Volume 4 – Issue 2

Canadian Diabetes & Endocrinology Today

ISSN 2817-4089 (print)
ISSN 2817-4097 (online)

Summer 2026

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doi.org/10.58931/cdet.2026.4254

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Losing Weight, Losing Muscle? Muscle Health During GLP-1-Based Obesity Therapy

Michael Tsoukas, MD

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related nutrient-stimulated hormone (NuSH) therapies have transformed obesity pharmacotherapy, delivering weight loss approaching that seen with bariatric surgery.[1-4] However, concerns have emerged regarding loss of fat-free mass, skeletal muscle mass, and possible sarcopenia. Reductions in lean mass occur during treatment with semaglutide and tirzepatide, but these changes are generally proportional to total weight loss and occur alongside greater reductions in fat mass, visceral adiposity, and ectopic lipid deposition.[1,5,6] The clinical interpretation of lean mass loss is further complicated by limitations of dual-energy X-ray absorptiometry, which cannot distinguish contractile muscle from body water, organs, and connective tissue.[6] Importantly, available data suggest that muscle quality and metabolic function may improve despite reductions in absolute lean mass.[6] Overall, current evidence does not support disproportionate skeletal muscle loss during GLP-1-based obesity therapy. This review summarizes current evidence on GLP-1RA and NuSH-associated changes in muscle mass, discusses mechanisms, identifies populations at risk, and outlines practical strategies to preserve muscle health during treatment.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related nutrient-stimulated hormone (NuSH) therapies have transformed obesity pharmacotherapy, producing weight loss that approaches outcomes historically associated with bariatric surgery.[1-4] The approval of GLP-1RAs, such as semaglutide and dual GIP/GLP-1 receptor agonists (GIP/GLP-1 RAs) such as tirzepatide, have changed the therapeutic landscape of obesity management. In the STEP 1 trial, once-weekly semaglutide 2.4 mg produced a mean body-weight reduction of 14.9% at 68 weeks,[1] while in the SURMOUNT-1 trial, tirzepatide produced mean reductions of up to 20.9% at 72 weeks.[3] Current evidence indicates that reductions in lean mass occur during treatment with semaglutide and tirzepatide, but these changes are generally proportional to total weight loss and occur alongside larger reductions in fat mass, visceral adiposity, and ectopic lipid deposition.[1,5,6]

These benefits have raised an important clinical question: does incretin-based pharmacological weight loss compromise skeletal muscle? This question is particularly relevant for those at higher risk for muscle loss, including older adults, patients with sarcopenic obesity, and individuals with low baseline muscle reserve. Skeletal muscle is central to mobility, insulin-stimulated glucose disposal, resting energy expenditure, and healthy aging.[7,8] Loss of muscle mass and strength is associated with frailty, falls, disability, and adverse metabolic outcomes.[9]

However, lean-mass loss during weight reduction is not unique to GLP-1RAs or other NuSH therapies. Across dietary restriction, bariatric surgery, and pharmacotherapy, approximately 20–40% of total weight loss may derive from fat-free mass.[8,10] Therefore, the central clinical issue is not whether lean mass decreases, but whether the magnitude, composition, and functional consequences of this decrease are maladaptive.

Recent expert analyses have challenged the assumption that reductions in lean mass necessarily indicate clinically meaningful muscle loss. Neeland et al. highlighted the substantial variability in reported lean-mass changes across GLP-1-based therapies and emphasized that lean mass should be interpreted in the context of muscle composition, function, metabolic health, and overall weight loss.[11] Likewise, Conte et al. argue that weight-loss–associated reductions in fat-free mass are expected physiological adaptations and should be evaluated according to their effects on strength, mobility, physical function, and long-term health outcomes rather than body-composition measurements alone.[12] Together, these perspectives suggest that the effects of GLP-1-based therapies on skeletal muscle are more complex than changes in lean mass alone and require a broader assessment of muscle health.

Evidence of Body Composition Changes

Body Composition Changes With Liraglutide

Liraglutide was the first GLP-1 receptor agonist approved for obesity treatment, with efficacy established in the SCALE trial program. Although body-composition data are limited, a magnetic resonance imaging (MRI)-based randomized controlled trial involving 128 participants demonstrated a significant reduction in thigh muscle fat infiltration with liraglutide compared with placebo, while muscle volume remained unchanged.[13] These findings suggest that liraglutide may improve muscle quality through reductions in intramuscular fat without adversely affecting muscle mass, a pattern that is consistent with observations reported for newer GLP-1-based therapies. However, functional muscle outcomes were not assessed.

Body Composition Changes With Semaglutide

The STEP 1 body-composition substudy provides the most frequently cited and robust semaglutide data. In adults with overweight or obesity without diabetes, semaglutide 2.4 mg reduced total fat mass by 19.3% and visceral fat mass by 27.4% over 68 weeks.[1] Lean body mass also declined by 9.7%; however, fat mass decreased to a substantially greater extent. Consequently, the proportion of body weight represented by lean mass increased by approximately 3 percentage points, and the lean mass-to-fat mass ratio improved.[1] These findings suggest favourable body-composition remodelling despite reductions in absolute lean mass.

The commonly cited concern is that a sizable fraction of total weight loss observed in the STEP 1 trial reflected lean mass. This finding should be interpreted cautiously. First, dual-energy X-ray absorptiometry (DXA)-derived lean mass includes not only contractile skeletal muscle,

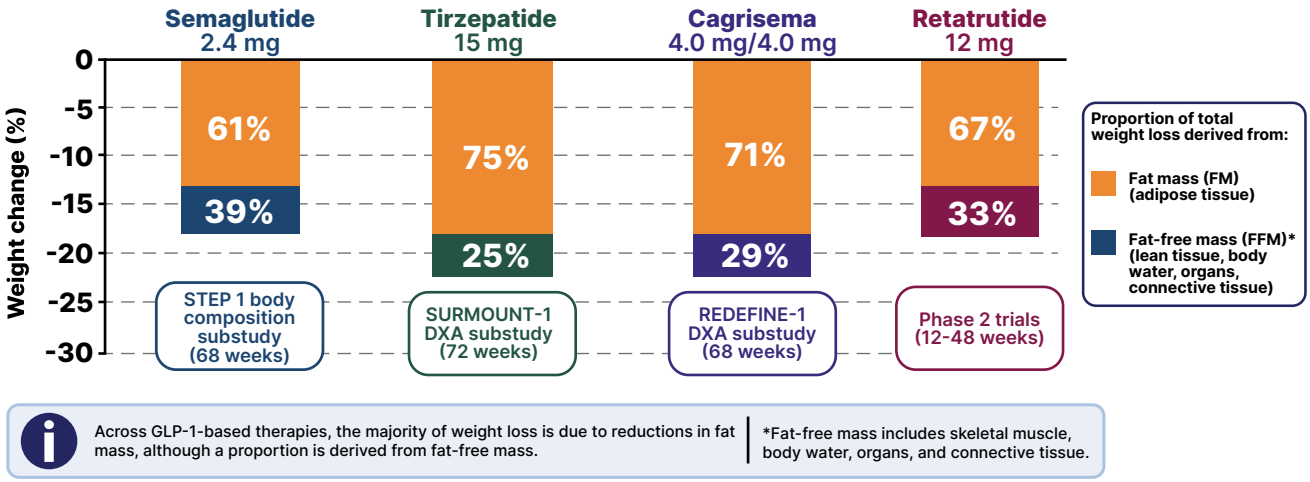

Figure 1. Composition of Weight Loss During GLP-1-Based and NuSH-Based Obesity Pharmacotherapy; *adpted from Rubino D et al. Diabetes Care. 2021;44:1988-1996 (STEP 1 body composition substudy); Look AHEAD et al. JAMA. 2022;327:1389-1400 (SURMOUNT-1 DXA substudy); Aronne LJ et al. Obesity (Silver Spring). 2024;32:2326-2334 (REDEFINE-1 DXA substudy); Rosenstock J et al. N Engl J Med. 2023;389:514-526 (retatrutide phase 2 body composition analysis).*

Note: Percentages may not sum to 100% due to rounding.

Abbreviations: DXA: dual-energy X-ray absorptiometry; **GLP-1RA:** glucagon-like peptide-1 receptor agonists

but also water, organs, connective tissue, and other non-fat compartments. Second, loss of lean tissue is expected when total body weight and mechanical loading decrease. Third, the direction of overall body-composition change was favourable, with greater reductions in adiposity than lean mass, and a relative increase in lean mass.[1,6]

Longer-term semaglutide data from the STEP 5 trial demonstrated sustained body-weight reduction over 104 weeks, although detailed muscle-function outcomes were limited.[2] Taken together, findings from the STEP program support the interpretation that semaglutide produces substantial fat loss accompanied by expected reductions in lean mass, rather than selective muscle wasting.[1,2]

Body Composition Changes With Tirzepatide

Tirzepatide produces greater mean weight loss than semaglutide in placebo-controlled obesity trials. In the SURMOUNT-1 trial, adults with obesity or overweight without diabetes treated with tirzepatide lost up to 20.9% of body weight at 72 weeks.[3]

The SURMOUNT-1 DXA substudy reported that tirzepatide reduced body weight by 21.3%, fat mass by 33.9%, and lean mass by 10.9% at week 72.5 Approximately 75% of weight lost was fat mass and 25% was lean mass, a distribution consistent with many intensive weight-loss interventions.[5] These findings are clinically reassuring because they suggest preferential reduction in adiposity rather than disproportionate depletion of lean tissue.

Direct comparisons between semaglutide and tirzepatide body-composition studies is limited by differences in trial design, populations, and methodology. Nevertheless, both agents appear to produce favourable remodelling of body composition, with fat mass accounting for the majority of total weight lost.[1,5]

Emerging New Treatments

Amylin-based therapies may represent an important development in obesity pharmacotherapy. Cagrilintide, a long-acting amylin analog, is being evaluated both as monotherapy and in fixed-dose combination with semaglutide (CagriSema). In the REDEFINE-1 trial, CagriSema produced mean weight reductions of up to 22.7% at 68 weeks. In a prespecified DXA substudy, fat mass decreased by 35.7% while lean soft-tissue mass decreased by 14.4%, with approximately two-thirds of total weight loss

Study/Source	Population	Intervention	Duration	Body-composition Findings	Clinical Interpretation
Pandey et al.[13]	Adults with overweight or obesity (n=128)	Liraglutide 3.0 mg vs placebo	36 weeks	Significant reduction in thigh muscle fat infiltration on MRI; muscle volume unchanged	Suggests improved muscle quality without adverse effects on muscle volume
STEP 1 body-composition substudy[1]	DXA substudy of STEP 1	Semaglutide 2.4 mg vs placebo	68 weeks	Fat mass—19.3%, visceral fat mass—27.4%, lean body mass—9.7%; relative lean mass proportion increased by 3.0 percentage points	Favourable body-composition remodelling despite absolute lean-mass reduction
SURMOUNT-1 DXA substudy[5]	DXA substudy (n=160)	Tirzepatide vs placebo	72 weeks	Body weight—21.3%, fat mass—33.9%, lean mass—10.9%; approximately 75% of weight lost was fat mass and 25% was lean mass	Lean-mass reduction appears proportional and not excessive relative to fat loss
REDEFINE-1 DXA substudy[14]	Adults with overweight or obesity (DXA subgroup, n=252)	CagriSema (cagrilintide + semaglutide) vs placebo	68 weeks	Fat mass—35.7%, lean soft-tissue mass—14.4%; approximately 67% of total weight loss attributable to fat mass	Suggests favourable body-composition remodelling with preferential fat-mass reduction despite absolute lean-mass loss
Linge et al.[6]	Narrative review/primer	GLP-1RA and dual incretin therapy	—	Emphasized muscle quantity, composition, and function	Argues many observed muscle changes may be adaptive rather than maladaptive

Table 1. Evidence Summary Table, Summarizing Body Composition Findings; *courtesy of Michael Tsoukas, MD.*

Abbreviations: DXA: dual-energy X-ray absorptiometry; **GLP-1RA:** glucagon-like peptide-1 receptor agonists; **MRI:** magnetic resonance imaging

attributable to fat mass and one-third attributable to lean soft tissue.[14] These findings suggest favourable body-composition remodelling similar to that observed with semaglutide and tirzepatide. The RASMUS study, which is currently ongoing, is specifically designed to evaluate the effects of CagriSema on skeletal muscle insulin sensitivity, composition, and function. However, dedicated studies evaluating skeletal muscle quality, myosteatosis, strength, and long-term functional outcomes remain limited.

