
CSEM SCEM
The Canadian Society of Endocrinology and Metabolism
La Société canadienne d'endocrinologie et de métabolisme


50

Perspectives on Practice Changing Research

CSEM Endocrinology & Diabetes

2023 Year in Review

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The program was planned independently by CSEM to achieve scientific integrity and balance.

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Accreditation

- This activity is an accredited group learning activity under Section 1 as defined by the Royal College of Physicians & Surgeons of Canada for the Maintenance of Certification program.
- Approved by CSEM for a maximum of **2.0 hours**
  (credits are automatically calculated)

Discussion

Join at **slido.com** with **#1803685**

Put your questions in the Q&A

Learning Objectives

At the end of this symposium, participants will be able to:

- review and synthesize key scientific developments in diabetes and endocrinology over the past year
- evaluate the relevance and implications for diabetes management within a Canadian context
- identify important elements of emerging research that can be applied to clinical practice

Agenda

7:00 pm Introduction - *Hertzel Gerstein*

7:05 pm Medical therapy for non-diabetes obesity to improve patient outcomes: Ongoing trials in prevention of diabetes, MAFLD, and cardiovascular events, and quality of life enhancement - *Heidi Dutton*

7:25 pm Discussion

7:35 pm Novelties in hypoparathyroidism: Current and future therapies - *Claudia Gagnon*

7:55 pm Discussion

8:05 pm Novel approaches to insulin therapy: Challenges and opportunities with new basal insulins - *Heidi Dutton*

8:15 pm Discussion

8:25 pm Benefits and risks of androgen replacement in middle-aged and older men with low testosterone levels - *Claudia Gagnon*

8:35 pm Discussion

8:45 pm Wrap Up

DISCLOSURES OF INTEREST DECLARATION: HERTZEL GERSTEIN

I have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria	Sanofi, Lilly, Novo Nordisk, Abbott, Pfizer, Kowa, Hanmi	Honoraria for consulting
Membership on advisory boards or speakers' bureaus	Sanofi, Lilly, DKSH, AstraZeneca, Zuellig, Carbon Brand, Jiangsu-Hansen	Honoraria for speaking
Funded grants or clinical trials	CIHR, Diabetes Canada, Sanofi, Lilly, Novo Nordisk	Grant to my institution for research
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

DISCLOSURES OF INTEREST DECLARATION – HEIDI DUTTON

I have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria	Thrombosis Canada CSEM CPD committee CPD Network Association	Financial payments/Honoraria
Membership on advisory boards or speakers' bureaus	Lilly	Advisory Board
Funded grants or clinical trials		
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

MITIGATION OF BIAS – HEIDI DUTTON

POTENTIAL SOURCE OF BIAS	MITIGATION MEASURES
Advisory board payment x 1 received from a company whose medications will be discussed	Discussion of the highest level evidence available, focus on objective data, avoiding personal opinion

DISCLOSURES OF INTEREST DECLARATION – Claudia Gagnon

I have a relationship with for-profit/not-for-profit organizations to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria		
Membership on advisory boards or speakers' bureaus		
Funded grants or clinical trials	Shire/Takeda, Ascendis Pharma, Amolyt Pharma	Participation in clinical trials on PTH drugs or PTH analogs for the treatment of hypoparathyroidism
Patents on a drug, product or device		
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity		

MITIGATION OF BIAS

POTENTIAL SOURCE OF BIAS	MITIGATION MEASURES
PTH products will be discussed in the hypoparathyroidism presentation	The presenter will avoid making personal recommendations and will limit the presentation to a discussion of the evidence; all the future developments will be discussed.

Medical therapy for non-diabetes obesity to improve patient outcomes

Ongoing trials in prevention of diabetes, MAFLD, and cardiovascular events, and quality of life enhancement

Heidi Dutton, MD, MSc, FRCPC, DIPL.ABOM & ABLM
The Ottawa Hospital

Obesity and outcomes – Where do we stand?

- For weight loss pharmacotherapy to be approved, must demonstrate > 5% total weight loss
  - Initial RCTs designed with weight loss as primary outcome
- Growing interest in proving health improvements beyond weight loss
  - Important to patients, physicians and insurers
- Review recent evidence on the following outcomes:
  - Cardiovascular outcomes
  - Quality of life (QOL)
  - Metabolic-associated fatty liver disease (MAFLD)

CADTH

What is the CADTH Reimbursement Recommendation for Wegovy?

CADTH recommends that Wegovy should not be reimbursed by public drug plans for chronic weight management in adult patients.

Why Did CADTH Make This Recommendation?

- Even though results from 4 clinical trials showed that patients treated with Wegovy for 68 weeks lost more body weight compared to those who received placebo, there was no evidence to show this weight loss translates to improvements in weight-related comorbidities (e.g., cardiovascular complications, osteoarthritis [the most common form of arthritis], and sleep apnea) because they were not studied.

https://www.cadth.ca/semaglutide-1. Oct 2022.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 14, 2023 VOL. 389 NO. 24

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

Rationale and Trial Design

- Overweight and obesity associated with increased risk of CV events
- Does treating obesity with lifestyle or pharmacotherapy interventions reduce CV risk?
- Some GLP-1 RAs are known to reduce major adverse CV events in patients with Type 2 DM at high CV risk
  - Do they reduce CV risk in those without diabetes who are living with overweight and obesity??

- Trial design:
  - Multicentre, double-blind RCT, event-driven superiority trial
  - Population: BMI ≥ 27, no diabetes
    - History of: MI, stroke or symptomatic PAD
  - Intervention: semaglutide 2.4 mg sc weekly vs placebo
  - Primary composite outcome: death from CV causes, nonfatal MI, nonfatal stroke

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N = 8803)	Placebo (N = 8801)
Age — yr	61.6±8.9	61.6±8.8
Male sex — no. (%)	6355 (72.2)	6377 (72.5)
Race or ethnic group — no. (%)†		
White	7387 (83.9)	7404 (84.1)
Asian	720 (8.2)	727 (8.3)
Black	348 (4.0)	323 (3.7)
Other	253 (2.9)	273 (3.1)
Hispanic or Latino	914 (10.4)	908 (10.3)
Body weight — kg	96.5±17.5	96.8±17.8
BMI‡	33.3±5.0	33.4±5.0
Waist circumference — cm	111.3±13.1	111.4±13.1
Glycated hemoglobin level — %	5.78±0.34	5.78±0.33
Distribution — no. (%)		
<5.7%	2925 (33.2)	2980 (33.9)
≥5.7%	5877 (66.8)	5819 (66.1)

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Semaglutide (N=8803)	Placebo (N=8801)
Cardiovascular inclusion criteria — no. (%)		
Myocardial infarction only	5962 (67.7)	5944 (67.5)
Stroke only	1578 (17.9)	1556 (17.7)
Peripheral arterial disease only	376 (4.3)	401 (4.6)
Two or more inclusion criteria	718 (8.2)	719 (8.2)
Other§	169 (1.9)	181 (2.1)
Median lipid level (IQR) — mg/dl		
Total cholesterol	153 (131–182)	153 (131–183)
HDL cholesterol	44 (37–52)	44 (37–52)
LDL cholesterol	78 (61–102)	78 (61–102)
Triglycerides	134 (99–188)	135 (100–190)
Systolic blood pressure — mm Hg	131.0±15.6	130.9±15.3
Diastolic blood pressure — mm Hg	79.4±10.0	79.2±9.9

LDL 78 mg/dl
= 2.02 mmol/L

Figure 1

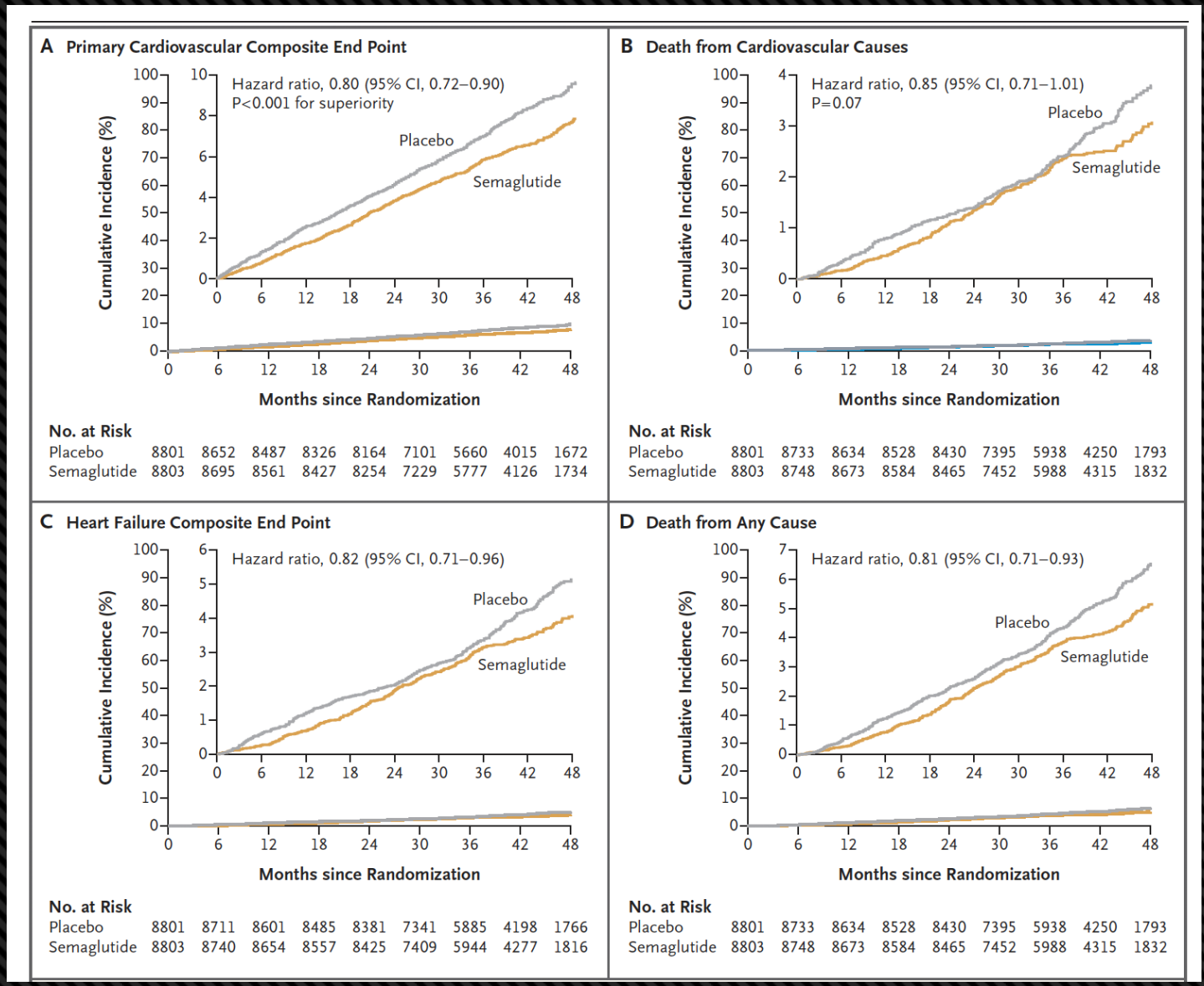

A Primary Cardiovascular Composite End Point
Hazard ratio, 0.80 (95% CI, 0.72–0.90)
P<0.001 for superiority
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8652 8487 8326 8164 7101 5660 4015 1672
Semaglutide 8803 8695 8561 8427 8254 7229 5777 4126 1734
B Death from Cardiovascular Causes
Hazard ratio, 0.85 (95% CI, 0.71–1.01)
P=0.07
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8733 8634 8528 8430 7395 5938 4250 1793
Semaglutide 8803 8748 8673 8584 8465 7452 5988 4315 1832
C Heart Failure Composite End Point
Hazard ratio, 0.82 (95% CI, 0.71–0.96)
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8711 8601 8485 8381 7341 5885 4198 1766
Semaglutide 8803 8740 8654 8557 8425 7409 5944 4277 1816
D Death from Any Cause
Hazard ratio, 0.81 (95% CI, 0.71–0.93)
Placebo
Semaglutide
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 8801 8733 8634 8528 8430 7395 5938 4250 1793
Semaglutide 8803 8748 8673 8584 8465 7452 5988 4315 1832

