versus the study population of 3,746 patients, the small number of patients on GLP-1ra (n=43), and the absence of information regarding concomitant use of medications or conditions that could affect gastric motility.

Diabetes itself could be a risk factor for RGC at the time of surgery, with or without the use of GLP-1ra. This possibility was evaluated in a meta-analysis that assessed RGC by ultrasonography and demonstrated a 2-fold higher prevalence of a "high-risk stomach" (increased antral cross-sectional area or gastric residual volume) in participants with diabetes mellitus. This study, however, did not specify the medication(s) used by these individuals and whether the use of GLP-1ra mediated this association.[39]

Another meta-analysis, which defined RGC as the finding of solid/food contents retained in the stomach assessed during gastroscopy, demonstrated a significantly higher risk among participants taking GLP-1ra compared to placebo (odds ratio [OR] 4.2).[40] While the duration of fast prior to the procedure did not appear to be protective against this risk,[41,42] most patients with RGC had been treated with a GLP-1ra for 2 months or less.[42,43] Although RGC was still experienced by some patients despite withholding the GLP-1ra for 7 days prior to the procedure,[44] the odds of RGC were higher in short term users (<12 weeks) versus long term users (>12 weeks) users of GLP-1ra (OR 2.48), providing credence to the view that the GLP-1ra-mediated effects on delayed GE may be partially reversible with long term use.[45]

GLP-1ra and the Risk of Aspiration

Although GLP-1ra have been linked with delayed gastric emptying of solids and the risk of RGC, let us turn our attention to the risk of aspiration in patients taking these agents prior to elective procedures. Much of the available data derives from observational studies with a high degree of heterogeneity. In many reported cases, pulmonary aspiration was experienced by individuals who had received their last dose of GLP-1ra within one week prior to the procedure,[46,47] with treatment durations ranging from very recent use up to 20 weeks.[47,48] Notably, this timeframe corresponds to the dose escalation phase or the period shortly thereafter for weekly GLP-1ra. Despite these observations, the overall risk of pulmonary aspiration remains low. In a meta-analysis comprising 13 studies involving 84,065 patients, use of GLP-1ra was associated with elevated rates of RGC and aborted procedures, no significant differences in aspiration rates were found between those taking GLP-1ra and those who were not.[40] Findings from a separate meta-analysis of 13 studies yielded a non-significant increased risk of pulmonary aspiration with GLP-1ra treatment (OR 1.20), with at least moderate heterogeneity across studies (I^2=59%).[11] In contrast to these reports, a recent large retrospective database analysis identified that preoperative use of GLP-1 ra was associated with a lower risk of pneumonitis within 7 days post-surgery compared to non-use of these agents.[49] Among GLP-1 users, pneumonitis risk was increased in those with asthma, chronic obstructive pulmonary disease, and heart failure. Taken together, these data suggest that despite the delay in GE, and possibility of RGC, the risk of aspiration may not be universal in patients using GLP-1ra agonists in the perioperative period. These findings call for an individualized approach to preprocedural management rather than a universal strategy for withholding these agents.

Recommendations for Perioperative Management

Based on our understanding of the available data surrounding the risk of RGC and pulmonary aspiration associated with GLP-1ra, we suggest a personalized approach when deciding whether to withhold these agents prior to procedures involving deep sedation, general anesthesia, or upper endoscopy. These recommendations are consistent with our previously published guidance and are presented in **Figure 2**.[11]

1. All Individuals undergoing these procedures should follow standard fasting recommendations and adhere to a liquid diet for 8–12 hours prior to the procedure. The decision to withhold GLP-1ra should be individualized.
2. In most individuals, GLP-1ra therapy may not need to be routinely withheld prior to their procedure, since the risk of pulmonary aspiration remains low.
3. Individuals at higher risk of RGC or pulmonary aspiration, including those taking short-acting GLP-1ra; long-acting GLP-1ra initiated within the past 16 weeks, or currently undergoing dose titration; those experiencing ongoing gastrointestinal symptoms or diagnosed with gastroparesis; individuals with poor glycemic control (HbA1c >9%); or those taking other medications known to increase GE time (**Figure 1**), should have their GLP-1ra withheld.
4. If GLP-1ra is withheld, it should occur for >3 half-lives for weekly agents, and for >5 half-lives for daily agents (**Table 1**). In these cases, consideration should be given to bridging therapy for antihyperglycemic and anti-obesity effects.
5. In high-risk individuals who did not withhold their GLP-1ra prior to the procedure or have ongoing symptoms on the day of the procedure, or who require urgent procedures, point-of-care gastric ultrasound should be considered to assess for RGC. If ultrasound is unavailable, inconclusive, or reveals RGC, full stomach precautions should be implemented, or if possible, the procedure should be delayed.