NuSH triple agonists may further reshape the field of obesity treatment. Retatrutide, a GLP-1/GIP/glucagon receptor agonist, has demonstrated weight reductions approaching 24–28% in studies, approaching outcomes observed after bariatric surgery.[15] Glucagon receptor activation may enhance energy expenditure, lipid oxidation, and reductions in adiposity, but human evidence regarding its independent effects on body composition, particularly lean mass and skeletal muscle, is currently limited. Ongoing TRIUMPH trials

may provide important insights regarding body composition, muscle quality, and functional outcomes during large-magnitude pharmacologically induced weight loss.

Oral incretin therapies may further expand access to obesity treatment. Orforglipron, a non-peptide oral GLP-1 receptor agonist, has demonstrated clinically meaningful weight loss in phase 3 obesity trials, although detailed body-composition and muscle-function data remain limited.[16] Future studies are needed to determine whether oral GLP-1 therapies produce muscle and body-composition effects comparable to injectable incretin-based treatments.

Mechanistic Considerations

Several mechanisms may explain the observed changes in body composition.

First, GLP-1RAs reduce energy intake through appetite suppression, delayed gastric emptying, and central satiety signalling.[1,3] The resulting reduced caloric intake inevitably creates a catabolic state in which both fat and lean tissues may decrease. If protein intake is insufficient, muscle protein synthesis may be impaired, especially in older adults with anabolic resistance.[9,11]

Second, GLP-1RA and NuSH therapies improve insulin sensitivity and reduce visceral and ectopic fat.[1,3] Skeletal muscle is the major site of insulin-stimulated glucose disposal. Improved insulin action may enhance muscle metabolic function even when absolute lean mass decreases.[8]

Furthermore, reductions in myosteatosis may improve muscle quality. Intramuscular lipid accumulation has been associated with impaired strength, poor physical performance, and metabolic dysfunction.[6,12] Reducing ectopic lipid within and around muscle may therefore improve the functional capacity of remaining muscle tissue.

Finally, GLP-1 signalling exerts anti-inflammatory and mitochondrial effects. Obesity is characterized by chronic low-grade inflammation, oxidative stress, and impaired mitochondrial function, all of which may contribute to muscle dysfunction.[6,13] Whether GLP-1RAs directly protect skeletal muscle independent of weight loss remains uncertain and requires further study.

Muscle Mass Versus Muscle Function

A major limitation of current evidence is that most trials assess body composition rather than muscle function. Sarcopenia is not defined by low muscle mass alone; contemporary consensus definitions emphasize low muscle strength as the primary parameter, with low muscle quantity or quality used to confirm the diagnosis.[9]

Therefore, a reduction in DXA-derived lean mass should not automatically be interpreted as sarcopenia. Measures of muscle quality, strength, gait speed, chair-rise performance, and patient-reported function are clinically more relevant than lean mass alone.[9] Available reviews conclude that GLP-1RA-associated reductions in lean mass may often represent adaptive remodelling during weight loss rather than pathological muscle wasting.[6]

However, the absence of robust long-term functional data is an important evidence gap. Few GLP-1RA obesity trials have systematically measured grip strength, walking speed, falls, frailty, or physical-performance batteries. This limits confidence when extrapolating trial results to frail older adults or patients with established-sarcopenia.

Muscle Quality: The Emerging Paradigm

One of the most important developments in obesity medicine is the distinction between muscle quantity and muscle quality. Traditional body-composition techniques such as DXA provide estimates of lean mass but offer limited information regarding muscle composition, strength, mitochondrial function, or intramuscular lipid accumulation. Consequently, reductions in lean mass may not accurately reflect a deterioration in skeletal muscle health.

Neeland et al. reviewed body-composition outcomes across multiple GLP-1-based clinical trials and demonstrated substantial heterogeneity in reported changes in lean mass.[11] The authors noted that lean-mass changes are influenced by baseline adiposity, diabetes status, age, imaging methodology, and magnitude of weight loss. Importantly, improvements in insulin sensitivity and reductions in ectopic fat may improve muscle quality despite reductions in absolute lean tissue.

Similarly, Conte et al. questioned whether weight-loss–induced reductions in muscle mass are clinically relevant in the absence of impaired physical function.[12] Successful weight-loss interventions, including caloric restriction, bariatric surgery, and pharmacotherapy, consistently reduce both fat mass and fat-free mass. However, available evidence does not demonstrate that these reductions necessarily translate into weakness, disability, or adverse functional outcomes.[20] Rather, improvements in mobility, cardiometabolic health, and physical performance frequently accompany substantial weight reduction.

These observations support a shift toward multidimensional assessment of muscle health incorporating muscle composition, strength, function, mobility, and physical performance rather than relying on lean-mass measurements alone.[6,9,12,19] Future obesity trials should therefore prioritize clinically meaningful measures of muscle function alongside body-composition assessments.

High-Risk Populations

Older adults deserve particular attention. Aging is associated with progressive loss of muscle mass, impaired muscle protein synthesis, reduced neuromuscular function, and lower levels of physical activity.[9] Patients with sarcopenic obesity may have high adiposity but low muscle reserve, making them vulnerable to functional decline during rapid weight loss.

Other high-risk groups include patients with chronic inflammatory disease, advanced heart failure, chronic kidney disease, cancer survivorship, prolonged immobility, very low protein intake, or prior bariatric surgery. In such patients, GLP-1RA therapy should not necessarily be avoided, but it should be paired with proactive nutritional and exercise strategies.

Clinical Strategies to Preserve Muscle

The most important clinical approach is to treat incretin-based obesity pharmacotherapy as part of a comprehensive lifestyle and nutrition program rather than as stand-alone drug therapy.

Resistance training should be recommended at least two to three times weekly, targeting major muscle groups. Resistance exercise is the most effective intervention for preserving or increasing muscle strength during weight loss.[10,17] Aerobic exercise remains valuable for cardiometabolic health but is less potent than progressive resistance training for preserving lean mass.

Emerging evidence suggests that structured exercise may be particularly important when combined with GLP-1-based pharmacotherapy. Lundgren et al. demonstrated that the combination of supervised exercise and GLP-1 receptor agonist therapy resulted in more favourable long-term body-composition outcomes compared with pharmacotherapy alone.[19] Participants receiving combined treatment maintained greater reductions in body-fat percentage and were more likely to sustain clinically significant weight loss after treatment discontinuation.[20] These findings support the concept that exercise should not be viewed merely as an adjunct to pharmacological therapy but rather as an integral component of obesity treatment aimed at preserving lean tissue, maintaining physical function, and improving long-term weight-loss maintenance. Furthermore, resistance exercise may partially offset lean-mass reductions associated with rapid pharmacologically induced weight loss while simultaneously improving muscle strength and functional capacity.[14,20]

Protein intake should be explicitly assessed. A practical target for many adults undergoing weight loss is approximately 1.0–1.5 g/kg/day of protein, individualized by renal function, age, comorbidities, and obesity severity.[17] Older adults and patients with sarcopenic obesity may require higher protein density because total caloric intake often falls substantially during GLP-1RA therapy.

Clinicians should monitor more than body weight. Waist circumference, dietary intake, resistance-training adherence, symptoms of weakness, functional capacity, and, when feasible, grip strength or chair-rise performance may provide clinically meaningful information. DXA, computed tomography (CT), MRI, or bioimpedance can be considered in selected high-risk patients, but results should be interpreted in context.

Future Directions

Future trials should include standardized measures of muscle strength and physical performance, rather than relying soley on DXA-derived lean mass. MRI and CT may better

distinguish skeletal muscle from non-contractile lean tissue and quantify myosteatosis. Studies are also needed in older adults, frail patients, and those with sarcopenic obesity, because these groups are underrepresented in pivotal obesity trials.

Another emerging strategy is the combination of incretin-based therapies with muscle-preserving agents. Bimagrumab, an activin type II receptor antagonist, has been shown to reduce fat mass while increasing lean body mass in individuals with obesity and type 2 diabetes.[20] Although still investigational, therapies targeting the myostatin/activin pathway may help mitigate lean-mass loss during pharmacological weight reduction and represent a promising future approach to optimizing body composition.

Randomized trials combining GLP-1RA therapy with structured resistance training, protein supplementation, or anabolic-preserving interventions would help determine optimal clinical protocols. Long-term follow-up is also needed to assess whether lean-mass reductions translate into meaningful differences in disability, falls, resting energy expenditure, or weight regain.

Conclusion

GLP-1RAs and related incretin-based therapies produce substantial and clinically meaningful weight loss. Although reductions in lean mass are observed, current evidence suggests that these changes are generally proportional to total weight loss and occur alongside larger reductions in fat mass and visceral adiposity. Semaglutide and tirzepatide appear to improve overall body composition rather than selectively deplete skeletal muscle. Emerging evidence further suggests that improvements in insulin sensitivity, reductions in myosteatosis, and enhanced muscle quality may offset reductions in absolute lean mass.[12,19] Nevertheless, caution is warranted in older adults and patients with low baseline muscle reserve. Muscle-preserving care should include resistance exercise, adequate protein intake, and functional monitoring. Future research should prioritize muscle strength, physical performance, muscle composition, and muscle quality rather than lean mass alone when evaluating the effects of GLP-1-based therapies on skeletal muscle health.

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Financial Disclosures

M.T.: Speaker honoraria and consulting fees: NovoNordisk, Eli Lilly, Bausch Health, CPD Network, Boehringer-Ingelheim, Amgen

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doi.org/10.58931/cdet.2026.4255

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Use of Once-Weekly Insulin Icodec in the Perioperative and Inpatient Settings

Robyn Houlden, MD, FRCPC

Introduction

Hyperglycemia in hospitalized patients is associated with increased morbidity, mortality, and healthcare utilization, and effective glycemic management remains a central component of inpatient care.[1] Basal insulin therapy is a cornerstone of this management strategy, traditionally relying on once-daily long-acting insulin analogs that allow for flexible titration.[1] Insulin icodec,[2] a once-weekly basal insulin analog, represents a significant therapeutic advance by reducing injection burden and providing stable pharmacokinetics; however, it also introduces new challenges in acute care settings.

Insulin icodec exhibits reversible albumin binding and a prolonged half-life of approximately 196 hours (~8 days).[3] It reaches a steady state after 3–4 weekly injections and is associated with a relatively flat, sustained glucose-lowering profile.[3] While these properties are advantageous in the outpatient setting, they limit the ability to rapidly titrate insulin dosing in response to acute illness, fasting, or surgical stress. This reduced flexibility raises concerns regarding its safety and practicality in hospitalized and perioperative patients, where insulin requirements may change abruptly. Diabetes Canada inpatient guidance emphasizes the importance of individualized insulin regimens and the ability to adjust therapy dynamically in response to changing clinical status, principles that may be more difficult to implement with once-weekly insulin formulations.[4] This review focuses on adults with type 2 diabetes, in whom most clinical experience with insulin icodec has been accumulated.

Use of Insulin Icodec During Hospitalization

A proposed approach to the management of patients receiving once-weekly insulin icodec during hospitalization is shown in **Figure 1**. Please see **clinical vignette cases 1 and 2** for the use of icodec insulin during hospitalization. Evidence supporting inpatient use of insulin icodec is primarily derived from post hoc analyses of the Once Weekly Analogue exploring DiabeteS (ONWARDS) phase 3 clinical trials. These analyses included three trials in insulin-naïve adults living with type 2 diabetes (ONWARDS 1, 3 and 5), two in insulin-treated participants living with type 2 diabetes (ONWARDS 2 and 4), and one in people living with type 1 diabetes (ONWARDS 6).[5-10] Across these analyses, hospitalization rates were similar between patients treated with insulin icodec and those receiving daily basal insulin analogs, with no signal of increased risk of hospitalization associated with icodec.[11] Length of stay was also comparable.[11]

Glycemic control was maintained throughout hospitalization, with stability in A1C observed before, during, and after admission.[11] Among 180 hospitalizations in participants receiving icodec, 97.8% had no additional daily basal insulin documented during hospitalization. More than 90% continued icodec according to their usual schedule after discharge, and 84.9% completed the trial without permanently discontinuing treatment.[11] Few clinically significant or severe hypoglycemic events were reported during hospitalization; however, the small number of events and reliance on participant reporting preclude reliable comparisons between treatment groups. The analysis suggested that once-weekly icodec could be managed similarly to once-daily basal insulin analogs during hospitalization.[11]

Despite these reassuring findings, important limitations constrain their interpretation. The generalizability of trial results to real-world hospitalized populations is uncertain, as patients enrolled in phase 3 studies are typically healthier and more closely monitored than those encountered in routine clinical practice. This distinction is particularly relevant in inpatient settings, where patients often have greater clinical complexity, including advanced age, renal impairment, and variable nutritional intake. As a result, the safety profile observed in clinical trials may underestimate the risks in more vulnerable populations.