Table 2. Primary and Secondary Time-to-First-Event Efficacy End Points.*

End Point	Semaglutide (N=8803)	Placebo (N=8801)	Hazard Ratio (95% CI)	P Value
	number of patients (percent)			
Primary cardiovascular composite end point†	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90)	<0.001
Confirmatory secondary end points‡				
Death from cardiovascular causes	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01)	0.07
Heart failure composite end point§	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)	NA
Death from any cause	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)	NA
Supportive secondary end points¶				
Cardiovascular expanded composite end point‖	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)	NA
Cardiovascular composite end point with death from any cause**	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.88)	NA
Nonfatal myocardial infarction	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)	NA
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)	NA
Hospitalization or urgent medical visit for heart failure	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)	NA
Coronary revascularization	473 (5.4)	608 (6.9)	0.77 (0.68 to 0.87)	NA

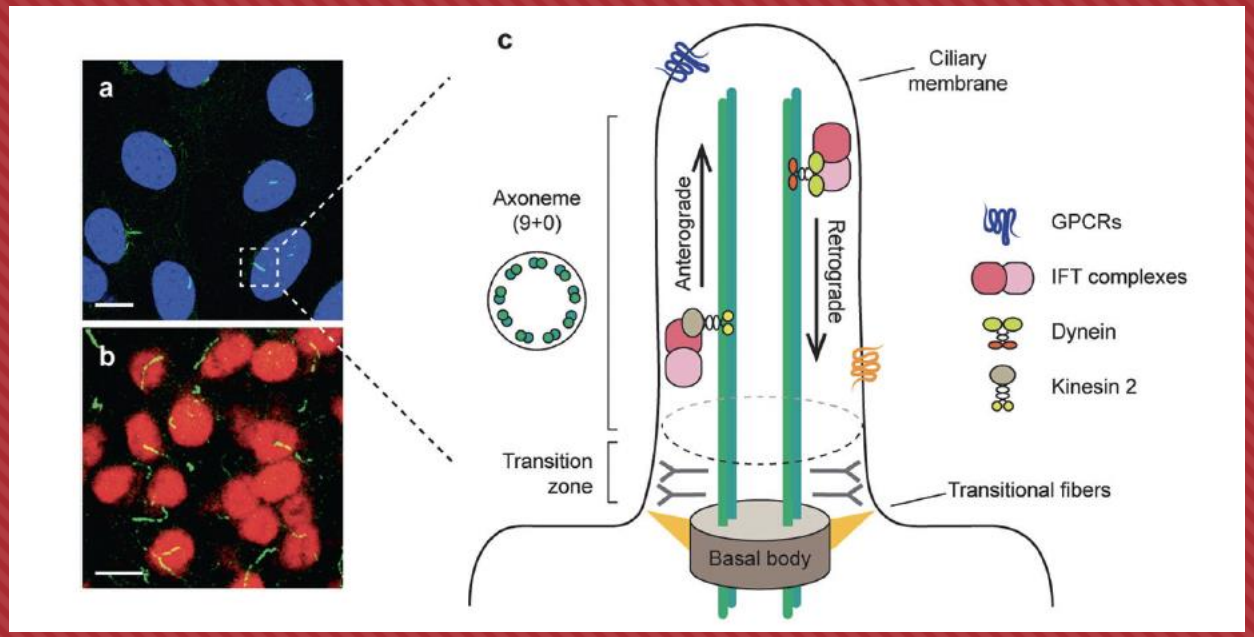
SELECT - Key Takeaways

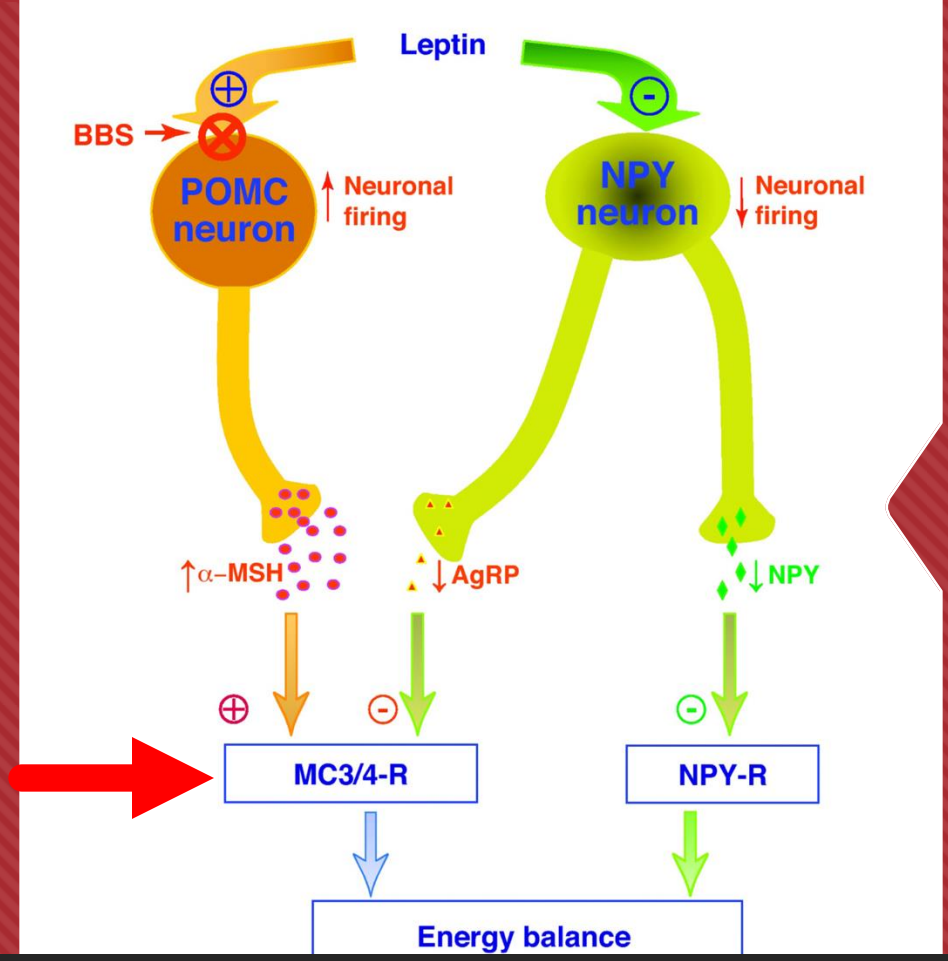
- In patients with history of MI, stroke or symptomatic PAD and BMI ≥ 27:
  - Once weekly semaglutide 2.4 mg sc for mean duration of 33 months reduced risk of composite death from CV causes, nonfatal MI, or nonfatal stroke by 20%
- Effects occurred early
  - Directionally similar across different CV endpoints
- Possible mechanism:
  - Reduce inflammation, improved endothelial/LV function, improved CV risk parameters (lipids, hs-CRP)
- Important to note the high baseline prevalence of prediabetes (66%) in the population studied

Setmelanotide – targeted obesity therapy

- Melanocortin 4 (MC4) receptor agonist
- Approved by Health Canada in May 2023
  - Patients age 6+
  - Obesity due to Bardet-Biedl syndrome (BBS), or genetically confirmed POMC, PCSK1 or LEPR deficiency
  - Has been recommended to be covered for patients age 6+ with BBS
- BBS → autosomal recessive → prevalence 1:120,000
  - 6 cardinal manifestations
  - Obesity → marked by hyperphagia
    - Retinal degeneration, polydactyly, renal anomalies, learning disabilities, hypogonadism/genitourinary abnormalities
  - Genetic confirmation in about 80% of cases

Melluso et al. Bardet-Biedl Syndrome: Current Perspectives and Clinical Outlook. Ther and Clin Risk Mgmt. 2023:19 115-132.





Setmelanotide – targeted obesity therapy

Yang DJ, Hong J, Kim KW. Hypothalamic primary cilium: A hub for metabolic homeostasis. Experimental & Molecular Medicine. 2021;53(7):1109-15
Guo D-F, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. Trends in Endocrinology & Metabolism 2011.

Forsythe *et al.*
Orphanet Journal of Rare Diseases (2023) 18:12
https://doi.org/10.1186/s13023-022-02602-4

Orphanet Journal of
Rare Diseases

RESEARCH **Open Access**

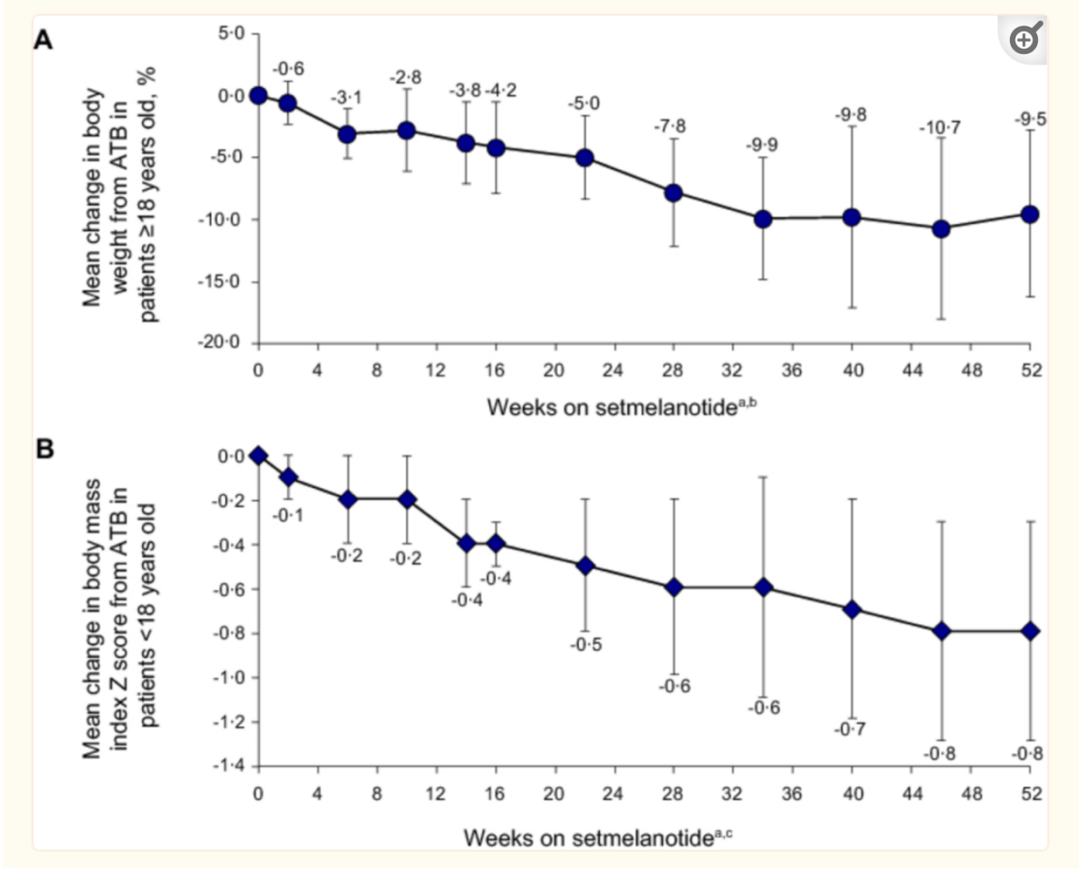
Quality of life improvements following one year of setmelanotide in children and adult patients with Bardet–Biedl syndrome: phase 3 trial results