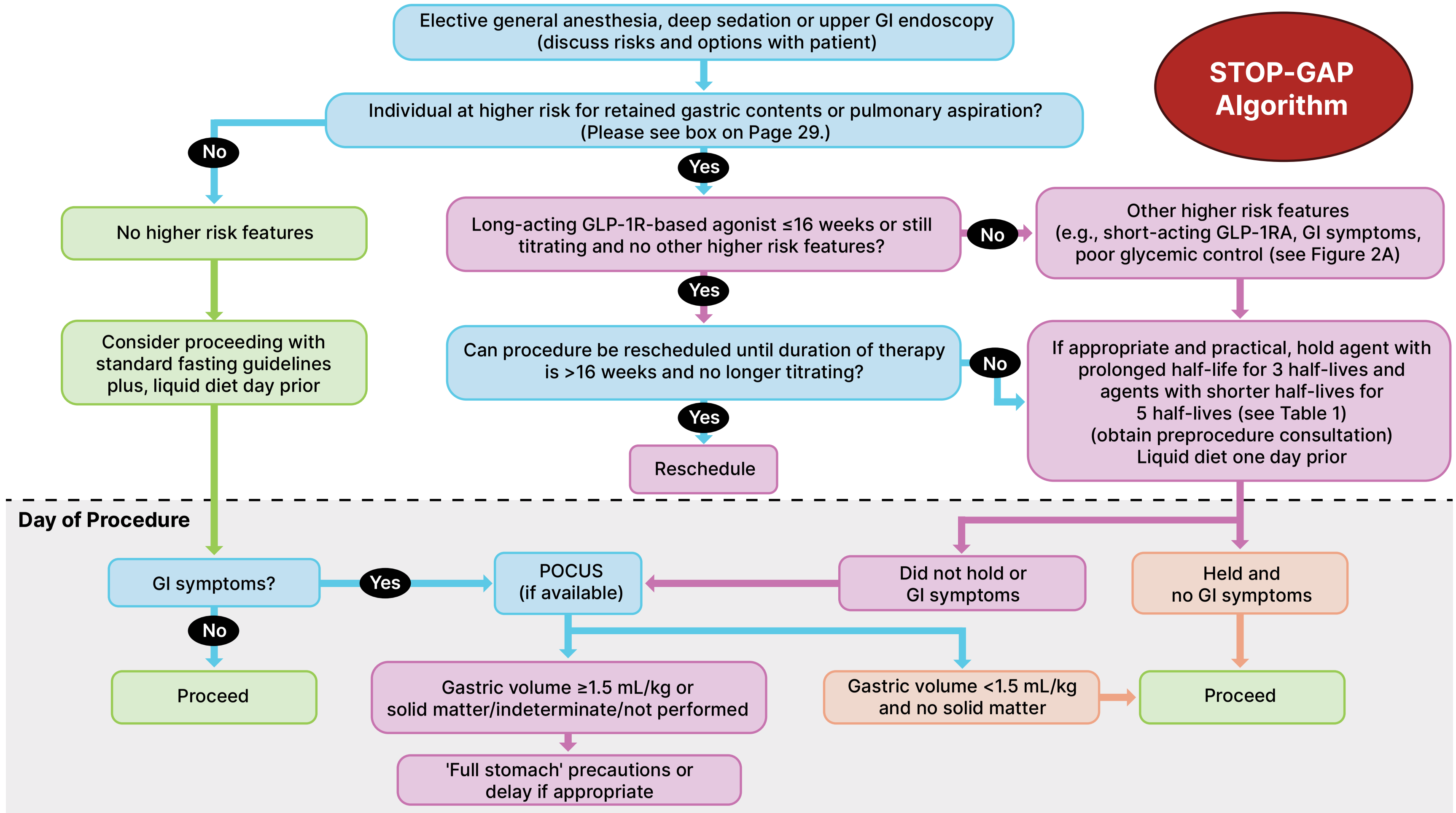

Figure 2. The STOP-GAP Algorithm.[11]

Abbreviations: GAP: GLP-ra related aspiration during procedures; **GI:** gastrointestinal; **POCUS:** point-of-care ultrasound.