In addition, the outcomes reported in these analyses are relatively coarse and do not capture other clinically meaningful aspects of inpatient glycemic control. Events were participant-reported and systematic inpatient glucose or continuous glucose monitoring data were unavailable. These gaps limit confidence in extrapolating trial findings to routine inpatient care.

When Icodec Is Unavailable or Conversion Is Required

On admission, the date, time, and dose of the last icodec injection should be confirmed. Because clinically relevant icodec activity persists beyond the weekly dosing interval, once-daily basal insulin should not routinely be added during the initial hospitalization solely because icodec is unavailable on the hospital formulary. Prandial, correctional, or intravenous insulin may be used according to nutritional intake, glucose levels, and clinical status.

If a prolonged admission necessitates conversion to once-daily basal insulin, an estimated daily dose may be calculated by dividing the most recent weekly icodec dose by seven. In the ONWARDS transition protocols, daily basal insulin was generally initiated two weeks after the last icodec injection, or earlier when prebreakfast glucose exceeded 10 mmol/L.[8,9] Earlier initiation should be individualized because residual icodec activity may increase the risk of hypoglycemia.

Use of Insulin Icodec Perioperatively

The perioperative period introduces additional complexity due to fasting, variable nutritional intake, and stress-induced alterations in insulin sensitivity. In this context, the prolonged duration of action of insulin icodec presents a fundamental challenge, as insulin exposure cannot be rapidly reduced or discontinued in response to changing metabolic demands. **Table 1** presents preoperative management approaches for insulin icodec.

Perioperative data remain particularly sparse, with no prospective studies specifically evaluating insulin icodec in surgical populations. Existing

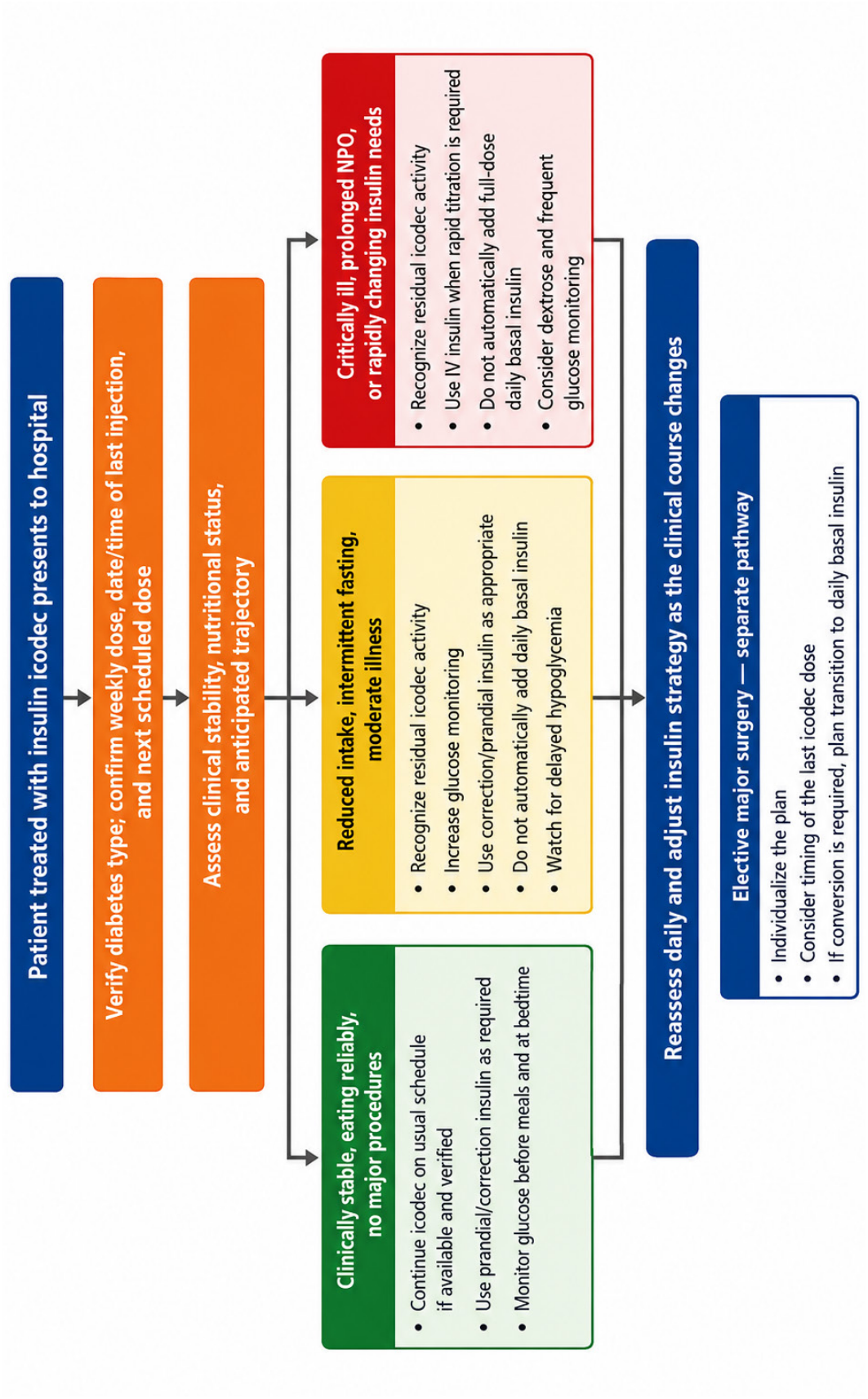

Figure 1. Proposed approach to inpatient management of patients treated with once-weekly insulin icodec; *courtesy of Robyn Houlden, MD, FRCPC.*

Case 1. Use of Icodec During Hospitalization
A 75-year-old man with type 2 diabetes was admitted with COVID-19 pneumonia. Prior to admission, his diabetes was well controlled on once-weekly insulin icodec 350 units, tirzepatide 5 mg subcutaneously weekly, and dapagliflozin 10 mg daily. His most recent dose of icodec was administered 2 days prior to admission. His medical history includes obesity, metabolic dysfunction-associated steatohepatitis (MASH), and stage 3 chronic kidney disease.
On admission, dapagliflozin was withheld due to dehydration risk, and tirzepatide was held due to concerns regarding nausea and reduced oral intake. Given the recent icodec dosing and its prolonged half-life (~8 days), it was assumed that a substantial proportion of his basal insulin requirements remained covered. Point-of-care capillary blood glucose monitoring was initiated before meals and at bedtime, and correctional insulin using a rapid-acting analog was administered at the same time points.
Over the first several days, he required frequent correction doses, with a pattern of postprandial hyperglycemia. In response, a low-dose prandial insulin regimen was initiated. Given the long half-life of icodec and the expected decline in insulin requirements with treatment of his pneumonia, close monitoring was provided for hypoglycemia with plans for de-escalation of insulin therapy.
As his clinical status improved, his insulin requirements decreased. By the time of discharge 5 days later, his glucose levels had stabilized, and he no longer required scheduled prandial or correctional insulin. Tirzepatide and dapagliflozin were restarted once oral intake, hydration, renal function and clinical stability were satisfactory. He was instructed to administer his next dose of insulin icodec 7 days after his last injection, coinciding with the day of discharge.
Practice Point: If insulin icodec is not available on the hospital formulary, arrangements should be made for the patient to bring their home supply. If a dose is missed, administer it as soon as feasible. The original weekly dosing day may be retained provided there will be at least four days between consecutive injections; otherwise, continue weekly dosing from the new administration day. Increase glucose monitoring during the transition.

Clinical Vignette: Case 1. Use of Icodec During Hospitalization

recommendations are therefore derived largely from expert opinion and pharmacologic principles rather than empirical evidence.[12,13] This represents a critical gap, given the dynamic and often unpredictable metabolic changes that characterize the perioperative period.

The prolonged half-life of insulin icodec represents an inherent limitation that is not easily mitigated. Unlike daily basal insulin analogs, its pharmacokinetic profile precludes rapid titration or withdrawal, which may increase the risk of hypoglycemia in the setting of reduced oral intake or, conversely, hyperglycemia when insulin requirements increase abruptly. These constraints are intrinsic to the molecule and limit its adaptability in acute care environments.

Current expert guidance suggests that continuation of insulin icodec may be appropriate for minor procedures in which reduced caloric intake is expected for less than 24 hours and no prolonged preoperative liquid diet is required. In this setting, capillary blood glucose should be monitored every 2–4 hours, with hyperglycemia managed with correctional doses of a rapid-acting insulin analog. Hypoglycemia should be managed according to standard protocols. Emergency surgery should not be delayed because of recent icodec administration. The dose and timing of the last injection should be established, residual icodec activity should be recognized, and glucose should be monitored frequently. Intravenous insulin, with dextrose when required, should be used when rapid titration is necessary.

Case 2. Use of Icodec with Steroid-Induced Hyperglycemia During Hospitalization
A 65-year-old man with type 2 diabetes was admitted for an exacerbation of chronic obstructive pulmonary disease and pneumonia. Prior to admission, his diabetes was well controlled with once-weekly insulin icodec 350 units, semaglutide 2 mg subcutaneously weekly, and metformin 1000 mg twice daily. His last dose of icodec was administered 4 days prior to admission. His medical history was significant for obesity, hypertension, obstructive sleep apnea, and cigarette smoking.
On admission, he was treated with short-acting bronchodilators, supplemental oxygen, and amoxicillin-clavulanate. Prednisone was started with a planned tapering regimen. Metformin was held initially and resumed once clinical stability was achieved. Semaglutide was held due to concerns about nausea and reduced oral intake. Given the recent administration of insulin icodec and its prolonged half-life (~8 days), it was assumed that a substantial proportion of his basal insulin requirements remained covered.
Point-of-care capillary blood glucose monitoring was initiated before meals and at bedtime, with correctional insulin using a rapid-acting analog administered at the same time points. Within 24–48 hours of starting prednisone, he developed marked hyperglycemia, predominantly in the afternoon and evening, with frequent need for correction insulin. In response, scheduled prandial insulin was initiated and titrated. Given the pattern of steroid-induced hyperglycemia, additional daytime insulin coverage was required despite recent icodec dosing. As hyperglycemia persisted, further intensification was required with escalation of prandial insulin doses. Consideration was given to adding intermediate-acting insulin timed to steroid administration; however, glycemic management was achieved with adjustment of prandial insulin alone. His regularly scheduled icodec dose became due on hospital day 3 and was administered at his usual dose. Glucose was monitored closely because prednisone treatment and acute illness had temporarily increased his prandial insulin requirements.
As his clinical status improved and a 5-day course of prednisone was completed, his insulin requirements declined rapidly. Prandial and correctional insulin were progressively reduced and ultimately discontinued to avoid hypoglycemia, recognizing the continued presence of long-acting basal insulin from prior icodec dosing. By the time of discharge 7 days later, his glucose levels had stabilized. Semaglutide was restarted. He was instructed to administer his next dose of insulin icodec seven days after the dose administered in hospital.
Practice Point: In patients receiving insulin icodec, glucocorticoid therapy may produce substantial daytime and postprandial hyperglycemia that is not adequately addressed by existing basal insulin coverage. Morning prednisone typically produces glucose excursions that peak in the afternoon and evening. Management generally requires glucose-guided titration of scheduled prandial and correctional insulin and, in selected patients, addition of intermediate-acting insulin timed to prednisone administration. Dexamethasone produces more sustained hyperglycemia and may require scheduled prandial and correctional insulin, intermediate-acting insulin in divided doses, or intravenous insulin in clinically unstable patients. Because icodec provides prolonged and relatively fixed basal insulin exposure, routine addition of another long-acting basal insulin should be avoided. Supplemental insulin should be reduced proactively as glucocorticoids are tapered or discontinued to minimize the risk of hypoglycemia.