Elizabeth Forsythe[1], Robert M. Haws[2], Jesús Argente[3,4,5], Philip Beales[1], Gabriel Á. Martos-Moreno[3,4], Hélène Dollfus[6], Costel Chirila[7], Ari Gnanasakthy[7], Brieana C. Buckley[8], Usha G. Mallya[8], Karine Clément[9,10] and Andrea M. Haqq[11*]

Rationale and Trial Design

- Primary study – Phase 3 RCT of setmelanotide
  - Patients age ≥ 6 with dx BBS or Alström syndrome + BMI ≥ 30 or weight > 97th percentile (pediatric)
  - Randomized double-blind placebo-controlled period x 14 weeks followed by open label setmelanotide for all
  - Primary outcome: proportion of patients with ≥ 10% reduction in body weight after 52 weeks of setmelanotide

- "Sub study" of the Phase 3 RCT → exploratory outcomes in BBS patients (20/32 patients)
  - Designed to evaluate impact on hunger scores, HRQOL
    - Pediatrics – PedsQL assessment
    - Adults - Impact of Weight on QOL (IWQOL-Lite)
    - Hunger scores in age ≥ 12 with no cognitive impairment
    - Not ITT analysis



Weight loss data from primary RCT

Haqq et al. Lancet Diabetes Endocrinol. 2022 Dec;10(12): 859-868

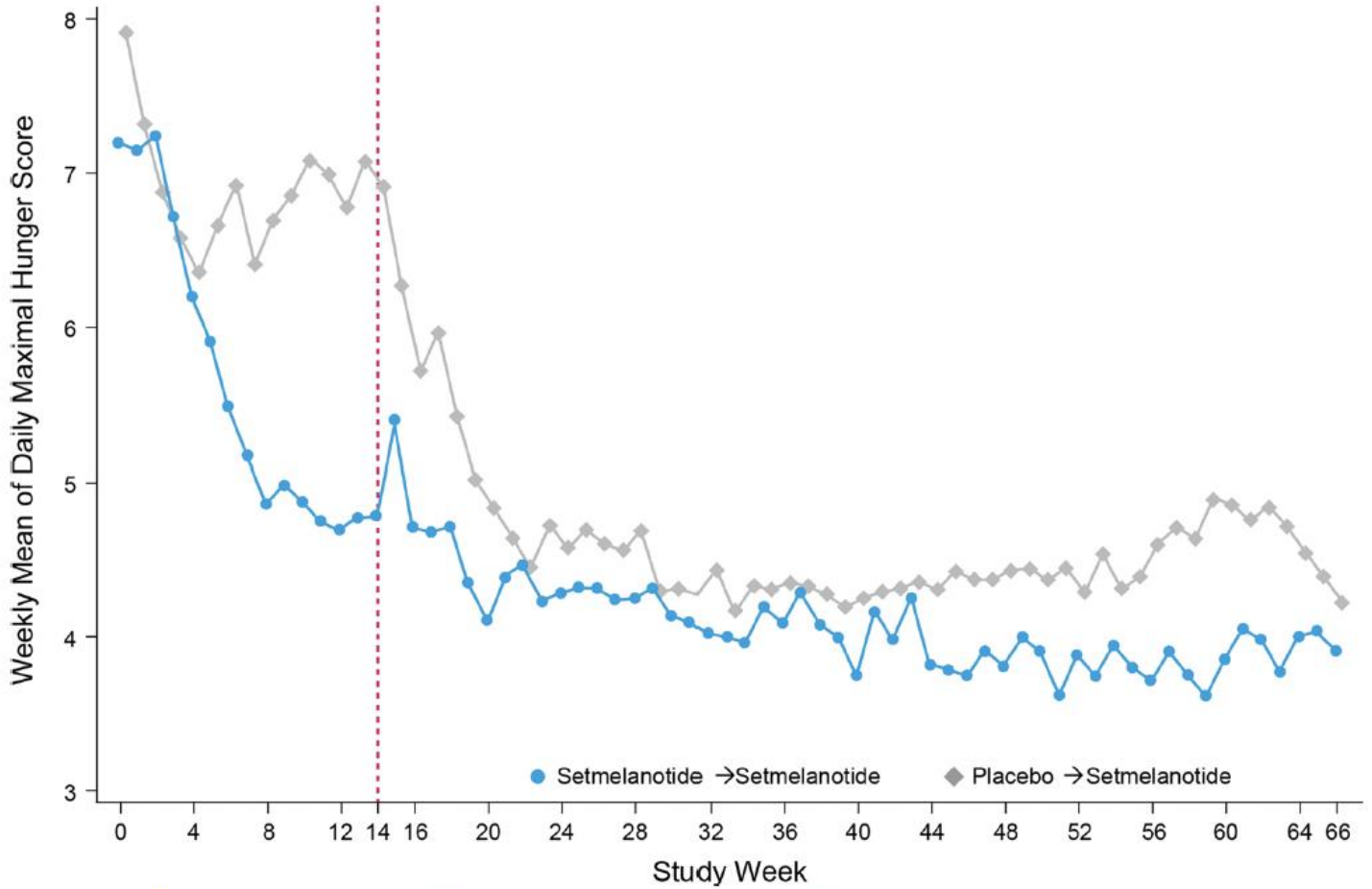


Fig. 1 Change in maximal hunger score over time. Weekly mean of the daily maximal hunger score over time across all patients enrolled in the Phase 3 trial with BBS who could self-report hunger (i.e., ≥ 12 years old without cognitive impairment). Patients were randomized to receive 14 weeks of setmelanotide (n = 5 at baseline) or placebo (n = 9 at baseline), followed by 52 weeks of open-label setmelanotide (n = 14 after 52 weeks). Vertical dashed pink line represents the Week-14 time point where all patients transitioned to open-label setmelanotide treatment

Table 2 Impact of setmelanotide in children (< 18 years old; self-reported) with baseline and week-52 PedsQL data

	Baseline		Change from baseline at week 52	
	All patients (n = 9)	Patients without cognitive impairment (n = 3)	All patients (n = 9)	Patients without cognitive impairment (n = 3)
PedsQL total score, mean (SD) [range]	67.2 (18.9) [33.7–90.2]	83.3 (2.7) [80.4–87.0]	+ 11.2 (14.3) [− 5.2 to 45.6]	+ 3.3 (6.6) [− 5.2 to 10.9]
PedsQL physical function score, mean (SD) [range]	60.4 (28.1) [0–93.8]	83.3 (7.8) [75.0–93.8]	+ 14.0 (27.7) [− 18.8–68.8]	+ 2.1 (14.7) [− 18.8–12.5]
PedsQL psychosocial score, mean (SD) [range]	70.7 (16.3) [46.7–90.0]	83.3 (5.4) [76.7–90.0]	+ 9.3 (9.9) [0.0–33.3]	+ 3.9 (4.4) [0.0–10.0]
BMI Z-score, mean (SD) [range]	3.7 (1.5) [1.8–7.1]	2.9 (1.4) [1.8–4.8]	− 0.7 (0.5)[a] [− 0.2 to − 1.9]	− 1.0 (0.7)[a] [− 0.2 to − 1.9]
Maximal hunger, mean (SD) [range]	–	6.0 (0.8) [5.0–7.0]	–	− 52.7% (23.2) [− 71.4% to − 20.0%]

[a] Absolute change. *BMI* body mass index, *PedsQL* pediatric quality of life inventory, *SD* standard deviation

Table 3 Impact of setmelanotide in adults (≥ 18 years old; self-reported) with baseline and week-52 IWQOL-Lite data

	Baseline		Change from baseline at week 52	
	All patients (n = 11)	**Patients without cognitive impairment (n = 7)**	**All patients (n = 11)**	**Patients without cognitive impairment (n = 7)**
IWQL-Lite total score, mean (SD) [range]	74.9 (12.0) [59.0–97.0]	70.7 (9.8) [59.0–88.0]	+ 12.0 (10.3) [1.0–28.0]	+ 17.6 (8.9) [1.0–28.0]
IWQOL-Lite physical function score, mean (SD) [range]	63.0 (13.3) [48.0–95.0]	60.0 (7.8) [52.0–73.0]	+ 15.3 (11.6) [0.0–34.0]	+ 21.7 (9.3) [5.0–34.0]
IWQOL-Lite sexual life score, mean (SD) [range]	90.1 (14.2) [63.0–100.0]	86.7 (15.7) [63.0–100.0]	+ 9.3 (13.4) [0.0–37.0]	+ 12.4 (14.8) [0.0–37.0]
IWQOL-Lite work score, mean (SD) [range]	83.7 (16.2) [50.0–100.0]	77.9 (17.6) [50.0–100.0]	+ 9.5 (14.0) [− 6.0 to 37.0]	+ 15.0 (14.8) [0.0–37.0]
IWQOL-Lite public distress score, mean (SD) [range]	75.0 (17.7) [50.0–100.0]	68.6 (13.6) [50.0–95.0]	+ 12.7 (15.0) [− 5.0 to 40.0]	+ 20.0 (14.1) [− 5.0 to 40.0]
IWQOL-Lite self-esteem score, mean (SD) [range]	79.1 (19.1) [32.0–100.0]	74.3 (21.3) [32.0–100.0]	+ 11.1 (15.9) [0.0–50.0]	+ 15.4 (18.4) [0.0–50.0]
BMI, kg/m^2, mean (SD) [range]	47.6 (5.8) [39.4–57.8]	50.3 (5.3) [43.0–57.8]	− 9.4% (6.7) [− 17.6 to 5.3%]	− 10.1% (7.4) [− 17.6 to 5.3%]
Maximal hunger, mean (SD) [range]	–	7.1 (1.2) [5.0–9.0]	–	− 39.6% (21.5) [− 71.4 to 0%]

BMI body mass index, *IWQOL-Lite* impact of weight on quality of life-lite, *SD* standard deviation

Key takeaways

- Challenges and limitations to RCTs in rare diseases
- Setmelanotide appears to improve QOL measures in addition to significant weight loss
- Hunger scores also improved in patients without cognitive impairment
- Important to show QOL improvement in addition to weight loss efficacy
  - Hyperphagic obesity is a large burden on affected individuals and families

Nomenclature change

NAFLD → MAFLD*

*= Metabolic-associated fatty liver disease

MAFLD

- Prevalence (interaction with obesity/type 2 DM)
  - Estimated 25% prevalence worldwide
  - Affects 60-70% of patients with T2DM
- Current therapeutic landscape is limited
  - Lifestyle intervention, bariatric surgery, vitamin E (bx proven MASH, non-diabetes)
  - GLP1RA → shorter duration RCTs with exenatide, liraglutide, dulaglutide, semaglutide
    - Mixed results
- Challenges
  - Liver histology required as primary surrogate endpoint → invasive, sampling variability, and poor intra/inter reader reliability
  - Ideal trial duration unknown/may vary

Harrison SA, Loomba R, Dubourg J, Ratziu V, Noureddin M. Clinical Trial Landscape in NASH. Clinical Gastroenterology and Hepatology. 2023;21(8):2001–14

Andreasen CR, Andersen A, Vilsbøll T. The future of incretins in the treatment of obesity and non-alcoholic fatty liver disease. Diabetologia. 2023;66(10):1846–58.

Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial

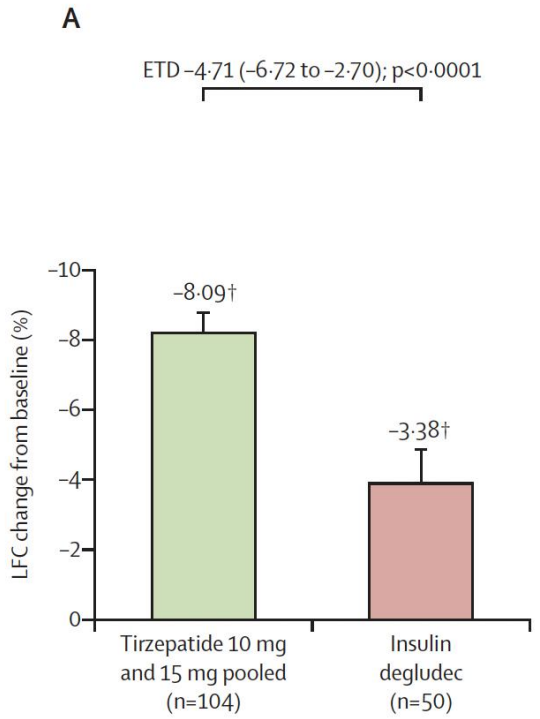
Amalia Gastaldelli, Kenneth Cusi, Laura Fernández Landó, Ross Bray, Bram Brouwers, Ángel Rodríguez

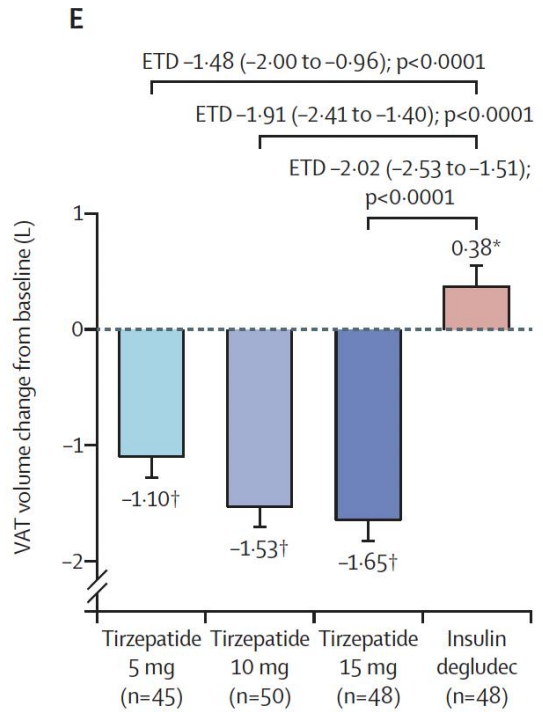
Lancet Diabetes Endocrinol. 2022 Jun;10(6):393-406

Trial Design and Baseline characteristics

- Substudy of phase 3, randomised, active controlled, open-label, SURPASS-3 trial
  - T2DM, on metformin +/- SGLT2i with A1c 7-10.5%
- Selected subgroup of patients for higher risk of MAFLD using Fatty Liver Index (FLI)
- Randomised (1:1:1:1) to tirzepatide 5, 10, 15 mg or insulin degludec
- MRI at baseline and study end:
  - Liver fat content (LFC)
  - Visceral adipose tissue (VAT)
  - Abdominal subcutaneous adipose tissue (ASAT)

Demonstrated improvements in LFC and VAT compared to insulin degludec





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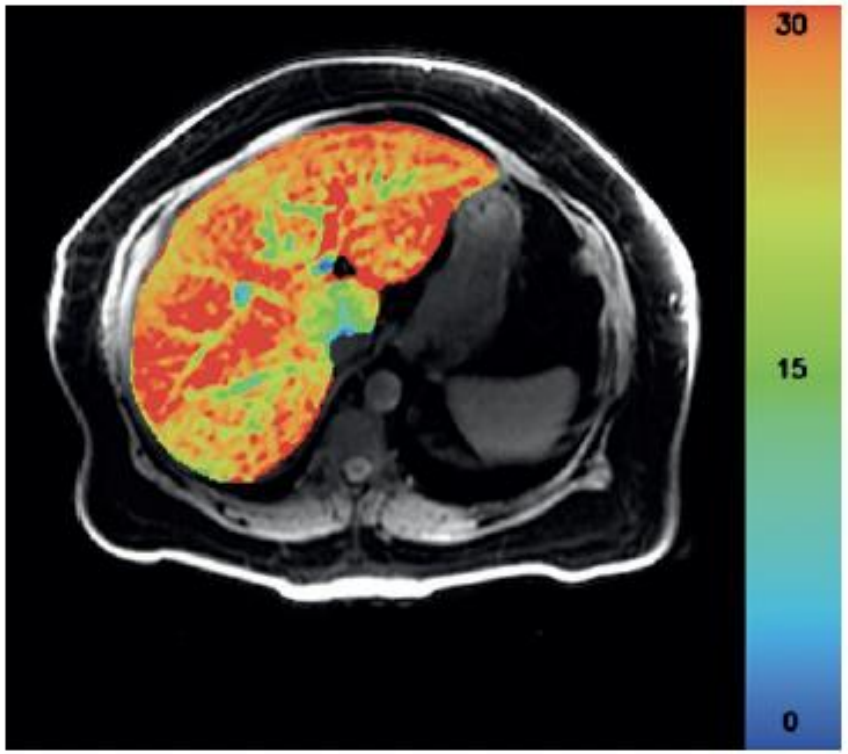

LFC at baseline: 27·3%

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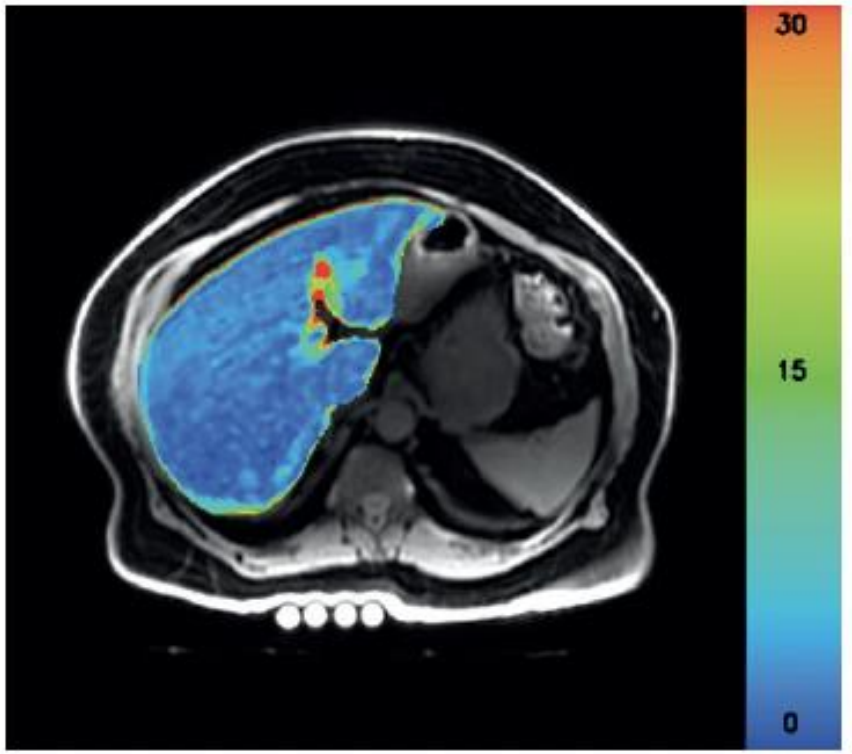


LFC at week 52: 2·6%

Future MAFLD incretin trials to watch for…

- ESSENCE trial
  - Phase III trial, semaglutide 2.4 mg sc weekly vs placebo
  - Outcomes evaluated via liver biopsy
  - Est trial completion in 2028

- SYNERGY-NASH
  - Dedicated phase II trial, tirzepatide 5, 10, 15 mg vs placebo
  - Outcomes evaluated via liver biopsy
  - Est trial completion in Feb 2024

https://classic.clinicaltrials.gov/ct2/show/NCT04822181

https://classic.clinicaltrials.gov/ct2/show/NCT04166773

What do all of these trials mean for clinical practice?

- Can reassure patients there is evidence that semaglutide 2.4 mg weekly for obesity also confers CV risk protection in patients with history of MI, stroke or symptomatic PAD
- Moving towards targeted therapy for genetic forms of obesity such as BBS
- More trials evaluating outcomes beyond weight loss, such as MAFLD
  - Clinically meaningful for patients and providers
- These types of trials may help improve access and public/private coverage for weight loss pharmacotherapy
  - "cosmetic" ➔ chronic disease management

Discussion

Join at **slido.com** with **#1803685**

Please put your questions in the Q&A

Novelties in hypoparathyroidism: Current and future strategies

Claudia Gagnon, MD, FRCPC

CHU de Québec Université Laval

Clinical scenario

- 50 year old woman with **postsurgical hypoparathyroidism** since 2010
- Treated with **calcium supplements** and **calcitriol**
- Several hospitalisations for hypo or hypercalcemia
- Daily symptoms of hypocalcemia
- Reports fatigue, "brain fog", and reduced quality of life
- Fasting serum calcium 2.15 mmol/L (2.15-2.55) and phosphorus 1.35 mmol/L (0.80-1.50), normal serum Mg and 25(OH)D, 24-h urinary calcium elevated (8 mmol/d)
- Decrease in eGFR since diagnosis, now 50 ml/min; no ectopic calcifications
- She enquires about novel treatments to improve her condition.

Treatment goals in hypoparathyroidism

- Serum calcium in the low-normal range
- Normal fasting serum phosphorus and calcium-phosphate product <4.4 $mmol^2/L^2$
- Alleviate/ ameliorate symptoms
- Avoid acute and long-term complications
- Normal 24-h urinary calcium
- Normal serum Mg and 25(OH)D

Khan A et al. *J Bone Miner Res*, 37(12), Dec 2022: 2663-2677.

Conventional therapy for hypoparathyroidism

Goals	Therapy or strategy
Serum calcium in the low-normal range	Calcium supplements and active vitamin D analogues (calcitriol, alfacalcidol)
Normal 24-h urinary calcium	Titrate calcium and active vitamin D to aim for target serum calcium Low-sodium diet and thiazides
Normal fasting serum phosphorus	Calcium supplements with meals (binder), low-phosphate diet and judicious use of active vitamin D
Avoid acute and long-term complications	Target low-normal calcium; normal phosphorus and 24-h urinary calcium

Khan A et al. *J Bone Miner Res*, 37(12), Dec 2022: 2663-2677.

Does conventional therapy achieve treatment goals?