Generic Name	Brand Name	Indications	Route and Frequency	Half-life	Cessation Time
Administered weekly (QW) or prolonged half-life					
Dulaglutide	Trulicity®	T2DM	SC QW	~5 days	~15 days[a]
Exenatide ER	Bydureon BCise®	T2DM	SC QW	~2 weeks	~6 weeks[a]
Semaglutide (injectable)	Ozempic®/Wegovy®	T2DM / Obesity	SC QW	~7 days	~21 days[a]
Semaglutide (oral)	Rybelsus®	T2DM	PO QD	~7 days	~21 days[a]
Tirzepatide	Mounjaro®/Zepbound®	T2DM / Obesity	SC QW	~5 days	~15 days[a]
Daily administered with shorter half-lives					
Exenatide IR	Byetta®	T2DM	SC BID	2.4 h	1 day[b]
Liraglutide[c]	Victoza®/Saxenda®	T2DM / Obesity	SC QD	13 h	3 days[b]
Lixisenatide[c]	Adlyxine	T2DM	SC QD	3.1 h	1 day[b]

Table 1. Half-lives and cessation times of GLP-1 receptor-based agonists.[11]

a: 3 half-lives;
b: 5 half-lives (rounded up to the nearest day);
c: also available as a fixed ratio combination (FRC) agent with basal insulin. If withholding an FRC agent, consider periprocedure use of the basal insulin component as per clinical judgement.

Abbreviations: BID: twice daily; **ER:** extended-release; **IR:** immediate-release; **PO:** per os (orally); **QD:** once daily; **QW:** once weekly; **SC:** subcutaneous; **T2DM:** type 2 diabetes mellitus.

Conclusion

GLP-1ra have transformed the treatment landscape for patients with type 2 diabetes and obesity. However, their use in the setting of procedures involving deep sedation, general anesthesia, or upper endoscopy have raised concerns about retained gastric contents and pulmonary aspiration. We provide an evidence-informed framework that emphasizes an individualized approach to decisions about preprocedural withholding of these agents. The current evidence, however, is based on observational studies with a high degree of heterogeneity. Well designed, prospective studies are required to further characterize this risk and elucidate the best strategies for risk mitigation.

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Androgenetic Alopecia: Pathogenesis, Evaluation, and Management

Anastasiya Muntyanu, MD, PhD, FRCPC, FAAD

Introduction

Androgenetic alopecia (AGA) is a common, non-scarring, alopecia characterized by the progressive transformation of terminal hairs into miniaturized vellus hairs in a patterned distribution. Female AGA—often termed female-pattern hair loss (FPHL)—and male AGA (often termed male-pattern hair loss, MPHL) share similar underlying pathophysiologic, histopathologic, and trichoscopic features; however, they differ in their clinical presentation and patterns of scalp distribution.[1]

AGA represents the most prevalent cause of hair loss in both men and women and can have a significant impact on quality of life. Evidence from a large meta-analysis demonstrates a moderate impairment in health-related quality of life and emotional well-being, underscoring the meaningful psychosocial burden of AGA.[2]

Although patients are often referred for dermatologic evaluation, AGA may also have important endocrine implications. In selected cases—particularly in women or in atypical presentations—it may reflect underlying endocrinologic abnormalities, warranting targeted screening and management.

Epidemiology

The prevalence and severity of AGA increases with age, affecting up to 80% of men and 50% of women over their lifetime.[3] In women, prevalence rises from approximately 12% by age 29 to 25% by age 50, reaching 41%–50% by age 70 and older.[4] In men, a US-based study reported a moderate MPHL in 48% of those aged 18–49 years, including 16% of those aged 18–29 and 53% of those aged 40–49.[5]

Although onset can occur in adolescence, pediatric AGA remains uncommon.

Pathophysiology

AGA is a polygenic, androgen-dependent condition characterized by progressive miniaturization of hair follicles, resulting in the conversion of terminal hairs to fine vellus-like hairs. Established risk factors include genetic predisposition and, in some cases, underlying endocrinologic conditions such as polycystic ovary syndrome (PCOS), congenital adrenal hyperplasia (CAH), and androgen-secreting tumours.