Clinical Vignette: Case 2. Use of Icodec with Steroid-Induced Hyperglycemia During Hospitalization

Clinical Scenario	Suggested Management Approach	Rationale
Minor procedure with minimal fasting and expected return to usual intake within 24 hours	Continue icodec at the usual dose and weekly schedule. Monitor glucose every 2–4 hours while fasting and use rapid-acting correction insulin as required.	The existing icodec dose provides basal coverage throughout the procedure. Brief fasting generally does not require conversion to another basal insulin.
Short-term fasting, reduced intake, or moderate acute illness	Recognize that residual icodec activity remains present. Increase glucose monitoring and use scheduled prandial insulin when eating and correction insulin as required. Do not automatically add once-daily basal insulin. Monitor for delayed hypoglycemia as illness resolves or intake decreases.	The prolonged action of icodec limits down-titration. Flexible short-acting insulin can address temporary hyperglycemia without creating prolonged basal-insulin overlap.
Emergency procedure or surgery	Do not delay the procedure because of recent icodec administration. Confirm the dose and timing of the last injection, account for residual icodec activity, and monitor glucose frequently. Use intravenous insulin, with dextrose when required, if rapid titration is necessary.	The administered icodec dose cannot be withdrawn. Intravenous insulin and dextrose permit rapid adjustment around changing operative and nutritional requirements.
Elective major surgery with anticipated fasting or reduced caloric intake for more than 24 hours, or a preoperative liquid diet lasting at least 2 days	Consider a planned transition to once-daily basal insulin. Administer the final icodec dose approximately 4 weeks before surgery. Estimate the daily basal requirement by dividing the weekly icodec dose by seven and generally initiate daily basal insulin approximately 2 weeks after the last icodec dose, or earlier if fasting glucose exceeds 10 mmol/L. Titrate according to fasting glucose.	Daily basal insulin provides greater perioperative flexibility. Delaying its initiation reduces the risk of excessive overlap with residual icodec activity.
High-risk patient, including frailty, renal impairment, recurrent hypoglycemia, or unpredictable nutritional intake	Develop an individualized plan before surgery and consider transition to once-daily basal insulin when time permits. Use more conservative dosing and more frequent glucose monitoring. Consider endocrinology consultation.	Reduced insulin clearance and changing nutritional intake may increase hypoglycemia risk, while daily insulin permits more responsive dose adjustment.
Critical illness or intensive care	Account for residual icodec activity. Use intravenous insulin when rapid titration is required; do not automatically add full-dose once-daily basal insulin. Provide dextrose when clinically indicated and monitor glucose frequently.	Icodec continues to provide basal insulin exposure during critical illness. Intravenous therapy allows rapid adjustment while avoiding unrecognized overlap with another basal insulin.
Postoperative period while residual icodec remains active	Monitor glucose frequently and use prandial, correctional, or intravenous insulin according to clinical status and nutritional intake. Reduce supplemental insulin proactively as stress hyperglycemia resolves or intake declines.	Persistent icodec activity may not match rapidly changing postoperative insulin requirements, increasing the risk of both hyperglycemia and delayed hypoglycemia.
Restarting icodec after temporary treatment with once-daily basal insulin	Once the patient is clinically stable and eating reliably, calculate the weekly icodec dose by multiplying the current daily basal requirement by seven. Administer the first icodec dose on the day following the final daily basal dose. Individualize—and consider omitting—the optional one-time additional dose when postoperative insulin requirements are reduced or unstable.	Using the current daily basal requirement reflects postoperative insulin needs and reduces the risk of excessive overlap or return to an inappropriate preoperative dose.

Table 1. Practical Perioperative Management of Insulin Icodec; *courtesy of Robyn Houlden, MD, FRCPC*

Case 3. Perioperative Management of Icodec for Major Surgery
A 70-year-old woman with a 15-year history of type 2 diabetes was scheduled for elective coronary artery bypass grafting. Her medical history included hypertension, hyperlipidemia, and stage 2 chronic kidney disease. Her outpatient diabetes regimen consisted of once-weekly insulin icodec 420 units, metformin, empagliflozin, and semaglutide. Her most recent A1C was 7.4%.
Because major surgery and a postoperative intensive care stay were anticipated, a planned transition from icodec to once-daily basal insulin was initiated four weeks before surgery. Her final 420-unit dose of icodec was administered at that time. Fasting glucose was measured daily. Two weeks after the last icodec injection, insulin glargine was started at 60 units daily, calculated by dividing the weekly icodec dose by seven. Earlier initiation would have been considered if fasting glucose had risen above 10 mmol/L. The glargine dose was subsequently reviewed every 2–3 days and adjusted according to fasting glucose and hypoglycemia. Before surgery, fasting glucose was generally 6.5–7.5 mmol/L without hypoglycemia.
Empagliflozin was discontinued three days before surgery to reduce the risk of perioperative euglycemic diabetic ketoacidosis. Metformin was withheld on the day of surgery. Semaglutide was managed according to institutional anesthesia guidance and the patient's gastrointestinal symptoms and aspiration risk. On the evening before surgery, she received 30 units of insulin glargine, representing 50% of her usual daily basal dose.
An intravenous insulin infusion was initiated on the morning of surgery and titrated according to the institutional cardiac-surgery protocol, targeting glucose between 6 and 10 mmol/L. Glucose was monitored hourly intraoperatively and while the infusion was being actively adjusted.
Postoperatively, intravenous insulin was continued in the intensive care unit. Once she was hemodynamically stable and eating reliably, she was transitioned to a subcutaneous basal–bolus regimen. Insulin glargine was administered before discontinuation of the intravenous insulin infusion according to institutional transition procedures. Her insulin requirements declined during recovery, and her final daily glargine requirement before discharge was 50 units.
At discharge, she was transitioned back to insulin icodec. Her new weekly dose was calculated from her current daily basal requirement: 50 units multiplied by seven, giving 350 units once weekly. The first 350-unit dose of icodec was administered on the day following her final glargine dose. The optional one-time additional icodec dose was omitted because her postoperative insulin requirements remained potentially unstable and her risk of hypoglycemia was increased. She was instructed to monitor fasting and premeal glucose closely and was contacted by the diabetes team within one week to review glucose levels and determine whether further dose adjustment was required. Resumption of her non-insulin glucose-lowering medications was individualized according to oral intake, renal function, hydration, and postoperative clinical status.
Practice Point: For planned major surgery, conversion from icodec to once-daily basal insulin should be managed as a glucose-guided transition. Dividing the weekly icodec dose by seven provides an initial estimate of the daily basal requirement, but daily basal insulin is generally not started until approximately two weeks after the last icodec injection, or earlier if fasting hyperglycemia develops. When restarting icodec, calculate the weekly dose from the patient's current daily basal requirement and administer the first weekly dose on the day following the final daily basal dose. The optional one-time additional dose should be individualized and may be omitted when postoperative insulin requirements are reduced or unstable.

Clinical Vignette: Case 3. Perioperative Management of Icodec for Major Surgery

For major surgery—particularly when reduced caloric intake is anticipated for more than 24 hours postoperatively or when a preoperative liquid diet of at least 2 days is planned—insulin icodec should be discontinued in advance due to its prolonged half-life. The final dose should be administered approximately 4 weeks prior to surgery or before initiation of the liquid diet. Transition to a daily basal insulin regimen should generally occur approximately 2 weeks after the last icodec dose, or sooner if fasting hyperglycemia develops. **Clinical vignette case 3** describes the use of icodec insulin during surgery.

A practical starting dose for daily basal insulin is one-seventh of the prior weekly icodec dose, with subsequent titration based on glycemic response and clinical judgment. During periods of reduced caloric intake, such as a preoperative liquid diet, the basal insulin dose should typically be reduced (e.g., by 50%), depending on the individual's risk of hypoglycemia.[12] Fifty percent of the usual daily basal insulin dose should be administered the night before or the morning of the procedure, or reduced according to an institution's usual practice.[12]

Perioperative glycemic control, including the management of hypo- and hyperglycemia, should align with established institutional practices. When restarting icodec after temporary treatment with daily basal insulin, administer the first icodec dose on the day following the last daily basal dose.[3] Calculate the maintenance weekly dose from the current daily basal requirement rather than automatically returning to the preoperative icodec dose. The one-time additional dose should be individualized, recognizing that postoperative insulin requirements may remain reduced or unstable.

Conclusion

Insulin icodec represents an important advancement in basal insulin therapy, offering simplified dosing and stable glycemic control in outpatient settings. Available evidence suggests that it can be continued in selected clinically stable hospitalized patients, although inpatient evidence remains limited. However, its prolonged pharmacokinetic profile introduces important limitations in the inpatient and perioperative setting, particularly when rapid titration is required. Given the limitations of the current evidence base, including reliance on post hoc analyses and the absence of prospective perioperative studies, clinical use of insulin icodec in hospital should be individualized. Further research is needed to define optimal management strategies, particularly in higher-risk populations and surgical settings, and to incorporate more detailed glycemic outcomes such as continuous glucose monitoring metrics.

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Financial Disclosures

R.H.: Speaking Honoraria: Boehringer Ingelheim, Sanofi; **Consultancy Fees:** Boehringer Ingelheim, Eli Lilly

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doi.org/10.58931/cdet.2026.4256

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Low Risk for Recurrence of Differentiated Thyroid Cancer: A Paradigm Shift to De-Escalation and Simplifying Care for Long Term Follow-up

Shivraj Singh Riar, MB, BCh, BAO, FRCP(C) Endocrinology and Metabolism

The incidence of thyroid cancer in Canada increased from 1984 to 2013, followed by a subsequent decline; the most recent projections estimate 6,100 cases in 2026.[1] Low-risk differentiated thyroid cancer (DTC), with an excellent treatment response, is associated with a recurrence risk of less than 2% and a 20-year disease specific mortality of less than 1%.[2] In alignment with the 2025 American Thyroid Association DTC Guidelines and the Follow-up and Transition of Care for Low Recurrence Risk Thyroid Cancer Patients in Canada, thyroid cancer care is undergoing a major evolution.[2,3] This shift is centred around de-escalation of care, and for the first time, provides guidance on when to consider cessation of surveillance. For patients who have undergone hemithyroidectomy, recommended follow-up includes a one-time post-operative measurement of thyroglobulin (TG) with thyroglobulin antibodies (TGAB), annual thyroid-stimulating hormone (TSH) monitoring (targeted within the reference range), and ultrasound surveillance at 1–3 years. Consideration may then be given to cessation of all monitoring after 5–8-years. For patients undergoing total thyroidectomy (TT) without radioactive iodine (RAI), the new target for a biochemical excellent response is <2.5 ng/mL as well as a TSH level within the normal reference range.

In this population, ultrasound is recommended at 1–3-year intervals following the initial assessment, with consideration of discontinuation between years 5–8 in patients demonstrating an excellent response; Canadian guidelines also recommend cessation of surveillance at year 5. Furthermore, for patients undergoing TT with or without RAI who maintain an excellent response, continued biochemical monitoring beyond 10–15 years is not required. Key elements of care for patients with low-risk thyroid cancer include reduced ultrasound surveillance, maintaining the TSH target within the normal reference range, annual TG/TGAB monitoring, and consideration of cessation of surveillance. Adoption of these principles will enhance patient care while maintaining excellent outcomes.

Introduction

The incidence of thyroid cancer in Canada increased from 1984 to 2013, followed by a subsequent decline, with the most recent projections estimating 6,100 new cases in 2026.[1] Differentiated thyroid cancer (DTC) is the most common subtype, which is further classified into low, low-intermediate, intermediate, intermediate-high, and high risk categories according to the 2025 American Thyroid Association (ATA) DTC Guidelines.[2] Low-risk DTC with an excellent treatment response is associated with an estimated risk of recurrence of less than 2% and a 20-year disease specific mortality of less than 1%.[2] This article focuses on the long term follow-up of patients with low-risk recurrence DTC who have an excellent response to therapy.