Serum calcium in the low-normal range[1,2]

59-86%

Normal fasting serum phosphorus[1] and calcium-phosphate product <4.4 mmol^2/L^2

67-100%

Alleviate/ ameliorate symptoms

Avoid acute and long-term complications

Normal 24-h urinary calcium[1,2]

45-90%

Normal serum Mg and 25(OH)D

[1]Mitchell DM et al. *J Clin Endocrinol Metab*, 2012; [2]Meola A et al. *J Endocrinol Invest*, 2018.

Does conventional therapy improve symptoms and reduce complications?

Symptom/complication	Prevalence, % Median	Adjusted risk vs controls HR/OR	Potential risk factors (Modifiable in bold)
Depression	**9**	**1.89**	Unclear
Nephrocalcinosis/ nephrolithiasis	**15**	**1.88**	**HyperPO4**, **higher Ca x P**
Renal insufficiency	**12**	**3.67**	Non-surgical hypopara, longer disease duration, **higher Ca x P**, more frequent **hyperCa**
Cataract	**17**	**2.13**	Non-surgical hypopara, longer disease duration
Seizures	**11**	**3.22**	Non-surgical hypopara, **hypoCa**
Infection	**11**	**2.30**	Non-surgical hypopara, longer disease duration, **hyperPO4**, more frequent **hyperCa**
Arrhythmia	**7**	**1.37**	**HypoCa**, longer disease duration, more frequent **hyperCa**
Ischemic heart disease	**7**	**1.26**	
All-cause mortality	**6**	**1.80**	Unclear

Yao L et al. *J Bone Miner Res*, Dec 2022; Khan A et al. *J Bone Miner Res*, 37(12), Dec 2022: 2663-2677.

Approved PTH or PTH analogues for hypoparathyroidism

- **PTH 1-84 (Natpar®, Natpara®)**
  - Approved by the FDA in 2015 and by the European Medicines Agency in 2017
  - Will be discontinued at the end of 2024
- **TransCon^{TM} PTH (palopegteriparatide)**
  - Approved by the European Medicines Agency on 20th November 2023
  - Under evaluation by the FDA

Is PTH therapy better than conventional therapy to reach treatment goals?

Systematic review and meta-analysis

- Less pill burden: more patients stopped/reduced calcitriol and calcium supplements
- Reduction in serum phosphate
- Small impact on HRQoL
- No data on other patient-important outcomes
- Data limited by small sample size, short follow-up, mainly off-label PTH (1-34) and PTH (1-84)

Yao L et al. *J Bone Miner Res*, Dec 2022.

CLINICAL TRIAL

JBMR®

Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial

Aliya A Khan,[1] Mishaela R Rubin,[2] Peter Schwarz,[3] Tamara Vokes,[4] Dolores M Shoback,[5] Claudia Gagnon,[6] Andrea Palermo,[7] Claudio Marcocci,[8] Bart L Clarke,[9] Lisa G Abbott,[10] Lorenz C Hofbauer,[11] Lynn Kohlmeier,[12] Susanne Pihl,[13] Xuebei An,[14] Walter Frank Eng,[14] Alden R Smith,[14] Jenny Ukena,[14] Christopher T Sibley,[14] Aimee D Shu,[14] and Lars Rejnmark[15]

J Bone Miner Res, 38(1), Jan 2023: 14-25.

PaTHway: phase 3 clinical trial

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group **26-week trial**
- TransCon PTH daily SC injection (n=61) or placebo (n=21)
- High completion rate (98% treatment vs 91% placebo)
- Ongoing 156-week open-label extension (until 2025)

Table 1. Baseline Demographics, Disease Characteristics, and Supplementation

Characteristics	TransCon PTH ($n = 61$)	Placebo ($n = 21$)
Age (years), mean (SD)	49.0 (13.1)	47.3 (11.4)
Age group (years), *n* (%)		
<50	28 (46)	14 (67)
≥50	33 (54)	7 (33)
Sex at birth, female *n* (%)	46 (75)	18 (86)
Postmenopausal, *n* (%)	19 (41)	3 (17)
Body mass index (kg/m^2), mean (SD)	27.3 (5.8)	29.5 (5.7)
Race, *n* (%)		
Asian	3 (5)	2 (10)
White	57 (93)	19 (91)
Other	1 (2)	0
Geographic region, *n* (%)		
North America	39 (64)	12 (57)
Europe	22 (36)	9 (43)
Hypoparathyroidism etiology, *n* (%)		
Acquired from neck surgery	52 (85)	18 (86)
Autoimmune disease	1 (2)	0
Intrinsic genetic defects of the parathyroid glands	3 (5)	0
Idiopathic disease	4 (7)	3 (14)
Other	1 (2)	0
Duration of hypoparathyroidism (years), mean (SD)	12.0 (11.4)	11.1 (8.5)
Baseline conventional therapy total daily doses, mean (SD)		
Elemental calcium (mg)	1748 (904)	2105 (1383)
Calcitriol (µg)	0.76 (0.34)	0.69 (0.33)
Alfacalcidol (µg)	2.5 (0.9)	2.0 (0.4)
Pill burden (active vitamin D and calcium), mean (SD)	6.7 (2.2)	6.7 (3.0)
24-hour urine calcium (mg/day), mean (SD)	392 (175)	329 (140)

Abbreviations: PTH = parathyroid hormone; SD = standard deviation.

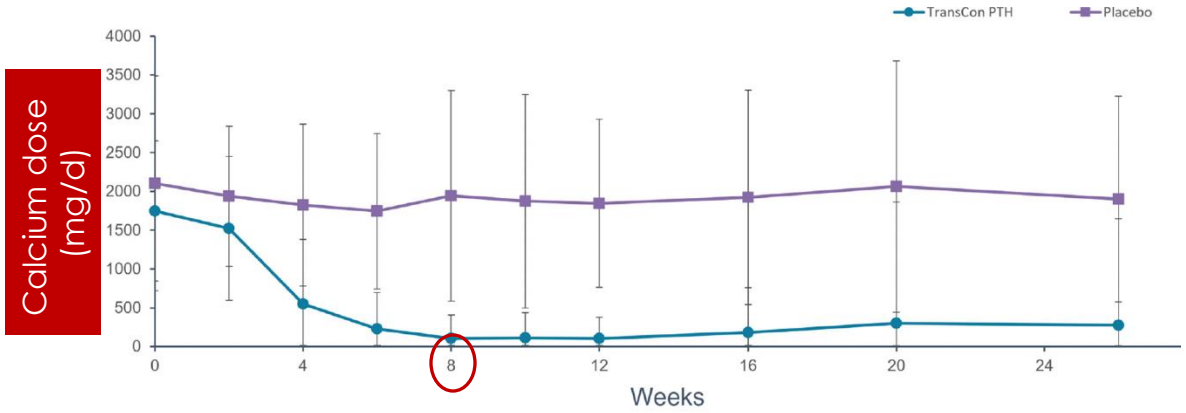
Mainly White women with postsurgical hypopara

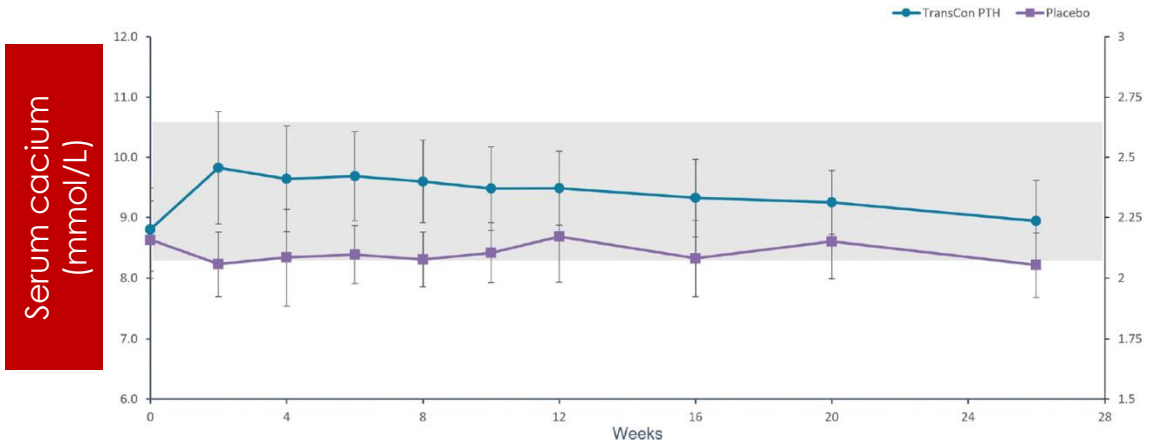
Mean age 48 years

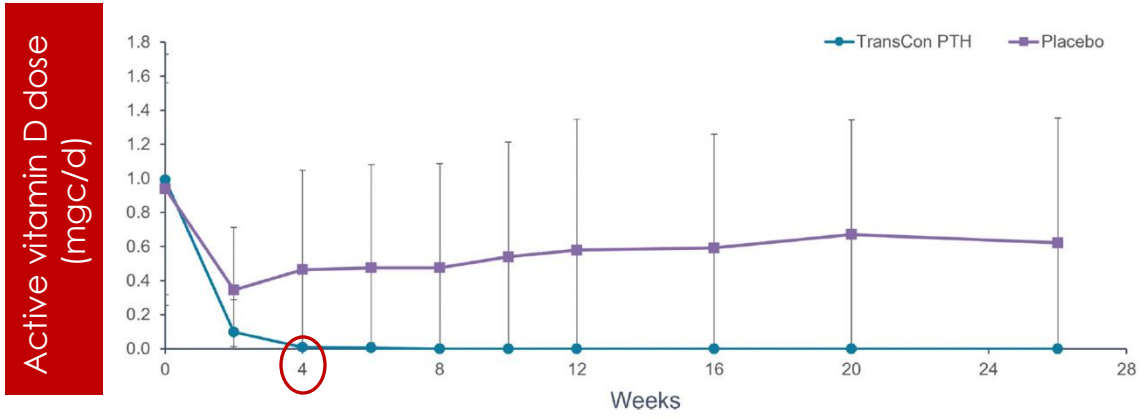
Mean duration of hypopara 12 years

Mean of 6.7 pills of calcitriol and calcium daily

Primary endpoint: independence from calcium and calcitriol while maintaining normocalcemia at week 26







79% in TransCon PTH

vs

5% in placebo

Other endpoints

- Mean serum **phosphate**, **Ca x P** and 1,25$(OH)_2$D normal
- Greater decrease in **24-h urinary calcium** (60.7% vs 28.6% normalized UCa)
- Less **episodes of hypocalcemia**
- Improved **HR-QoL** within the normal US general population norm
- Improved **physical and cognitive hypopara symptoms**, functioning and well-being
- TransCon PTH well tolerated

Longer-term outcomes

- **52-week results:** Endocrine Society meeting June 2023[1]
  - Sustained efficacy and safety; improved HR-QoL and hypopara symptoms
  - Those switched from placebo to treatment: same results
- Renal, bone and other outcomes from OLE expected in 2024-2025

[1]Clarke B et al. *J Endocrine Soc*, 7(S1), Oct-Nov 2023: A303-304.

Novel therapies on the horizon

- **Eneboparatide (AZP-3601)**
  - PTH1 receptor agonist
  - Phase 2 results: Endocrine Society meeting June 2023[1]
  - Phase 3 clinical trial underway: NCT05778071
- **PTH 1-34 extended release (EXT608)**
  - Phase 1 clinical trial results: 2023 ASBMR annual meeting[2]

[1]Kamenicky P et al. *J Endocrine Soc*, 7(S1), Oct-Nov 2023: A302-303; [2]Hales L et al. ASBMR 2023 meeting abstracts FRI-176.