Genetic Factors

AGA has a strong hereditary basis, with polygenic inheritance supported by findings from multiple genome-wide association studies. Variants influencing androgen receptor signalling appear to play a central role, particularly in men. In addition, genetic loci involved in hair follicle development and cycling pathways have been consistently implicated across populations.

Hormonal and Local Mechanisms

Dihydrotestosterone (DHT), produced from testosterone via 5α-reductase, is the key androgen driving AGA. Local DHT levels and 5α-reductase activity are increased in balding scalp compared with non-balding areas, contributing to progressive follicular miniaturization. Rather than acting in isolation, DHT also promotes structural changes around the follicle, including perifollicular fibrosis and reduced vascular support, which may impair nutrient delivery and limit hair growth.[6]

Importantly, most patients—particularly women—have normal circulating androgen levels, indicating that AGA reflects increased local follicular sensitivity to androgens rather than systemic androgen excess.

Clinical Presentation

Both MPHL and FPHL are characterized by progressive, non-synchronized follicular miniaturization, resulting in the replacement of terminal hairs with short, thin, vellus hairs and, with longstanding disease, reduced follicular density.

MPHL is characterized by frontotemporal recession and vertex thinning. In contrast, FPHL hair loss predominantly affects the mid-scalp and vertex, with relative preservation of the frontal hairline. Thinning may extend anteriorly along the central part, producing a characteristic “Christmas tree” pattern, with widening of the central part correlating with disease severity. Less commonly, women may exhibit a more extensive pattern with frontotemporal recession and vertex involvement resembling MPHL.[7]

Overlap between these patterns can occur, and a history of increased hair shedding (i.e., telogen effluvium) may precede the diagnosis of FPHL.

Severity Grading

MPHL

The Hamilton and Norwood scale is the most commonly used classification system for grading MPHL (**Figure 1**).

FPHL

In FPHL, the Ludwig classification (three grades) and the Sinclair scale (five stages) are commonly used to assess disease severity (**Figure 2A and Figure 2B**); however, no single grading system has been universally adopted.

Differential Diagnosis

The differential diagnosis includes telogen effluvium (TE), a common cause of diffuse hair shedding that may be triggered by physiological or psychological stress, rapid weight loss, systemic illness, or iron deficiency. TE may coexist with or precede the diagnosis of FPHL. Other considerations include alopecia areata (AA), which can occasionally present with diffuse thinning and mimic early AGA. It is also important to exclude inflammatory causes of hair loss, particularly scarring alopecias, which may present with scalp symptoms (e.g., burning or pruritus) and perifollicular erythema or scaling on dermoscopy.