According to the ATA 2025 DTC Guidelines, low-risk DTC is defined as unifocal tumours measuring ≤4 cm with ≤5 lymph nodes (LNs) each ≤2 mm and negative margins or only microscopically positive anterior margins (R1).[2] Specifically for follicular thyroid carcinoma and invasive encapsulated follicular variant of papillary thyroid carcinoma, tumours with capsular invasion alone are also regarded as low risk.[2] In papillary thyroid carcinomas ≤2 cm with a *BRAF* mutation may be considered low risk in the absence of other mutations, vascular invasion, or aggressive histologic features.[2] The absence of local or distant metastases, as well as the absence of radioactive iodine (RAI)-avid foci outside the thyroid bed on post treatment, and whole body RAI scanning, is classified as low risk. A recent Canadian Guideline also noted that lymph node metastases measuring <5 mm without extranodal extension can also confer a low-risk of recurrence, whereas others have identified a cutoff of 4 mm for defining low-risk recurrence; however, the evidence is mixed. A study proposed a low-risk of recurrence cutoff of 4 mm, and another identified LN size of >5.4 mm as a predictor of a structurally incomplete response.[3-5] Thus, defining low-risk disease as involvement of <5 LNs with a size cut off of <5 mm in the central neck may broaden the population of patients with DTCs categorized as low-risk for recurrence.[3]

In alignment with the 2025 ATA DTC Guidelines and the Follow-up and Transition of care for Low Recurrence Risk Thyroid Cancer Patients in Canada, cancer care is undergoing a notable evolution.[2,3] The core theme of this shift is centred around the de-escalation of care, including, for the first time, providing guidance on when to consider cessation of surveillance. Patients with low-risk DTC can be further subdivided into patients who undergo hemithyroidectomy (HT), and those treated with total thyroidectomy (TT), with or without RAI.[2,3]

Hemithyroidectomy Follow-up

Follow-up after hemithyroidectomy (HT) or lobectomy in patients with low-risk DTC has been variable.[6,7] Most recent guidelines provide clarity in terms of TSH targets, thyroglobulin (TG) and thyroglobulin antibody (TGAB) monitoring, and the appropriate frequency of ultrasound surveillance.[2,3] For patients with T1 tumours (< 2cm), HT is preferred, while with unilateral T2 tumours (2–4 cm), either HT or TT can be considered.[2]

Historically, there has been a lack of clarity about the role of TG and TGAB monitoring following HT.[6] The 2025 ATA DTC Guidelines and the Canadian consensus statement have both reinforced that serum TG levels do not predict recurrence in patients treated with HT.2,3[2,3] A systematic review comprising 37 studies similarly reported that TG measurement lacks accuracy for detecting DTC recurrence.[8] However, it is recommended that a baseline post-operative TG and TGAB level should be obtained to ensure values are not unexpectedly elevated

Hemithyroidectomy Targets	ATA DTC 2025	Canadian Consensus Guidelines
TG and TGAB	• No Target • Assess TG and TGAB at 6–12 weeks post surgery to ensure not metastatic.	• No Target • Assess TG and TGAB once post-operatively. Consider further imaging if TG >100 ng/mL
TSH Target	• TSH within the normal laboratory reference range.	• TSH within the normal laboratory reference range.
Ultrasound Surveillance	• **Neck U/S:** Perform at 6–12 months post-operatively. If clear, continue every 1–3 years for 5–8 years.	• **Neck U/S:** Perform at 6–12 months post-operatively. If clear, perform a repeat exam at 3–5 years, with either discontinuation or continued monitoring at 5-year intervals.
Cessation of All Surveillance	• **TSH:** Annual monitoring (no end date) • **TG/TGAB:** Not applicable • **U/S:** Discontinue between years 5–8. Follow contralateral nodules as per ATA Thyroid Nodule guidelines.	• **TSH:** Annual monitoring (no end date) • **TG/TGAB:** Not Applicable • **U/S:** Consider every 5 years (no end date) or as determined by nodule findings.

Table 1: Long Term Follow-up of Low-Risk DTC Patients who Undergo Hemithyroidectomy Who Demonstrate an Excellent Response; *courtesy of Shivraj Singh Riar, MB, BCh, BAO, FRCP(C) Endocrinology and Metabolism.*

Abbreviations: ATA: American Thyroid Association; **DTC:** differentiated thyroid cancer; **TG:** thyroglobulin; **TGAB:** thyroglobulin with thyroglobulin antibodies; **TSH:** thyroid-stimulating hormone; **U/S:** ultrasound

(TG >100 ng/mL), which should prompt further investigation.[3] An elevation in TGAB levels has also not been shown to predict recurrence in patients who undergo HT, thus serial monitoring of these levels is not recommended.[2] Accordingly, a single post-operative assessment of TG and TGAB levels should suffice when these criteria are met.

Optimal TSH targets in patients with low-risk DTC have been evaluated in several studies. The 2015 ATA guidelines previously recommended a TSH target of 0.5–2 mIU/L for all low-risk patients with an excellent response to treatment.[9] However, a randomized controlled trial has shown no significant difference in disease-free survival between patients with a normal TSH level (TSH 0.4–5 mIU/L) and the cohort with suppressed TSH levels.[10] Additionally, two large retrospective studies reported no association between mean TSH levels and the risk of recurrence following HT.[11,12] TSH targets are particularly relevant in these patients, as a primary rationale for selecting HT is to avoid thyroid hormone replacement. Prior studies have shown that when TSH is maintained within the normal reference range, approximately 70–80% of patients avoid the need for thyroid hormone replacement, compared with only 20–30% when targeting a narrower TSH range of 0.5–2 mIU/L.[2] From a practical standpoint, achieving stricter TSH targets may also be challenging, with one study reporting that only 29% of patients were able to meet the targets outlined in the 2015 ATA DTC guidelines.[13]

For ultrasound monitoring, an assessment should be performed at 6–12 months post HT.[2,3] In the absence of suspicious lesions or nodules, Canadian guidelines suggest that a subsequent ultrasound at 3–5 years is reasonable, with further imaging at 5-year intervals based on patient preference.[3] The ATA guidelines recommend a somewhat more intensive follow-up initially, with ultrasound at 1–3 year intervals, though only for a duration of 5–8 years as a good practice statement.[3] Overall, there is no strong evidence to recommend one practice over another; however, both guidelines recommend discontinuing routine ultrasound surveillance after 5–8-years.[2,3] Tailoring follow-up to individual patients, depending upon resource availability and patient preferences, is therefore reasonable. Notably, these guidelines recommend, for the first time, clear guidance on when to discontinue monitoring patients with low-risk DTC following HT.[2,3] Transition to primary care can also be considered at year 2 post HT3 (**Table 1**).

In patients who have undergone HT, follow-up may include a one-time post-operative

measurement of TG with TGAB, annual TSH monitoring (targeting within the reference range), and ultrasound surveillance at 1–3 years. In the absence of concerning findings, discussion of cessation of all monitoring at the 5–8-year mark is reasonable.

Total Thyroidectomy With and Without Rai Follow-up

Remnant ablation with RAI is not routinely offered for patients with low-risk DTC; thus, the historical targets for TG and TSH have been extrapolated from cohorts undergoing RAI with total thyroidectomy.[9] TT is recommended in the context of pathological features on fine needle aspiration, patient preference, completion in the context of findings post HT, thyroid nodularity, and age.[2] RAI usage in patients with low-risk DTC has evolved, with accumulating evidence showing a lack of benefit. In studies with approximately 10 years of follow-up, RAI offered no benefit for disease-free survival in patients with low-risk disease, thus, the use of RAI in these patients is limited.[14]

Initial TG and TGAB should be assessed 6–12 weeks post surgical intervention to evaluate biochemical response.[2,3] The 2015 ATA guidelines defined an excellent biochemical response in patients who underwent TT without RAI as a TG level of <0.2 ng/mL in the presence of negative TGAB.[9] Practically speaking, some patients would demonstrate an indeterminate or biochemically incomplete response according to the older definition.[9] Subsequent evidence, including a meta-analysis, has shown that patients with TG levels between 1–2.5 ng/mL with negative TGAB while on levothyroxine therapy remained at low risk for persistent or metastatic disease.[8] Accordingly, updated guidance has revised the threshold for a biochemical excellent response to <2.5 ng/mL in patients undergoing TT without RAI[2,3] (**Table 2**). In contrast, for patients having undergone TT with RAI, the threshold for a biochemical excellent response remains TG <0.2 ng/mL2,3 (**Table 3**).

Ultrasound is recommended at 6–12-month intervals post-operatively.[2,3] In the absence of suspicious findings, ultrasound monitoring thereafter has varied in clinical practice. Notably, routine ultrasound in this population can increase the risk of false positive findings without improving the identification of clinically significant disease.[15] Although the recurrence risk is low, the majority of recurrences occur within the first 5 years following intervention in patients with low-risk DTC.[2] Studies have shown that recurrence is rarely identified earlier than 3 years post-operatively, supporting less intensive surveillance strategies. Accordingly, current recommendations advise ultrasound at 1–3-year intervals after the initial examination, with consideration of discontinuation between years 5–8.[2] Similarly Canadian guidelines recommend cessation of ultrasound monitoring at year 5.[3] Collectively, these updated recommendations reflect a shift toward de-escalated, risk-adapted follow-up in patients with an excellent response to therapy.

A TSH target within the normal reference range represents one of the most revolutionizing recommendations introduced in the 2025 ATA DTC guidelines for patients demonstrating an excellent response to therapy. Although the Canadian guidelines recommend a narrower TSH target of 0.5–2 mIU/L, partially reflecting their publication before the 2025 ATA update, the ATA now indicates that there is insufficient evidence to support TSH suppression in patients with low-risk disease.2 Even among patients with intermediate- to high- risk disease, the utility of TSH suppression remains uncertain. For example, a study involving 867 patients has shown no association between TSH suppression and progression free survival at 5 years.[16] Given these findings, the low likelihood of recurrence, low mortality, and the goal of reducing treatment burden, it is reasonable to maintain TSH within the normal reference range in these patients. Furthermore, even in patients with low-risk DTC who demonstrate an indeterminate response, such as nonspecific ultrasound findings, non-stimulated TG levels of 0.2–1ng/mL following TT with RAI, or TG levels of 2.5–5 ng/mL following TT without RAI, the recommended TSH target remains within the normal reference range.[2] One of the key takeaways from the recent guidelines is that in the absence of confirmed biochemical or structural recurrence, TSH suppression is not required. This simplified approach is crucial for the long-term follow-up of patients with low-risk DTC.[2] The key for managing indeterminate findings is longitudinal monitoring. Over time, these findings will either become relevant for intervention or resolve without clinical consequence in low-risk patients, supporting a conservative, risk-adapted strategy.[2]

The 2025 ATA guidelines introduce, for the first time, explicit recommendations regarding the cessation of surveillance in patients with low-risk

Total Thyroidectomy Without RAI Targets	ATA DTC 2025	Canadian Consensus Guidelines
TG and TGAB	• Non-stimulated TG <2.5 ng/mL with negative TGAB and no evidence of disease on imaging: Excellent Response. • Annual monitoring of TG/TGAB.	• Non-stimulated TG <2.5 ng/mL with negative TGAB and no evidence of disease on imaging: Excellent Response. • Annual monitoring of TG/TGAB.
TSH Target	• TSH within the normal laboratory reference range: • Annual monitoring of TSH.	• TSH within the normal laboratory reference range: • Annual monitoring of TSH.
Ultrasound Surveillance	• **Neck U/S:** Perform at 1–3 years for 5–8 years with discontinuation after unless changes are observed in TG or TGAB levels.	• **Neck U/S:** Perform within the first 2 years post-operatively, followed by a repeat exam at 3–5 years.
Cessation of ALL Surveillance	• Consider at 10–15 years.	• **TSH:** Annual monitoring (no end date) • **TG/TGAB:** Discontinue at 10 years. • **U/S:** Consider discontinuation at 5 years.