Eneboparatide phase 2 results

- Similar patient population than PATHWAY trial
- Cohort 1 (n=12) and cohort 2 (n=16)

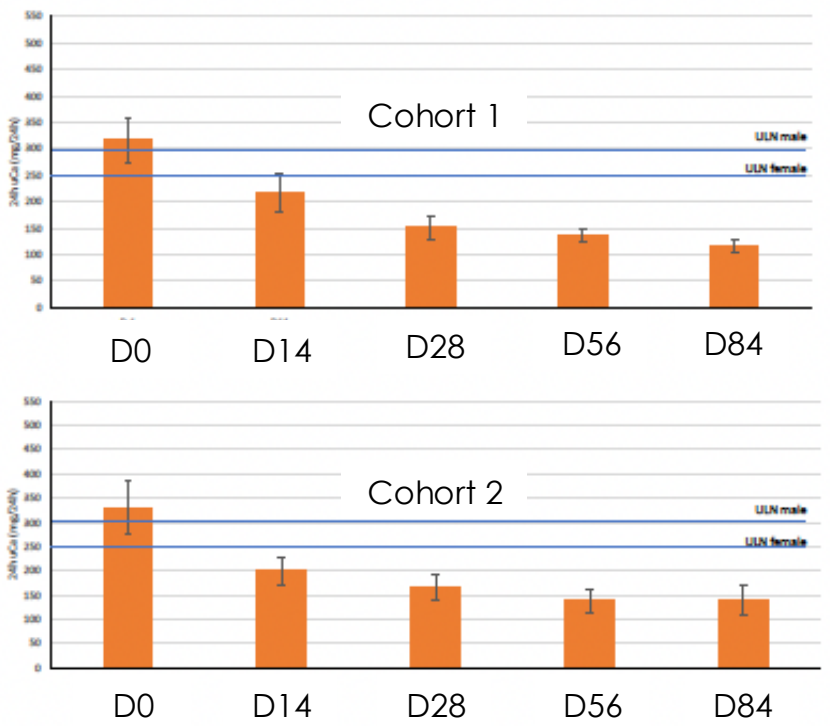
- ➢ Most patients rapidly off calcitriol and calcium
- ➢ Mean serum calcium maintained within normal

Kamenicky P et al. *J Endocrine Soc*, 7(S1), Oct-Nov 2023: A302-303.

Eneboparatide phase 2 results

SERUM PHOSPHATE

24H URINARY CALCIUM (All patients)



Kamenicky P et al. *J Endocrine Soc*, 7(S1), Oct-Nov 2023: A302-303.

Canada's first parathyroid transplant!

CTV NEWS

NEWS VIDEO LOCAL SHOWS ABOUT SHOPPIN

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Canadian patient receives groundbreaking treatment for a disabling disorder, with a parathyroid transplant into her arm

Parathyroid allotransplantation for refractory hypoparathyroidism

- Single US center: NCT05114980

Take-home messages

1. First-line treatment: conventional therapy
   - Cheap, effective in several patients
2. Second-line: novel treatments (e.g., PTH analogues)
   - May restore PTH physiology
   - May improve long-term clinical and patient-important outcomes

Discussion

Join at **slido.com** with **#1803685**

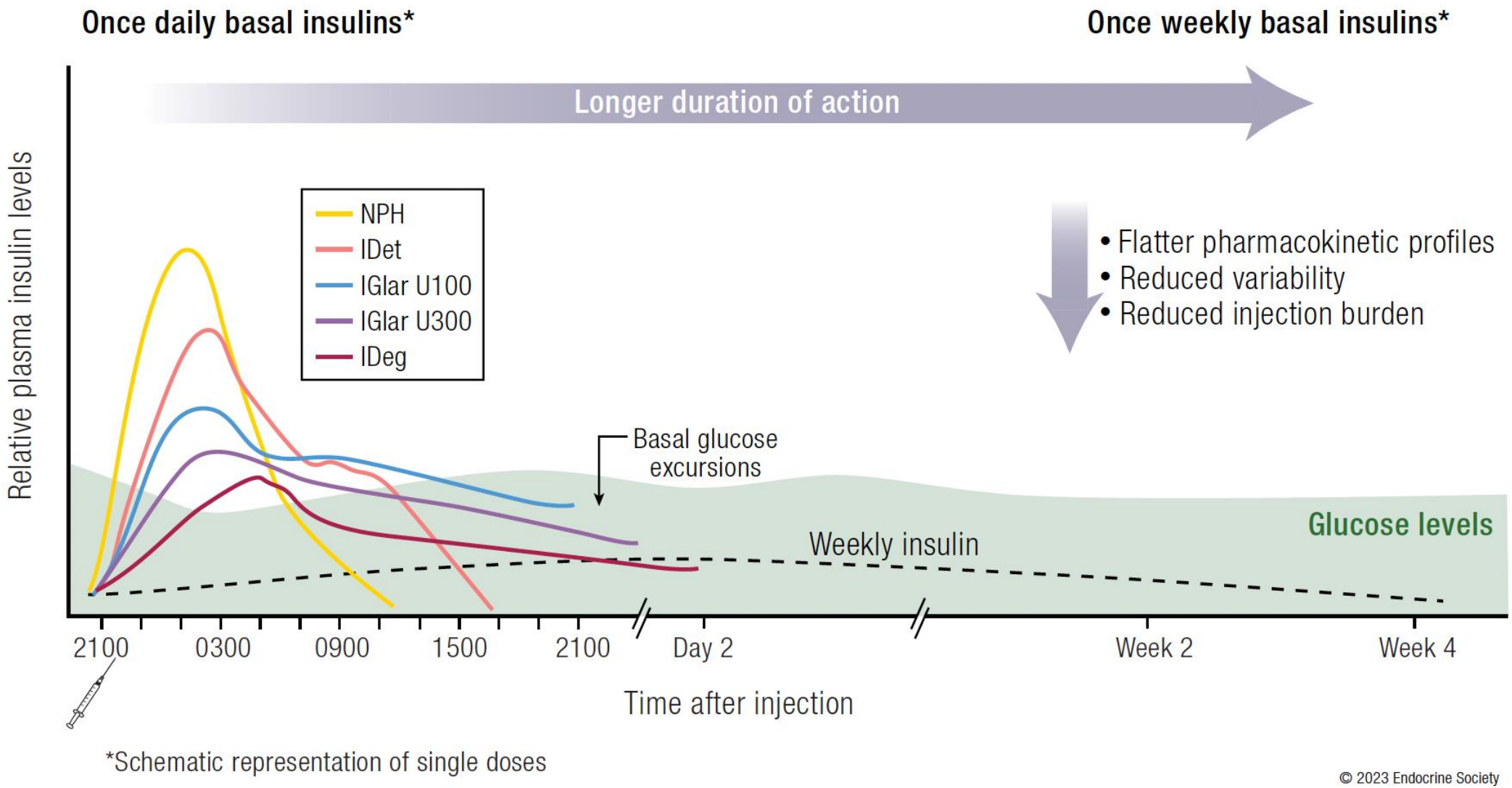
Please put your questions in the Q&A

Novel approaches to insulin therapy: Challenges and opportunities with new basal insulins

Heidi Dutton, MD, MSc, FRCPC, DIPL.ABOM & ABLM
The Ottawa Hospital

Novel Insulin Therapies - Case

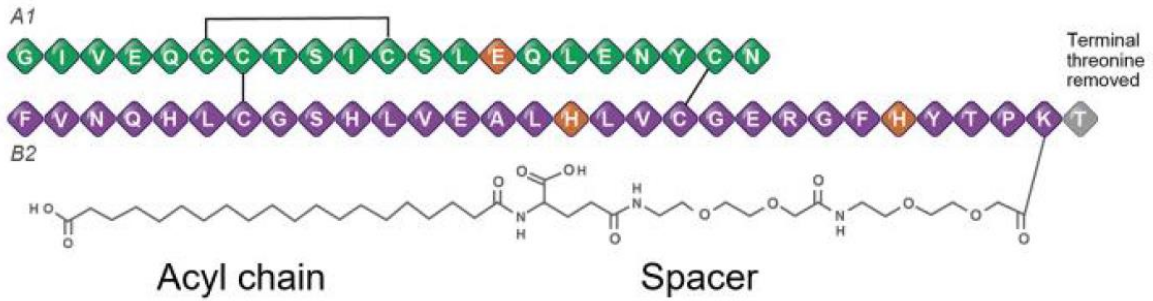
- 60 year old male with Type 2 DM x 25 years
- Currently on metformin, semaglutide sc weekly, dapagliflozin all at max tolerated doses
  - A1c 7.8%
- Prescribed glargine U300 48 units at hs → patient reports missing doses
  - Does not like daily injections, and reports weight gain since starting
- He asks you if there is a once per week injection for insulin that he could take at the same time as semaglutide to improve his adherence to insulin therapy



Rosenstock J et al. The Basis for Weekly Insulin Therapy: Evolving Evidence With Insulin Icodec and Insulin Efsitora Alfa. Endocrine Reviews. 2024;.