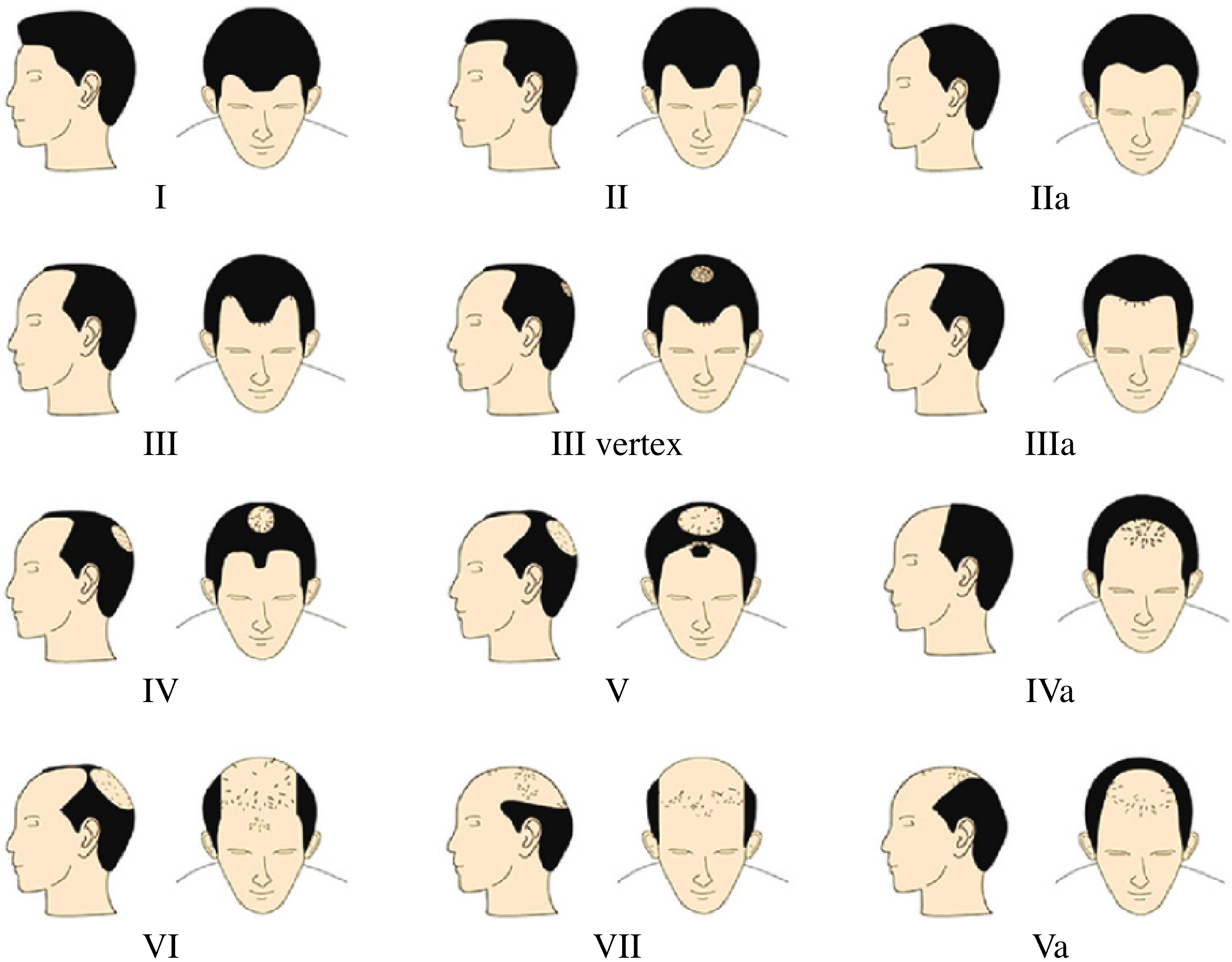

Figure 1. Male pattern baldness: classification and incidence; *adapted from Norwood, O.T.*[8]

These conditions can lead to permanent hair loss and require alternative management strategies.

Endocrine disorders should be considered in the differential diagnosis. Thyroid dysfunction may present with diffuse hair loss, while hyperandrogenic states—including PCOS, CAH, and androgen-secreting tumours—may contribute to or mimic AGA. In women, early-onset or rapidly progressive patterned hair loss, particularly when accompanied by clinical features of androgen excess, should prompt evaluation for hyperandrogenism.

Diagnosis and Investigations

The diagnosis of AGA is primarily clinical, based on patterned thinning, gradual progression, and follicular miniaturization. Trichoscopy can support the diagnosis, demonstrating variation in hair shaft diameter, an increased proportion of single-hair follicular units, and the presence of yellow dots representing follicular openings filled with sebum and keratin. Scalp biopsy is rarely required but may be helpful when the diagnosis is unclear or when scarring alopecia, AA, or chronic TE are suspected.

From an endocrine perspective, the key consideration is whether hair loss reflects local follicular sensitivity to androgens or an underlying systemic disorder. Although AGA is androgen-mediated, most patients have normal circulating androgen levels, and AGA alone is not a reliable marker of hyperandrogenism. Consequently, routine endocrine testing is not required in the absence of clinical features of androgen excess. However, evaluation should be considered in cases of early-onset or rapidly progressive/severe hair loss, or when accompanied by hirsutism, acne, menstrual

Figure 2A. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex; *adapted from Ludwig E.*[9]

Figure 2B. The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women; *adapted from Sinclair R. et al.*[10]

irregularity, infertility, galactorrhea, virilization, or features of thyroid disease. Initial investigations may include total and free testosterone, dehydroepiandrosterone sulfate (DHEA-S), 17-hydroxyprogesterone, and prolactin, with additional testing guided by clinical suspicion. In men with typical MPHL, hormonal testing is not required.