Table 2. Long Term Follow-up for Low-Risk DTC Patients who Undergo Total Thyroidectomy without RAI with and Demonstrate an Excellent Response; *courtesy of Shivraj Singh Riar, MB, BCh, BAO, FRCP(C) Endocrinology and Metabolism.*

Abbreviations: ATA: American Thyroid Association; **DTC:** differentiated thyroid cancer; **RAI:** radioactive iodine; **TG:** thyroglobulin; **TGAB:** thyroglobulin with thyroglobulin antibodies; **TSH**: thyroid-stimulating hormone; **U/S:** ultrasound

Total Thyroidectomy With RAI Targets	ATA DTC 2025	Canadian Consensus Guidelines
TG and TGAB	• Non-stimulated TG <0.2 ng/mL with negative TGAB and no evidence of disease on imaging: Excellent Response.	• Non-stimulated TG <0.2 ng/mL with negative TGAB and no evidence of disease on imaging: Excellent Response.
TSH Target	• TSH within the normal laboratory reference range.	• **TSH level:** 0.5-2 mIU/L
Ultrasound Surveillance	• **Neck U/S:** Perform at 1–3 years for 5–8 years with discontinuation after unless changes are observed in TG or TGAB levels.	• **Neck U/S:** Perform within first 2 years post-operatively, followed by a repeat exam at 3–5 years.
Cessation of ALL Surveillance	• Consider at 10–15 years	• **TSH:** Annual monitoring (no end date) • **TG/TGAB:** Discontinue at 10 years. • **U/S:** Consider discontinuation at 5 years.

Table 3. Long Term Follow-up for Low-Risk DTC Patients who Undergo Total Thyroidectomy with RAI with and Demonstrate an Excellent Response; *courtesy of Shivraj Singh Riar, MB, BCh, BAO, FRCP(C) Endocrinology and Metabolism.*

Abbreviations: ATA: American Thyroid Association; **DTC:** differentiated thyroid cancer; **RAI:** radioactive iodine; **TG:** thyroglobulin; **TGAB:** thyroglobulin with thyroglobulin antibodies; **TSH:** thyroid-stimulating hormone; **U/S:** ultrasound

DTC. A good practice statement noted that patients with an ongoing excellent response at 10–15 years do not require continued biochemical monitoring.[2] This guidance provides an integral insight for primary care and specialists on when it may be appropriate to discontinue surveillance in these patients.

Key elements of contemporary management for patients with low-risk thyroid cancer include decreased ultrasound surveillance, maintaining the TSH target within the normal reference range, annual monitoring of TG/TGAB, and consideration of cessation of surveillance. Together, these principles are important landmarks in the evolution toward a de-escalated, risk-adapted approach to low-risk for recurrence thyroid cancer care.

Transition and Cessation of Care/Conclusion

Another important contribution of both the Canadian and 2025 ATA DTC guidelines is the provision of recommendations on the transition to primary care and when to consider cessation of follow-up.[2,3] The Canadian guidelines recommend transition of primary care between years 2–5.[3] For patients who maintain an excellent response following HT or TT with or without RAI, transfer to primary care can be considered at year 2.[3] For patients with an ongoing indeterminate response, along with stable TG levels, or declining TGAB levels following TT with or without RAI, indeterminate lesion findings on ultrasound, or nonspecific thyroid bed lesions representing benign etiology, transition to primary care can be considered between years 3–5.[3] As with other guidance, decisions regarding transition should be individualized, taking into account patient-specific factors and the comfort level of the primary care provider, particularly given that earlier transition to primary care is a novel concept. Thus, practically speaking, engaging patients in shared decision-making rather than having strict criteria may be a more appropriate course of action. The guidance on this transition will aid and hopefully empower primary care providers to take a more central role, especially in the context of simplified monitoring as noted above.

Cessation of surveillance is likely to remain a topic of ongoing debate, given the potential for late recurrence, although the likelihood of this is very low in patients with low-risk disease.[2] Current guidance, which suggests consideration of discontinuation of surveillance at 10–15-years (**Tables 2 and 3**) and at 5–8 years (**Table 1**) based upon initial surgical management provides greater confidence for implementation in clinical practice.[2] In practice, patient-specific factors should continue to be considered in decision-making; however, the adoption of cessation strategies has the potential to reduce unnecessarily long term follow-up and associated healthcare costs in patients with low-risk disease.[17]

The Canadian and 2025 ATA DTC guidelines support a transition away from lifelong specialist follow-up in patients with stable low-risk disease. Key components of these recommendations include reduced emphasis on TSH targeting, decreased frequency of imaging, and the introduction of defined points at which surveillance can be discontinued. For most patients with low-risk DTC who achieve an excellent response to therapy, prolonged intensive follow-up is unnecessary. Adoption of these principles will enhance patient care while maintaining excellent outcomes.

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Financial Disclosures:

S.S.R.: Speaking Fees: Abbott, 24th Annual BC Endocrinology Day and 2026 NP Conference; **Consultation Fees:** Abbott and Novo Nordisk

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doi.org/10.58931/cdet.2026.4257

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Perimenopause: Considerations for the Endocrinologist

Michelle Jacobson, MD

Perimenopause is a clinically defined reproductive transition characterized by menstrual-cycle variability, fluctuating ovarian hormone secretion, and symptoms that often overlap with endocrine disease. Endocrinologists are well positioned to distinguish physiological reproductive aging from thyroid disease, hyperprolactinemia, pregnancy, premature ovarian insufficiency, and other causes of oligo-amenorrhea; to identify abnormal uterine bleeding requiring gynecologic evaluation; and to address the concurrent emergence of cardiometabolic and skeletal risk. Management should be symptom-directed and should explicitly separate the need for contraception and cycle control from the use of menopausal hormone therapy. This review presents a practical, evidence-based approach to diagnosis, risk assessment, and treatment for the endocrinology setting.

Introduction

Perimenopause spans the menopausal transition and the first year after the final menstrual period. The Stages of Reproductive Aging Workshop (STRAW)+10 framework defines early transition by a persistent difference, often a shortening, of at least seven days between consecutive cycle lengths, whereas late transition is characterized by amenorrhea lasting 60 days or longer.[1] The underlying physiology is driven not by a simple linear decline in estradiol, but by diminishing follicular reserve, which produces variable inhibin B and anti-Müllerian hormone, rising and increasingly erratic follicle-stimulating hormone (FSH), intermittent anovulation, and marked intra- and inter-cycle fluctuations in estradiol and ovulatory function.[1,2] Consequently, patients may experience heavy or irregular bleeding, vasomotor symptoms, sleep disruption, mood changes, breast tenderness, migraine, and genitourinary symptoms despite intermittently normal or high estradiol levels. For the endocrinologist, the central task is to recognize a physiological transition without attributing all midlife symptoms to menopause.

Diagnosis: Clinical First, Selective Testing

In otherwise healthy patients aged 45 years or older, perimenopause is usually diagnosed clinically, making routine measurement of FSH, estradiol, anti-Müllerian hormone, or ovarian reserve unnecessary. A single FSH value is particularly unhelpful because secretion fluctuates and does not reliably predict either the final menstrual period or the need for contraception.[1,3] Laboratory testing should instead be reserved for evaluating a specific alternative diagnosis. Pregnancy testing is appropriate whenever pregnancy is biologically possible. Thyroid-stimulating hormone is appropriate in patients with new cycle disturbances or symptoms suggestive of thyroid dysfunction, whereas prolactin measurement is indicated for those with galactorrhea, marked oligomenorrhea, or amenorrhea. Targeted evaluation for hyperandrogenism or hypothalamic-pituitary disease should be guided by the phenotype. New-onset flushing accompanied by diarrhea, wheezing, episodic hypertension, or other atypical features warrants investigation beyond menopause.

Age influences the threshold for evaluation. Menstrual irregularity or symptoms of estrogen deficiency before age 40 should prompt assessment for premature ovarian insufficiency (POI), generally using one elevated FSH measurement above 25 IU/L and oligomenorrhea.[4] Between the ages of 40 and 45, early menopause should also be considered given the implications of prolonged estrogen deficiency for bone and cardiovascular health. Because hormonal contraception can obscure bleeding criteria and complicate laboratory interpretation, menstrual history before initiation of contraception, treatment goals, and age are more informative than indiscriminate testing.

Abnormal Uterine Bleeding is Not an Endocrine Diagnosis

Although anovulation is common during the transition period, heavy, prolonged, intermenstrual, or postcoital bleeding should not be presumed physiological. Initial assessment should include pregnancy testing, complete blood count, ferritin, medication review, and evaluation for structural and non-structural causes using the polyp; adenomyosis; leiomyoma; malignancy and hyperplasia; coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; and not yet classified (PALM–COEIN) framework. Thyroid testing is appropriate when clinically indicated, but thyroid disease should not become a default explanation that delays uterine assessment. Transvaginal ultrasonography is the preferred first-line imaging modality when structural pathology is suspected. Endometrial sampling is generally recommended for abnormal uterine bleeding in patients aged 45 years or older and in younger patients with persistent bleeding or risk factors for endometrial hyperplasia, including obesity, chronic anovulation, diabetes, or prolonged unopposed estrogen exposure.[5,6] Iron deficiency may precede anemia and should be treated while the bleeding source is investigated.

A Cardiometabolic and Skeletal Inflection Point

Although midlife aging and ovarian aging occur together, longitudinal data support menopause-related changes in body composition and cardiovascular risk beyond those attributable to chronological aging alone. Across the transition, fat mass and waist circumference increase, lean mass declines, and adverse changes in lipids, blood pressure, insulin sensitivity, and metabolic syndrome become more common.[7,8] These observations should be interpreted without implying that menopause makes weight gain inevitable or that hormone therapy is a weight-loss treatment. Patients may benefit from attention to sleep, engaging in resistance exercise, improving dietary quality, ensuring protein adequacy, avoidance of alcohol and medications that promote weight gain, and evidence-based obesity treatment when indicated. For those with diabetes, changes in body composition and sleep may complicate glycemic control. Oral estrogen may affect triglycerides and binding proteins, whereas transdermal estradiol usually produces fewer hepatic metabolic effects.

Perimenopause provides an opportunity for a useful prevention visit. Evaluation should include blood pressure, adiposity, smoking and alcohol use, sleep, physical activity, and screening for diabetes and dyslipidemia according to local guidelines. A history of hypertensive disorders of pregnancy, gestational diabetes, preterm birth, or early menopause can further refine lifetime cardiovascular risk. Menopausal hormone therapy (MHT) should not be prescribed to prevent cardiovascular disease, but neither should it be

withheld from appropriately selected symptomatic patients who are younger than 60 years or within 10 years of menopause, a group in whom there is generally a more favourable benefit–risk profile than that for older initiators.[3,9]

Bone loss accelerates during late perimenopause and continues through the early postmenopausal years.[10] Routine dual-energy x-ray absorptiometry is not required solely because perimenopause has begun; however, earlier testing is appropriate for patients with POI, early menopause, fragility fracture, prolonged glucocorticoid exposure, low body weight, malabsorption, or other major risk factors. Counselling should emphasize resistance and weight-bearing exercise, adequate protein and calcium intake primarily from food, vitamin D sufficiency, fall prevention, smoking cessation, and moderation of alcohol use.

Symptom Clusters and Competing Diagnoses

Vasomotor symptoms are often the most recognizable manifestation of perimenopause, but the clinical burden frequently arises from the interaction of multiple symptom clusters. Night sweats can fragment sleep, and poor sleep can worsen quality of life, energy, appetite regulation, concentration, and mood. Heavy menstrual bleeding can produce iron deficiency that can mimic or amplify fatigue and cognitive complaints. The term "not feeling like myself" has been tied to perimenopause.[11] A symptom inventory should therefore be paired with a basic differential rather than viewed as evidence of estrogen deficiency. Palpitations may accompany vasomotor symptoms such as hot flashes but still require appropriate cardiovascular assessment. Similarly, diffuse hair loss may reflect iron deficiency or thyroid disease; and new-onset severe headache, focal neurologic symptoms, or rapidly progressive cognitive change is not typical "brain fog."