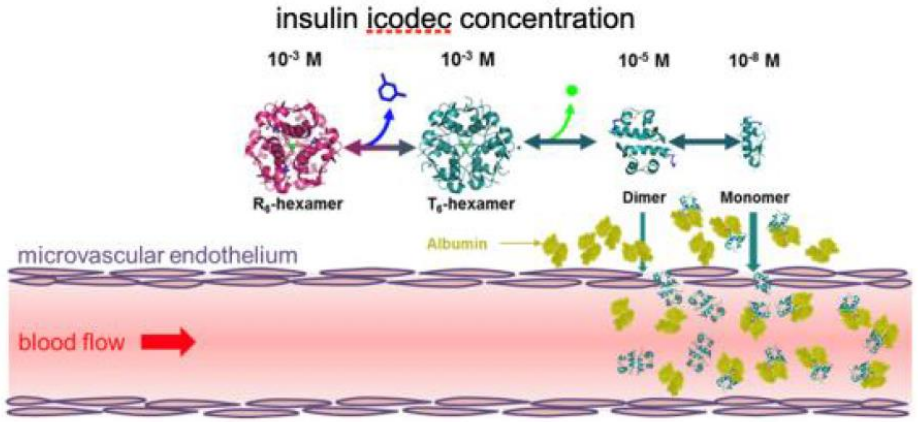
A

Icodec Structure



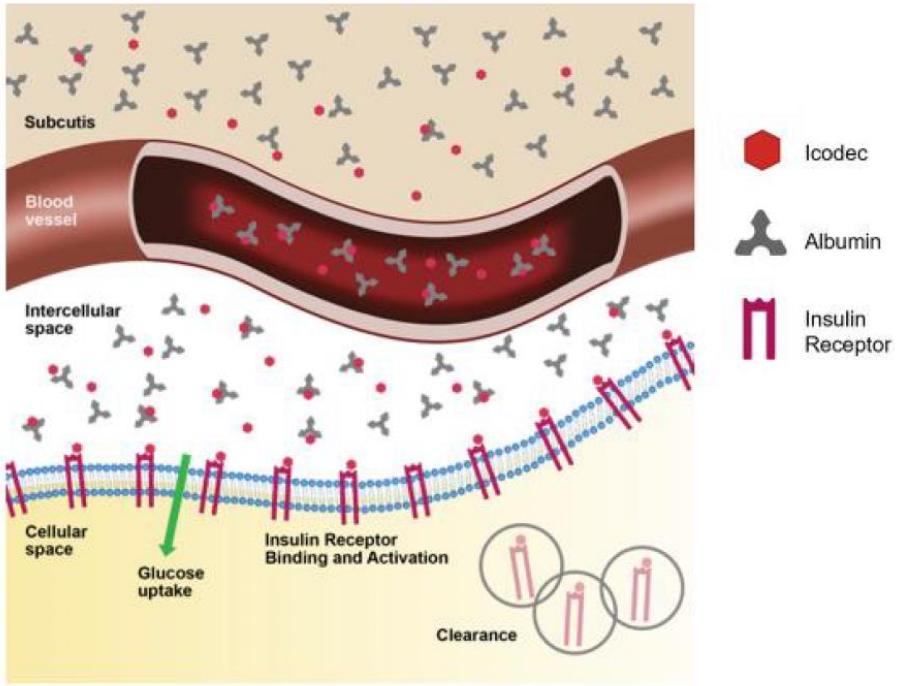
B

Icodec Absorption



C

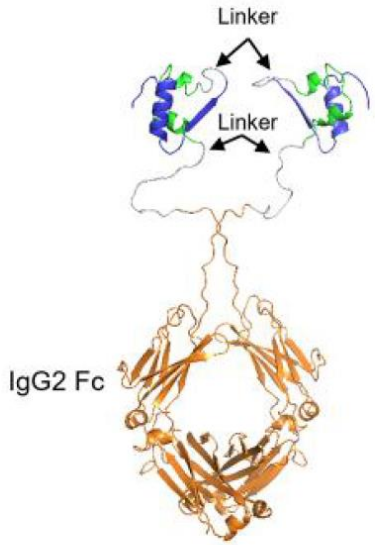
Icodec Distribution

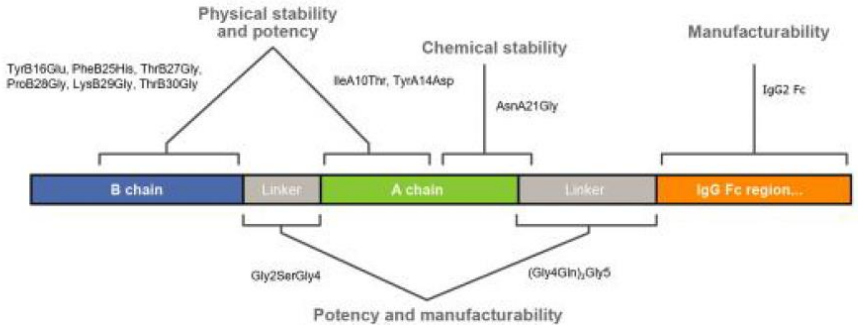


Half life: ~ 8 days

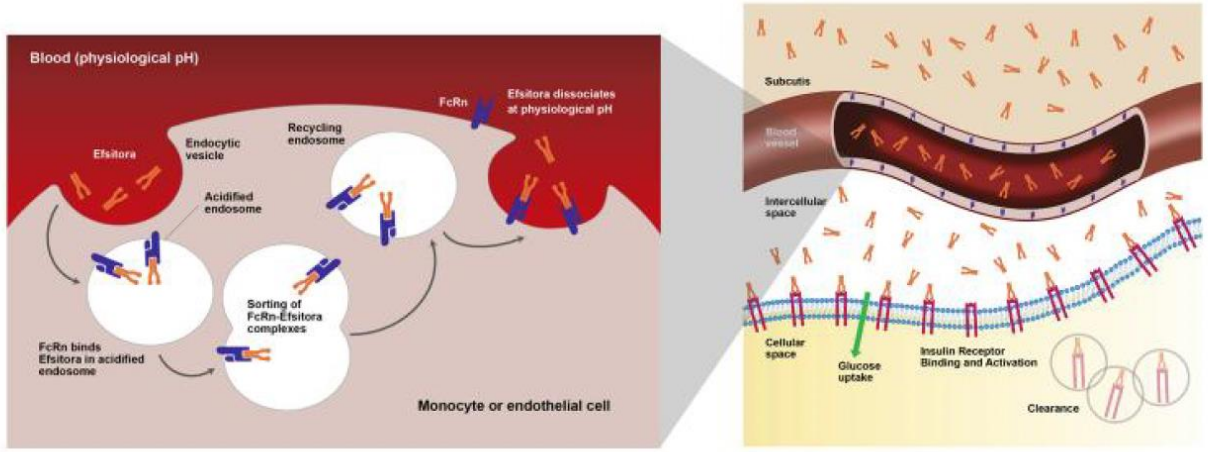
Rosenstock J et al. The Basis for Weekly Insulin Therapy: Evolving Evidence With Insulin Icodec and Insulin Efsitora Alfa. Endocrine Reviews. 2024;.

A **Basal insulin Fc (BIF) Structure**





B **Basal insulin Fc (BIF) Structure**



Efsitora

Neonatal Fc Receptor (FcRn)

Insulin Receptor

Half life: ~ 17 days

Aka basal insulin Fc, BIF, insulin efsitora alfa

Adapted from: Rosenstock J et al. The Basis for Weekly Insulin Therapy: Evolving Evidence With Insulin Icodec and Insulin Efsitora Alfa. Endocrine Reviews. 2024;.

Clinical Trial Programs

	Icodec			Basal Insulin Fc (BIF)		
Trial Phase	T2DM Insulin naive	T2DM On basal (switch)	T1DM	T2DM Insulin naive	T2DM On basal (switch)	T1DM
Phase II	2 trials	1 trial		**1 Trial**	**1 Trial**	**1 Trial**
Phase III	**ONWARDS 1,3**	**ONWARDS 2,4**	**ONWARDS 6**	QWINT 1, 2	QWINT 3,4	QWINT 5

Bold = published in 2023

Once weekly basal insulins – new features

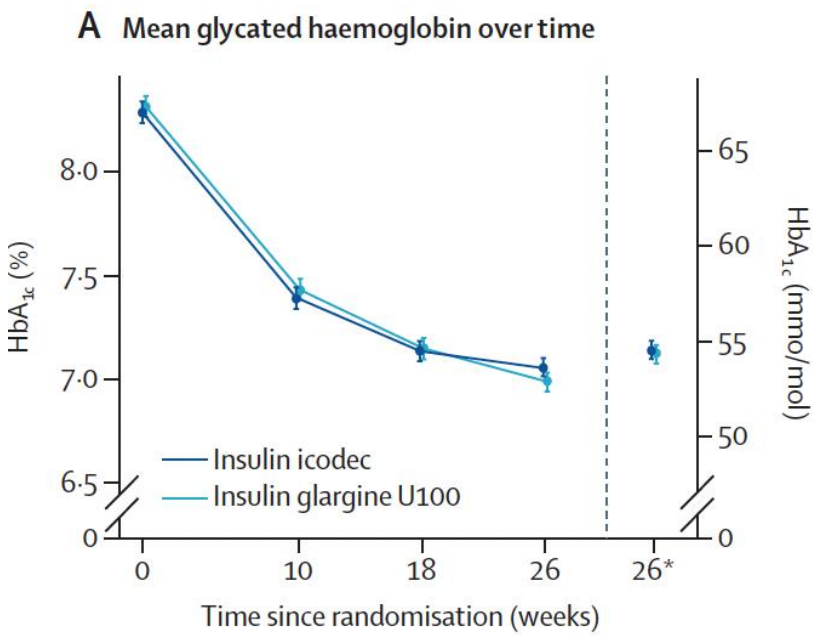
- Loading dose due to long half life → reduce time to reach steady state
- Less frequent titration
- High weekly dose (daily dose x 7)
- Protection from missed delayed doses
- Convenience

ONWARDS 4 – Icodec vs glargine U100

- Population: longstanding Type 2 DM on basal-bolus insulin, A1c 7-10%
- Intervention: Icodec 700 U/mL weekly
  - Calculate weekly dose: daily pre-trial basal insulin x 7
  - For 1st injection only → one time additional 50% icodec dose given (loading dose)
  - Titrated weekly
- Comparator: glargine U100 (same dose as pre-trial basal)
- Outcome: change in A1c over 26 weeks
  - % TIR week 22-26, change in body weight, hypoglycemia

Mathieu et al. Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4). Lancet 2023; 401: 1929–40

ONWARDS 4 - results



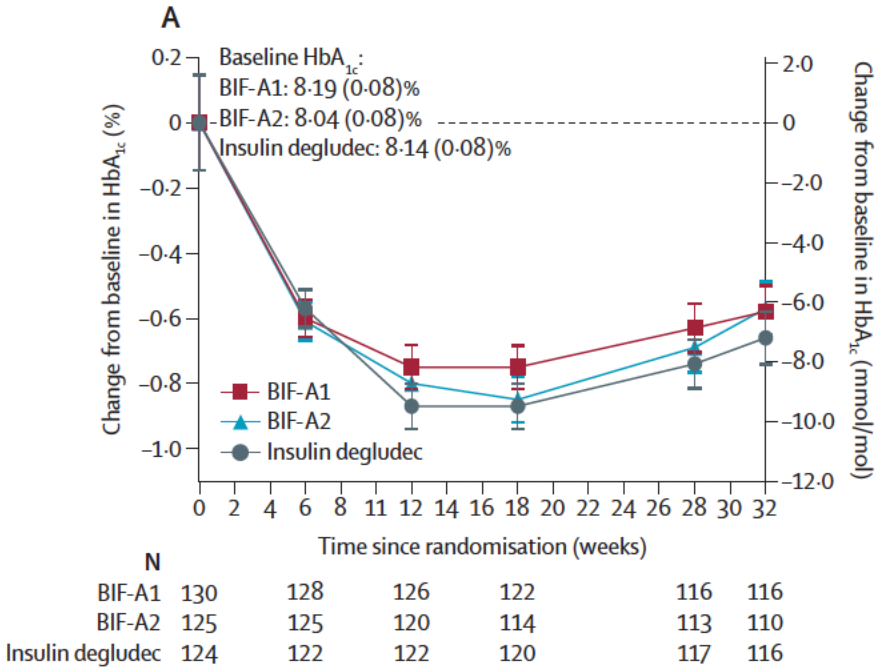
- Non inferiority of icodec to glargine U100
- TIR similar between both groups
- Higher rates of level 1 (mild) hypoglycemia in icodec group, similar rates of level 2/3
- Total weekly insulin dose lower in icodec group vs. glargine U100
  - 514 vs 559 U/week → driven by lower doses of aspart
- Mean increases in body weight similar
  - 2.7 kg icodec vs. 2.2 kg glargine U100

Phase 2 – basal insulin Fc (BIF) vs degludec

- Population: Type 2 DM, A1c 6.5-10%, already on basal insulin
- Intervention: BIF in mg increments from reconstituted powder (two groups with different FPG targets/titration frequency)
  - Switch:
    - Both groups → one time loading dose 1.5-3 times higher than calculated weekly dose
      - Higher dose if A1c > 8.5%
    - Titration → q 2 weeks and q 4 weeks
- Comparator: once daily degludec U100 insulin
- Outcome: change in A1c over 32 weeks
  - Hypoglycemia, weight change, % TIR