FPHL is relatively common among patients with PCOS, with reported prevalence estimates ranging from 20%–30%.[11] In a cohort study of 254 patients, FPHL was identified in 22% of women with PCOS and was more frequently associated with clinical features of hyperandrogenism, such as acne and hirsutism, compared with those without FPHL (96.3% vs. 70.6%).[12] However, no significant differences were observed between groups in terms of biochemical hyperandrogenism or metabolic parameters. A meta-analysis further demonstrated an increased risk of FPHL in patients with PCOS compared to controls (odds ratio [OR] 4.74, 95% confidence interval [CI] 0.57–39.52).[13] Conversely, the pooled prevalence of PCOS among patients with FPHL was estimated at 32.3% (range 13.6%–59.1%).[13] Overall, the available data are heterogeneous and of modest quality, suggesting that while FPHL frequently coexists with PCOS, it is not a reliable independent marker of endocrine or metabolic severity.

Beyond PCOS, the association between AGA and broader metabolic comorbidities has also been investigated. A meta-analysis demonstrated a significantly higher prevalence of metabolic syndrome among patients with AGA compared to controls (pooled OR 3.46, 95% CI 2.38–5.05; $p<0.001$).[14] The association with metabolic syndrome appears stronger in women, patients with early-onset disease, and individuals of African ethnicity. However, these associations are not consistent across studies. In clinical practice, targeted screening and longitudinal assessment may be considered in selected patients.

Treatments

Treatment options for AGA include topical and systemic therapies, many of which target androgen pathways by reducing androgen production, altering androgen metabolism, or blocking androgen receptor activity. Systemic antiandrogen therapies are contraindicated during pregnancy due to the risk of fetal abnormalities. In patients with an identified underlying endocrine disorder, management should be directed according to established endocrinologic guidelines.

Early diagnosis and initiation of treatment are desirable because treatments are more effective at preventing progression of hair loss than stimulating regrowth.

A Canadian consensus statement has outlined interventions with high levels of agreement (**Table 1**) and proposed a stepwise approach to the management of MPHL and FPHL (**Table 2**).[15]

Topical Minoxidil

Topical minoxidil is approved by Health Canada for the treatment of AGA in both males and females. It promotes hair growth primarily through vasodilation, prolongation of the anagen phase, increases shaft diameter, and activation of follicular signalling pathways (including Wnt/β-catenin). It is typically applied to affected scalp areas as a 5% foam once daily (women) or twice daily (men), or as a 2% solution twice daily. Clinical response is expected after 3–6 months and continued use is required to maintain therapeutic effects.

Topical Finasteride

Topical finasteride has emerged as an alternative to oral therapy, with studies showing increased hair density at 24 weeks compared to placebo, with efficacy comparable to oral finasteride.[16] It exerts its effect via local inhibition of 5α-reductase, thereby reducing scalp DHT levels. Topical formulations (e.g., 0.25% once daily) are generally well tolerated and are associated with fewer systemic adverse effects, particularly sexual side effects, compared to oral finasteride.

Oral Minoxidil

A 2024 randomized study published in *JAMA Dermatology* demonstrated that oral minoxidil (5 mg daily) was non-inferior to 5% topical minoxidil applied twice daily over 24 weeks, with a comparable safety profile.[17] Although oral therapy showed a trend toward greater improvement—particularly at the vertex—this did not reach statistical significance. In parallel, an international modified Delphi consensus reported 97.7% expert agreement supporting the use of low-dose oral minoxidil in AGA.[18]

Low-dose oral minoxidil is generally well tolerated. The most common adverse effect is hypertrichosis (24% overall), followed by transient shedding, which typically peaks at 4 weeks and resolves by 12 weeks.[18] Cardiovascular-related effects are dose-dependent and include peripheral edema (1.3–16.4%), tachycardia/palpitations (0.9–4%), and orthostatic symptoms (1.7–4.5%).

Oral Spironolactone

Spironolactone is the most commonly used off-label systemic antiandrogen for the treatment of FPHL. It functions as a competitive androgen receptor antagonist and reduces androgen production. Typical dosing ranges from 100–200 mg daily, with treatment durations of at least 6–12 months required to assess efficacy. Available evidence suggests benefit in both stabilizing hair loss and promoting regrowth, with response rates reported between approximately 44% to 74%, and higher responses observed in patients with concomitant hirsutism or acne.[11]

Adverse effects are related to its antiandrogenic and mineralocorticoid activity and may include menstrual irregularities, breast tenderness, fatigue, postural hypotension, and electrolyte disturbances. Spironolactone is contraindicated in pregnancy due to the risk of feminization of a male fetus and should be used with reliable contraception in women of childbearing potential.