Subjective cognitive symptoms during perimenopause commonly involve attention, word retrieval, and verbal learning difficulties. Longitudinal studies suggest a modest, time-limited decrement in verbal memory across the transition rather than a global loss of executive function.[12] Although reassurance is useful, active treatment of contributors—including insomnia, depression, vasomotor symptoms, medication effects, alcohol, anemia, thyroid dysfunction, and sleep-disordered breathing—are equally important. Obstructive sleep apnea may present in midlife women with insomnia, fatigue, mood changes, or morning headaches rather than classic witnessed apneas. Chronic insomnia should be diagnosed and treated as a distinct condition, with cognitive behavioural therapy for insomnia as first-line care. MHT is most likely to improve sleep when vasomotor symptoms are the principal driver.[13]

Treatment: Separate Contraception from Hormone Therapy

Treatment should be driven by symptom burden, bleeding pattern, contraceptive requirements, comorbidities, and patient preferences. Combined hormonal contraception suppresses ovulation, stabilizes hormonal fluctuation, controls bleeding, and provides contraception, making it a useful option for medically eligible patients with irregular cycles and vasomotor symptoms. Eligibility must be reassessed over time, as age-related vascular risk accumulates, particularly in the presence of smoking, hypertension, migraine with aura, obesity, or thromboembolic history.[14] A 52 mg levonorgestrel intrauterine system is highly effective for both heavy bleeding and contraception, and systemic estrogen may be added for vasomotor symptoms, although local regulatory approval for endometrial protection with MHT varies.[15]

MHT does not reliably suppress ovulation and is not a contraceptive method. It becomes attractive when contraception is no longer required or can be provided separately, particularly during the late transition. In patients with a uterus, systemic estrogen requires adequate endometrial protection, often with a progestogen. In still-cycling patients, a sequential regimen often produces more predictable bleeding than continuous combined therapy, though either is acceptable when individualized to the patient's needs. Transdermal estradiol avoids first-pass hepatic effects and is generally preferred in patients with elevated triglycerides or increased risk of venous thromboembolism.[3,9] Oral micronized progesterone may offer a more favourable metabolic and thrombotic profile than some synthetic progestins, although the choice of regimen must ensure endometrial protection. Custom-compounded hormones and salivary hormone testing are not recommended when regulated products are available.[16]

For patients with vasomotor symptoms who cannot or prefer not to use estrogen, evidence-based options for vasomotor symptoms include neurokinin receptor antagonists, carefully selected selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors, gabapentin, and oxybutynin.[3,17] Cognitive behavioural therapy and hypnosis can reduce the impact of vasomotor symptoms. Mood symptoms require screening for major depression, anxiety, suicidality, sleep disorders, and substance use. Although estradiol may help some patients with perimenopausal depression, it should not displace established psychiatric treatment when diagnostic criteria for a mood disorder are met.[18,19] Genitourinary symptoms can begin before the final menstrual period; moisturizers and lubricants are appropriate for mild symptoms, while low-dose vaginal estrogen or dehydroepiandrosterone is effective for persistent genitourinary syndrome with minimal systemic absorption.[3]

Practical Endocrine Follow-up

Follow-up at approximately three months permits assessment of symptom response, bleeding patterns, blood pressure, adherence, and adverse effects, with subsequent monitoring individualized to clinical need. Persistent or new unscheduled bleeding requires evaluation rather than repeated empiric hormone adjustment. The endocrinologist should also revisit contraception requirements because fertility declines but does not disappear until menopause is confirmed. For contraceptive purposes, one year of amenorrhea in those aged over 50 years is acceptable, or two years before age 50. Treatment duration should not be governed by an arbitrary age threshold; instead, the benefits, risks, dose, route of therapy, and the ongoing indication should be reviewed periodically.[3,9]

Conclusion

Perimenopause is best approached as a dynamic clinical transition rather than a laboratory diagnosis. Endocrinologists contribute particular value by excluding endocrine mimics selectively, recognizing POI and early menopause, integrating bone and cardiometabolic prevention, and prescribing hormone therapy with attention to route, progestogen, and contraceptive needs. Equally important is recognizing when abnormal bleeding or atypical symptoms require gynecologic or broader medical investigation. A structured, individualized approach can relieve symptoms while using midlife as an opportunity for long-term health protection.

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Financial Disclosures

M.J.: AbbVie, Astellas, Bayer, BioSyent, Duchesnay, Eisai, Hologic, Idorsia, Kye, Knight, Lupin, Lilly, Pfizer, Searchlight, Sanofi

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doi.org10.58931/cdet.2026.4258

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Cardiovascular Risk with Gender-Affirming Hormone Therapy

Irena Druce MD, FRCPC, MSc

Historical Perspective

Gender incongruence refers to a persistent mismatch between an individual's experienced gender and the sex assigned at birth. While modern terminology is recent, descriptions of gender variance date back to antiquity, including writings attributed to Hippocrates.

By the 7th century, Paul of Aegina, in his *Medical Compendium*, described surgical procedures aimed at modifying sex characteristics. While these early interventions were not grounded in a modern understanding of gender identity, they reflect attempts to address distress related to discordance between physical characteristics and lived experience. For much of history, surgical intervention—most commonly orchiectomy—remained the primary medical approach.[1]

A more structured medical understanding began to emerge in the early 20th century, including the establishment of early centres dedicated to the study and care of gender-diverse individuals.

In modern practice, access to gender-affirming hormone therapy (GAHT) and surgical interventions has improved. However, there remains a relative paucity of high-quality clinical research to guide management. Randomized controlled trials are lacking, and current recommendations are largely based on retrospective observational studies and extrapolation from cisgender populations. This limited evidence base makes it challenging to balance treatment goals with risk mitigation—particularly with respect to cardiovascular disease. This brief review aims to summarize the current evidence and provide a practical framework for clinicians.

GAHT and Cardiovascular Disease and Mortality

Historically, concerns have been raised regarding the potential adverse cardiovascular effects of exogenous sex hormone therapy. Evidence from cisgender populations, however, suggests a more nuanced relationship. In appropriately selected individuals, hormone

therapy does not appear to confer uniform cardiovascular harm and may, in some contexts, be cardiometabolically neutral or beneficial.[2-5]

In gender-diverse populations, uncertainties remain, as the effects of GAHT occur in a different physiologic context. At present, there are no randomized controlled trials and limited prospective data evaluating the impact of GAHT on hard cardiovascular outcomes such as myocardial infarction, stroke, or cardiovascular mortality. Only a small number of observational studies have examined these outcomes directly.

One of the largest available datasets comes from a Dutch cohort study evaluating approximately 3,000 individuals assigned male at birth (AMAB) receiving feminizing hormone therapy and over 1,500 individuals assigned female at birth (AFAB) receiving masculinizing therapy between 1972 and 2018. In both cohorts, overall mortality was higher compared to age-matched cisgender controls. Among AMAB individuals, excess mortality was primarily driven by cardiovascular disease, lung cancer, HIV-related illness, and suicide. In the AFAB cohort, higher mortality from non-natural causes was observed, although no single predominant etiology was identified. These trends were consistent across the five decades of follow-up.[6]

Overall, data are limited and do not demonstrate a clear association between GAHT and major cardiovascular outcomes, including atherosclerotic cardiovascular disease, myocardial infarction, coronary intervention, cerebrovascular disease, and peripheral arterial disease.[7] One retrospective study did report an association between the use of GAHT and rates of myocardial infarction; however, traditional cardiovascular risk factors such as diabetes and hypertension were substantially stronger predictors of risk.[8] The most consistent signal across the literature is an increased risk of venous thromboembolism (VTE) among AMAB individuals receiving estrogen therapy. This association is biologically plausible and mirrors the known prothrombotic effects of systemic estrogen observed in cisgender women.

GAHT and Cardiometabolic Risk Factors

Sex hormones are known to influence lipid metabolism, and similar patterns are observed in both cisgender and transgender populations. Testosterone therapy is associated with a more atherogenic lipid profile, characterized by increases in low-density lipoprotein (LDL) cholesterol and reductions in high density lipoprotein (HDL) cholesterol, in both cisgender men and transgender individuals (**Figure 1**).[9]

Estrogen, in contrast, is associated with increases in triglyceride levels. This effect may be more pronounced in AMAB individuals initiating feminizing hormone therapy, in whom significant elevations in triglycerides can occur, particularly with oral formulations. These effects reflect the underlying hepatic and metabolic pathways through which sex hormones influence lipid metabolism.[10]

Emerging data suggest that GAHT may influence insulin sensitivity and diabetes risk, although findings remain heterogeneous. Testosterone therapy has been associated with increased insulin resistance and a shift toward central adiposity, both of which are established contributors to adverse metabolic risk.[11]

In contrast, estrogen therapy is more commonly associated with overall weight gain and increased adiposity, which may also contribute to worsening insulin sensitivity through a different metabolic pathway (**Figure 2**). As such, both feminizing and masculinizing hormone therapies may be associated with an increased risk of type 2 diabetes, albeit via distinct mechanisms. Observational data from large cohort studies support this signal, although findings are limited by potential confounding and should be interpreted with caution.[11]

Evidence regarding the impact of GAHT on blood pressure is limited and inconsistent. Both feminizing and masculinizing hormone therapies may influence blood pressure through distinct mechanisms, including effects on fluid balance, vascular tone, and body composition; however, no clear or consistent association with hypertension has been established. As such, blood pressure management in individuals receiving GAHT should follow standard approaches based on overall cardiovascular risk rather than being attributed solely to hormone therapy.[12]

The role of progesterone in feminizing GAHT remains unclear. While some patients and clinicians use it with the aim of improving breast development, mood, or sleep, supporting evidence is limited, and data on cardiovascular effects in transgender populations are sparse. Evidence from cisgender populations suggests that risk may vary by formulation, with synthetic progestins having less favourable cardiometabolic and thrombotic profiles compared to micronized progesterone. However, whether these findings

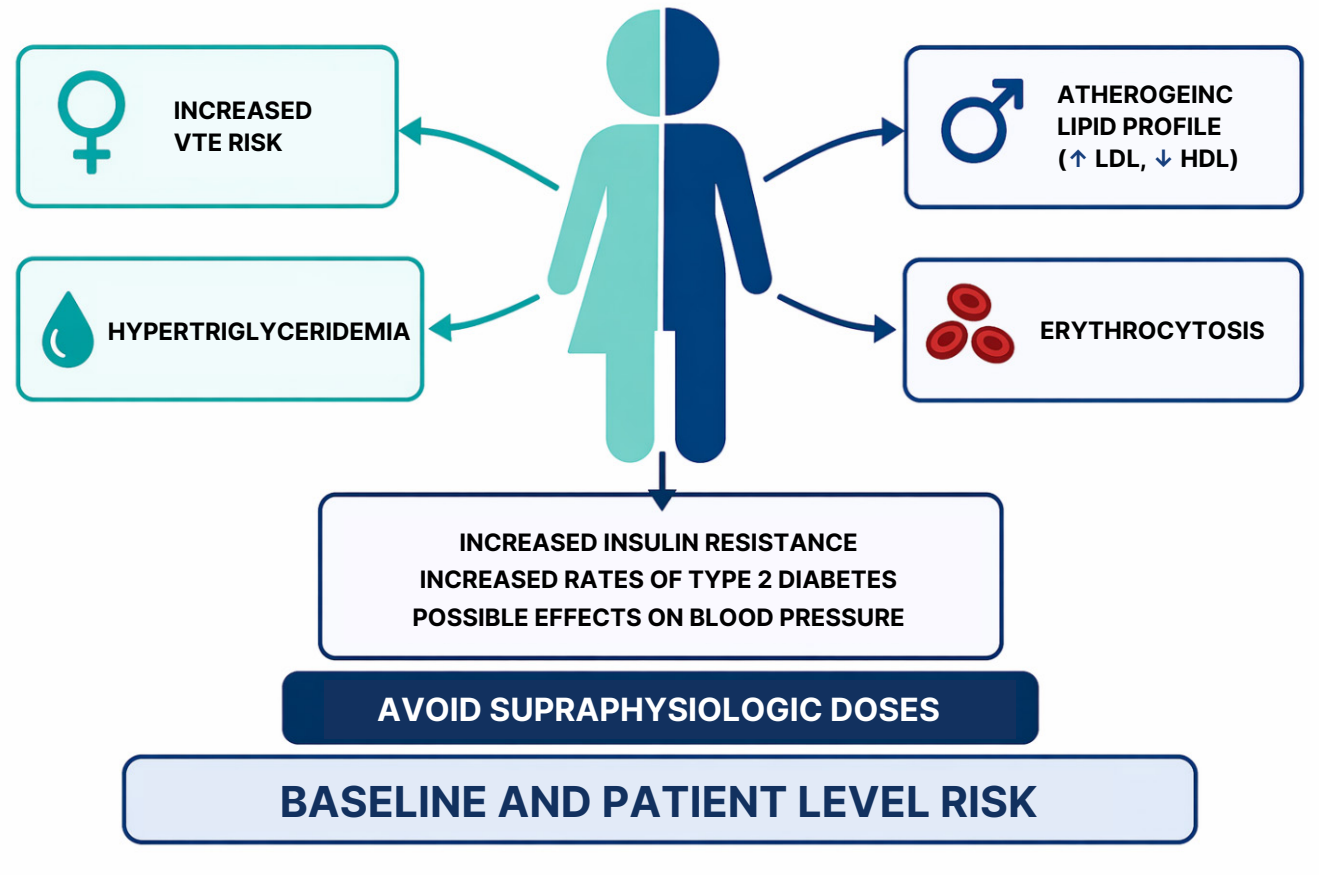

Figure 1. Summary of cardiovascular and venous thromboembolism risks associated with gender-affirming hormone therapy; *courtesy of Irena Druce MD, FRCPC, MSc.*

Abbreviations: HDL: high density lipoprotein; **LDL:** low-density lipoprotein; **VTE:** venous thromboembolism

apply to individuals receiving GAHT remains unknown.[13] In the absence of strong data, the use of progesterone should be individualized, with consideration of potential risks and uncertain benefits.