Consensus Level	Agreement Supporting the Use of the Intervention
Consensus (>75%)	• Oral dutasteride (100%) • Oral finasteride (100%) • Oral minoxidil (100%) • Platelet-rich plasma (100%) • Topical minoxidil (100%) • Topical finasteride (91%) • Microneedling (82%)
Near consensus (55–74%)	• Ketoconazole shampoo (73%) • Topical products as part of a regimen including shampoos (73%) • Intralesional dutasteride (55%) • Laser (55%) • Aminexil (55%)

Table 1. Final Recommendations for the Management of Androgenic Alopecia; *adapted from Landells I. et al.* ***A Canadian Consensus on Androgenetic Alopecia: Approach and Management***.[15] Please see the full publication for therapies that are not recommended.

Line of Therapy	MPHL	FPHL
First line	• 5% minoxidil foam (BID) • Oral finasteride 1 mg daily	• 5% topical minoxidil
Second line	• Topical finasteride 0.25% daily • Oral minoxidil 1.25–5 mg daily • Oral dutasteride 0.5 mg (2–3 times/week • LLLT • PRP	• Oral spironolactone ± oral minoxidil • Oral finasteride/dutasteride or spironolactone ± oral minoxidil
Third line	• Saw palmetto • Aminexil • Ketoconazole topical • Other adjuncts (topical caffeine, botox, topical cetirizine, mesotherapy with dutasteride)	• Procedural therapies (PRP, laser, mesotherapy)
Other options	—	• Cosmetics (aminexil, nutraceuticals, herbal products)

Table 2. Treatment Guidelines for Androgenic Alopecia (Males and Females); *adapted from Landells I. et al.* ***A Canadian Consensus on Androgenetic Alopecia: Approach and Management***.[15]

Abbreviations: BID: twice daily; **FPHL:** female-pattern hair loss; **LLLT:** low-level laser therapy; **MPHL:** male pattern hair loss; **PRP:** platelet-rich plasma

Oral Finasteride/Dutasteride

Finasteride and dutasteride are 5α-reductase inhibitors that reduce conversion of testosterone to DHT, a key mediator of follicular miniaturization in AGA. Finasteride selectively inhibits type II 5α-reductase and is approved by Health Canada for the treatment of MPHL at 1 mg daily, whereas dutasteride inhibits both type I and type II isoenzymes and is used off-label for AGA.

In men, both agents improve hair density and slow progression. In a randomized trial of 917 men, dutasteride 0.5 mg outperformed finasteride 1 mg at 24 weeks for hair count and photographic outcomes.[19] A meta-analysis similarly reported greater efficacy with dutasteride than finasteride, with no significant differences in sexual adverse events between the two treatments.[20]

Adverse effects may include decreased libido, erectile dysfunction, ejaculatory dysfunction, and mood-related symptoms. As these medications reduce prostate-specific antigen (PSA) levels, baseline PSA assessment and appropriate interpretation of subsequent PSA values should be considered in men undergoing prostate cancer screening. In women, finasteride and dutasteride are not considered first-line and are used off-label, generally in selected postmenopausal women or in premenopausal women only with reliable contraception.

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is a procedural therapy for AGA that involves injection of autologous platelet concentrates into the scalp. Its proposed mechanisms include the release of platelet growth factors that may support follicular function and angiogenesis.

A meta-analysis of randomized controlled trials has shown statistically significant increases in hair density compared to placebo at 3 and 6 months.[21] However, effects on hair thickness are less consistent, and overall study quality is variable. In clinical practice, responses are often heterogeneous. Combination therapy may improve outcomes, with greater benefit when PRP is used alongside topical minoxidil compared to either treatment alone. Overall, PRP may be considered an adjunctive option in selected patients.

Conclusion

AGA is a common form of hair loss that can significantly impact quality of life. Clinical presentation is sex-specific, with characteristic patterns observed in both male- and female-pattern hair loss. Although systemic causes are uncommon, clinicians should remain aware of potential associations with conditions such as PCOS and metabolic syndrome. A range of treatment options is available, with first-line therapies including topical minoxidil and, in men, oral finasteride.

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Financial Disclosures

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