Beyond hormone-related effects, it is important to recognize that cardiovascular risk in gender-diverse populations is shaped by broader social and structural factors. Transgender individuals experience higher rates of smoking, substance use, and psychosocial stress, as well as reduced access to primary and preventive healthcare. These factors likely contribute substantially to observed differences in cardiovascular outcomes and mortality and may represent a more significant driver of risk than GAHT itself. Accordingly, a comprehensive approach to cardiovascular risk reduction must extend beyond hormone management to include optimization of traditional risk factors and improved access to longitudinal, preventive care.[14,15]

Feminizing GAHT and Venous Thromboembolic Disease

Among the cardiovascular risks associated with GAHT, the most consistent and clinically relevant signal is an increased risk of venous thromboembolism (VTE) in AMAB individuals receiving estrogen therapy. This association is well established and reflects the known prothrombotic effects of systemic estrogen observed in cisgender women.[16]

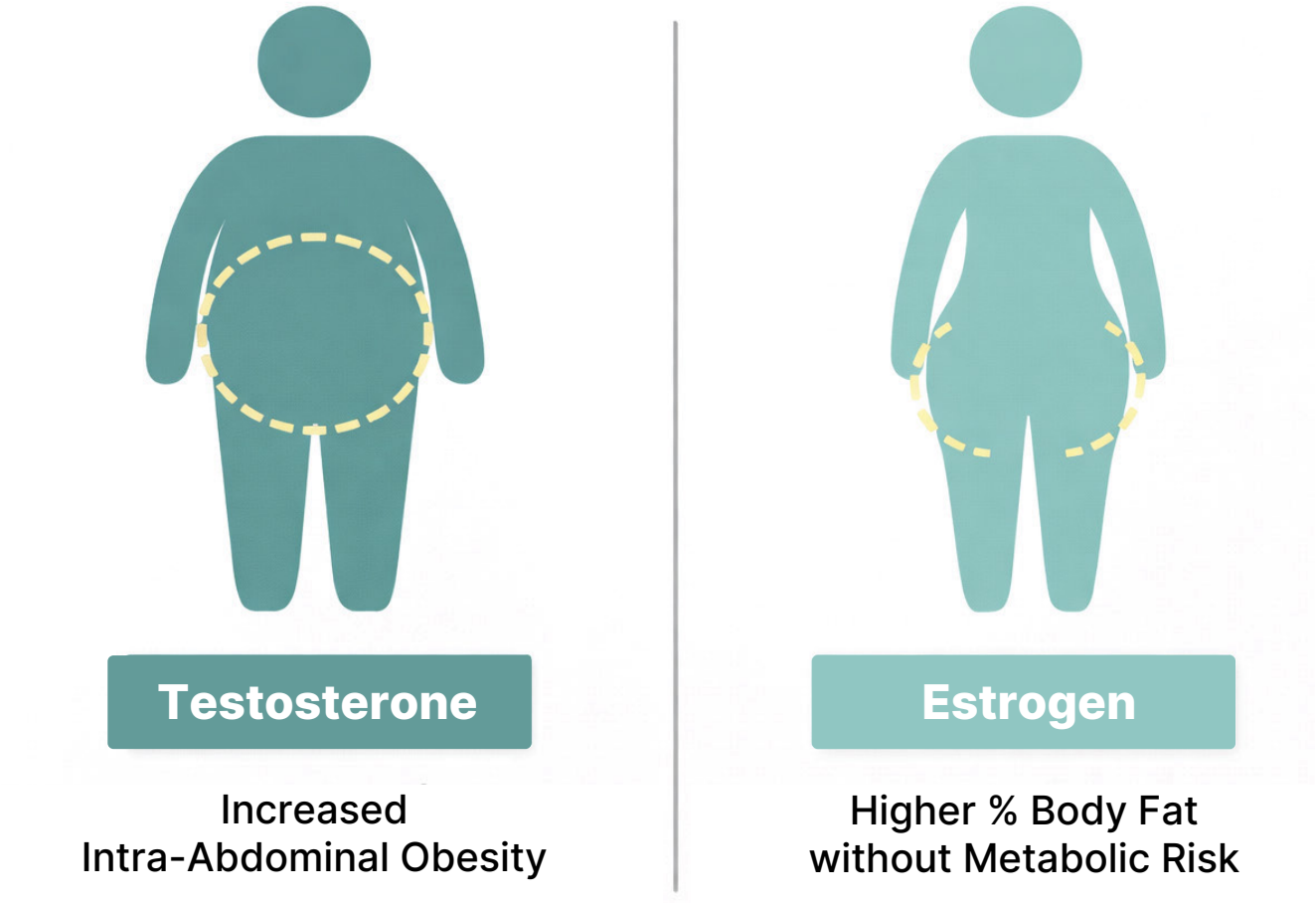

Figure 2. Sex hormone–associated patterns of adipose distribution; *courtesy of Irena Druce MD, FRCPC, MSc.*

Testosterone promotes an android pattern with increased visceral adiposity and higher cardiometabolic risk, whereas estrogen promotes a gynoid pattern with fat deposition in the hips and buttocks, which is typically metabolically less adverse despite higher total body fat.

However, the clinical context differs meaningfully in gender-diverse populations. In cisgender women, estrogen exposure may be time-limited and can often be discontinued if risks outweigh benefits. In contrast, for transgender women, estrogen therapy is a cornerstone of gender-affirming care, with important implications not only for physical characteristics but also for psychological well-being and quality of life. Consequently, discontinuation of estrogen is often not a feasible or appropriate option.[13]

Current practice generally supports the long-term continuation of GAHT, although data on the effects of prolonged estrogen exposure in this population remain limited. Transgender women do not typically undergo an equivalent of menopause, and long-term hormone therapy is commonly maintained. This underscores the importance of risk mitigation rather than treatment avoidance or discontinuation.[13]

In the context of VTE risk, the route of estrogen administration represents one of the few modifiable factors available to clinicians. Oral estrogen undergoes first-pass hepatic metabolism, leading to increased synthesis of clotting factors and a more pronounced prothrombotic effect. In contrast, transdermal estrogen largely bypasses hepatic first-pass metabolism and is associated with a lower impact on coagulation pathways.[17]

While direct comparative data in transgender populations remain limited, evidence from cisgender populations consistently demonstrates a lower risk of venous thromboembolism with transdermal formulations compared to oral estrogen.[18] Accordingly, the route of administration represents a key opportunity for risk reduction in clinical practice. When clinically appropriate, the use of transdermal estrogen should be strongly considered, particularly in individuals with additional risk factors for thrombosis, including increasing age, smoking, obesity, or a personal or family history of VTE.[17,18]

An additional layer of complexity lies in the lack of consensus regarding optimal estradiol targets for individuals receiving feminizing GAHT. In contrast, hormone targets for AFAB individuals on masculinizing therapy can reasonably align with cisgender male reference ranges and remain relatively stable over time. However, cisgender women of reproductive age exhibit wide physiologic variability in estradiol levels across the menstrual cycle, and there is no clear agreement in the literature on which values should be replicated or targeted in feminizing GAHT.[19]

In the context of cardiovascular risk mitigation, particularly VTE, a pragmatic approach is to use the lowest effective estradiol dose that achieves and maintains desired clinical outcomes. This is especially relevant in the maintenance phase, once secondary sexual characteristics have been established, as supraphysiologic exposure is unlikely to confer additional benefit and may increase risk.

In higher-risk individuals, including those with a history of VTE, multidisciplinary management is recommended. Collaboration with thrombosis specialists may help guide decisions regarding the safety of ongoing estrogen therapy, including consideration of anticoagulation when appropriate. Shared decision-making is essential, and should include clear discussion of the potential risks, benefits, and uncertainties surrounding long-term therapy.[17]

Practical Considerations for Cardiovascular Risk Management in Individuals Receiving GAHT

In the absence of robust long-term outcome data, a pragmatic and proactive approach to cardiovascular risk reduction is recommended:

- **Route of estrogen administration:** Prefer transdermal estrogen over oral formulations, particularly in individuals with additional risk factors for VTE, as transdermal preparations are associated with a lower impact on coagulation pathways. Consider injectable formulations where appropriate.
- **Lipid monitoring:** Obtain a baseline lipid profile and monitor it periodically. Consider earlier and more frequent screening, particularly in individuals receiving testosterone or oral estrogen. Include triglyceride measurement where clinically indicated.
- **Glucose metabolism:** Monitor body weight, fasting glucose, and/or HbA1c in individuals with risk factors or features of metabolic syndrome.
- **Blood pressure:** Measure blood pressure routinely and manage according to standard clinical guidelines. Current evidence does not support attributing hypertension solely to GAHT.
- **Weight and body composition:** Monitor weight and body mass index, and counsel patients regarding expected changes in body composition. Support lifestyle interventions where appropriate and pharmacotherapy for obesity as per Canadian guidelines.
- **Hematologic monitoring (testosterone therapy):** Monitor hemoglobin and hematocrit given the risk of erythrocytosis which may predispose to cerebrovascular events. Adjust therapy if levels are above normal cis-male range.

- **Hormone dosing:** Regularly review hormone regimens and ensure that achieved hormone levels remain within physiologic ranges. Supraphysiologic testosterone levels may exacerbate insulin resistance, adverse lipid changes, and erythrocytosis, and should be avoided.
    - For individuals receiving feminizing hormone therapy, maintaining estradiol levels within the physiologic range for premenopausal cisgender women is recommended, while avoiding supraphysiologic levels. In clinical practice, this often corresponds to approximately 200–400 pmol/L, although targets may be individualized based on clinical response and patient-specific goals.
- **VTE risk assessment and mitigation:** Assess individual thrombotic risk factors (e.g., smoking, obesity, personal or family history of VTE) and optimize modifiable risk factors.
- **Multidisciplinary care:** In individuals at higher risk, or those with a history of VTE, collaborate with thrombosis specialists when considering continuation of estrogen therapy, including the potential role of anticoagulation.
- **General preventive care:** Address traditional cardiovascular risk factors, including smoking and substance use, and ensure access to routine primary and preventive care.

Conclusion

At present, limited data directly links GAHT to major cardiovascular outcomes. While hormone-related effects on intermediate risk factors are increasingly recognized, the overall impact of GAHT on cardiovascular disease risk remains uncertain.

At the same time, a growing body of evidence highlights significant disparities in health outcomes and access to care among gender-diverse individuals. The higher rates of cardiovascular morbidity and mortality observed in this population are likely multifactorial, reflecting not only the physiologic effects of hormone therapy but also differences in baseline risk factors, barriers to care, and reduced access to preventive and longitudinal healthcare services.

These findings underscore the importance of a comprehensive approach to cardiovascular risk management in gender-diverse populations. In addition to thoughtful use of GAHT, clinicians should prioritize optimization of traditional risk factors, ensure access to appropriate screening and preventive care, and support ongoing engagement with the healthcare system.

As the evidence base continues to evolve, individualized care, multidisciplinary collaboration, and shared decision-making remain essential. Further research is needed to better define long-term outcomes and to inform strategies that both affirm gender identity and minimize cardiovascular risk.

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Financial Disclosures

I.D.: Speaking Honoraria: Abbott, Astra Zeneca, Amgen, Bayer, Boehringer Ingelheim, CCRN, CPD Network, Dexcom, Eli Lilly, GSK, HLS Therapeutics, Janssen, Merck, Novo Nordisk, Sanofi, Tolmar, UBC Canada; **Consultancy Fees:** Abbott, Amgen, Bayer, Dexcom, Eli Lilly, HLS Therapeutics, Novo Nordisk, Sanofi

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