Frias et al. Safety and efficacy of once-weekly basal insulin Fc in people with type 2 diabetes previously treated with basal insulin: a multicentre, open-label, randomised, phase 2 study. *Lancet Diabetes Endocrinol 2023; 11: 158–68*

RESULTS



- Non inferiority of Basal insulin Fc (BIF) vs. degludec U100
- Level 1 hypoglycemia rates 25% lower in Basal insulin Fc groups
  - But FPG levels higher in Basal insulin Fc groups
- Similar TIR between groups
- Basal insulin Fc groups had less weight gain
  - 1.0 kg in BIF vs. 2.0 kg in degludec U100
- Data will need to be confirmed in Phase 3 trials with stricter FPG targets

Key features of dosing

- Be prepared to see **LARGE** doses:
  - E.g. 40 units glargine U100 per day → **280 units per week** (potential loading dose of **420 units**)

- Less frequent titration
  - Basal insulin Fc – TBD (will need to wait for phase 3 trials)
  - Icodec – used weekly titration in ONWARDS 4

Advantages and Challenges

- Weekly administration is convenient and may improve adherence
  - Eg. Needle phobia, caregivers dosing insulin
- Combination therapy with GLP-1 RA also in development (icodec + semaglutide)

- Challenges:
  - Dosing, initiation/switching and titration are unfamiliar
  - Is fasting glucose best parameter to monitor?
  - Risk of prolonged/recurrent hypoglycemia?
  - How to manage during hospitalization, exercise and fasting?
  - Unclear role in T1DM

Discussion

Join at **slido.com** with **#1803685**

Please put your questions in the Q&A

Benefits and risks of androgen replacement in middle-aged and older men with low testosterone levels

Claudia Gagnon, MD, FRCPC
CHU de Québec Université Laval

Clinical scenario

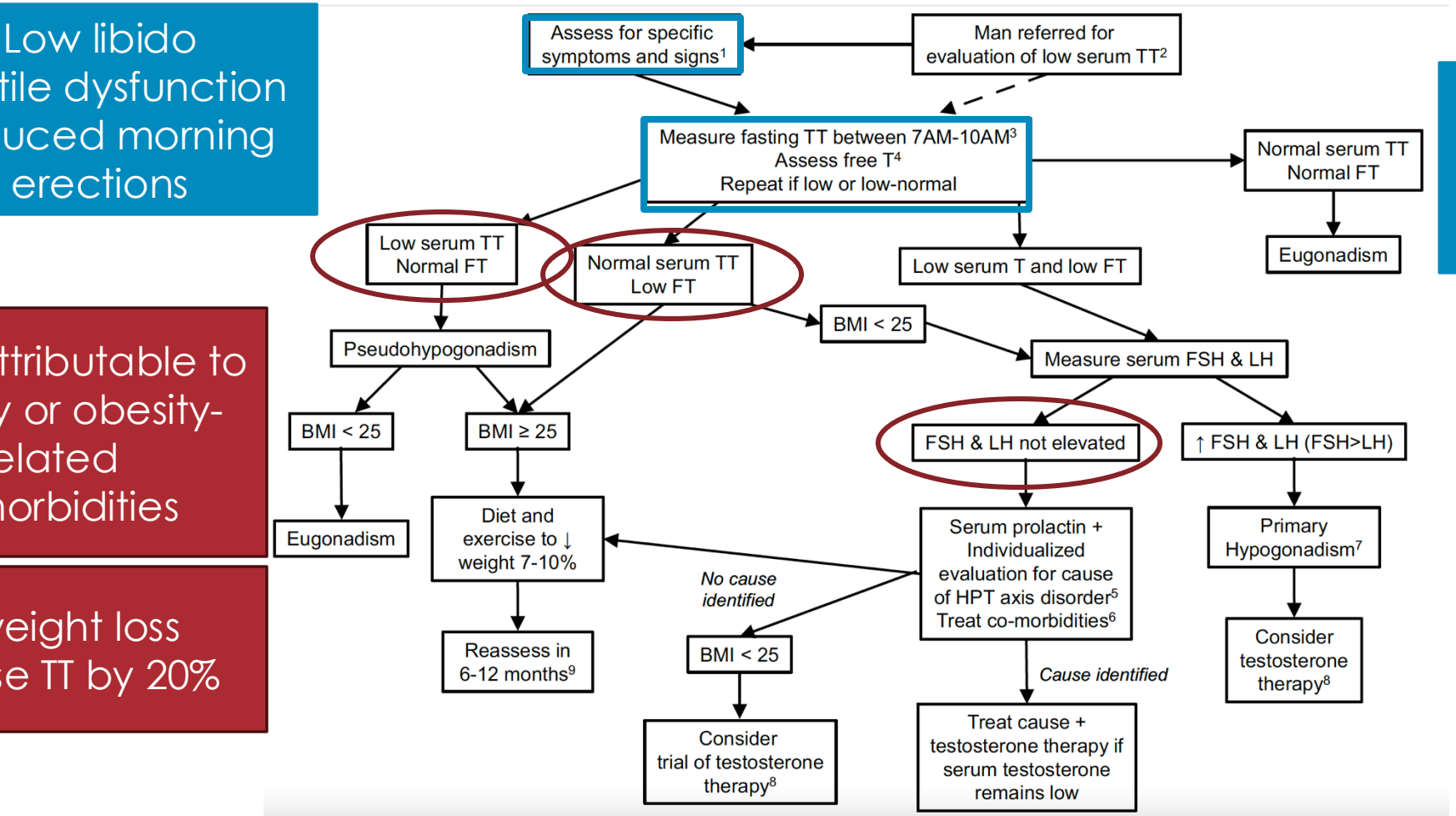
- 67 year old man referred for **possible hypogonadism**
- Reports **decreased libido** and **erections less firm** over the last 10 years
- **Fatigue** on most days, **low mood** since retirement 2 years ago
- Obesity (BMI 31), T2D (HbA1c 8.5%), HT, past smoking; no previous MI, stroke, TVE or prostate cancer
- Normal puberty, fathered two children without difficulty; no headache, visual impairment or symptoms of Cushing; symptoms suggestive of sleep apnea
- Never used anabolic steroids, opioids or glucocorticoids; current meds: lisinopril, metformin, sitagliptin, atorvastatin
- Normal appearance and genital exam, no gynecomastia
- **Nonfasting afternoon serum total testosterone** 4.9 nmol/L (normal 9.1-31.8)

Approach:
Man 50+ referred for low testosterone levels (T)

- Low libido
- Erectile dysfunction
- Reduced morning erections

Many attributable to obesity or obesity-related comorbidities

9% weight loss increase TT by 20%



- Fasting increases TT by 9-16%
- 30% have normal TT on repeat testing

Grossmann M et al. *J Clin Endocrinol Metab*, 108, April 2023: e871-e884.

Back to the clinical scenario

- Fasting early morning TT measured twice: 8.2 and 8.5 nmol/L (normal 9.1-31.8)
- Calculated free T: 194 pmol/L (229-710 pmol/L)
- Normal FSH, LH, PRL
- Moderately severe sleep apnea diagnosed
- The benefits of 7-10% weight loss, sleep apnea and diabetes treatment on general and CV health and potential normalization of TT discussed; PDE5-inhibitor initiated
- After 6 months, TT and free TT low despite 5% weight loss, HbA1c 7.3% and CPAP use. Improved fatigue and erectile dysfunction but libido still reduced.
- ➢ He wishes to discuss the benefits and risks of androgen replacement

Potential risks and benefits of androgen therapy in men 50+ with low serum T

Potential Benefits[1]

- Moderate improvement in sexual function
- Some benefit on mood
- Improved surrogate markers of bone health (**no data on fracture risk**)
- Increase in walking distance
- *Reduced incidence or amelioration of unexplained anemia*
- No benefit on vitality or cognition

Potential Risks

- Erythrocytosis, clinical implications unclear
- Suppression of endogenous testosterone production and spermatogenesis
- *Worsening of urinary symptoms*
- *Increased growth of high-grade or metastatic prostate cancer; increased risk of prostate biopsies and over-treatment*
- **Unclear risk of CVD**

[1]Snyder PJ et al. The Testosterone Trials. *NEJM*, 2016; Grossmann M et al. *J Clin Endocrinol Metab*, April 2023.

The TRAVERSE Study

The NEW ENGLAND JOURNAL of MEDICINE

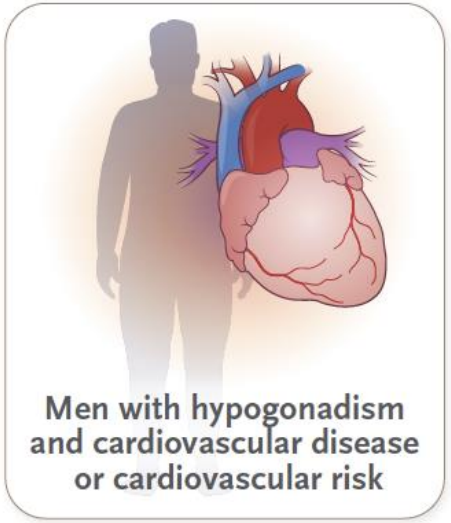
ESTABLISHED IN 1812 JULY 13, 2023 VOL. 389 NO. 2

Cardiovascular Safety of Testosterone-Replacement Therapy

A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Travison, and S.E. Nissen, for the TRAVERSE Study Investigators*

Study design and population

Phase 4, multicenter, double-blind, randomized, placebo-controlled, noninferiority trial



5246 men aged 45-80 years with:

1) preexisting CVD or an increased CVD risk
2) At least **one symptom** of hypogonadism: decreased libido, decreased spontaneous erections, fatigue, low or depressed mood, loss of axillary or public hair or decreased frequency of shaving, hot flashes
3) Two fasting serum TT < 10.4 nmol/L between 5AM-11AM

Main exclusion criteria:

1) Severe hypogonadism (TT <3.5 nmol/L)
2) History of prostate cancer or nodule, or elevated PSA, severe urinary symptoms
3) History of DVT or PE, thrombophilia, uncontrolled HF
4) Acute CAS, stroke, or coronary or peripheral revascularization within 4 months

Study population

Characteristic	Testosterone Group (N=2601)	Placebo Group (N=2603)
Mean age — yr	63.3±7.9	63.3±7.9
Age ≥65 yr — no. (%)	1241 (47.7)	1211 (46.5)
Race or ethnic group — no. (%)†		
White	2070 (79.6)	2084 (80.1)
Black	445 (17.1)	432 (16.6)
Other	86 (3.3)	87 (3.3)
Hispanic or Latinx	409 (15.7)	439 (16.9)
Body-mass index‡	35.0±5.7	34.8±6.0
Median testosterone level (IQR) — ng/deciliter	227 (189–258)	227 (188–258)
Cardiovascular risk category — no. (%)		
Preexisting cardiovascular disease	1410 (54.2)	1437 (55.2)
Increased cardiovascular risk	1191 (45.8)	1166 (44.8)
History of coronary artery disease — no. (%)	1158 (44.5)	1160 (44.6)
History of cerebrovascular disease — no. (%)	304 (11.7)	318 (12.2)
History of peripheral arterial disease — no. (%)	158 (6.1)	153 (5.9)
Cardiovascular risk factors — no. (%)		
Diabetes, type 1 or type 2	1788 (68.7)	1844 (70.8)
Hypertension	2423 (93.2)	2402 (92.3)
Dyslipidemia	2344 (90.1)	2332 (89.6)
Current smoker	527 (20.3)	534 (20.5)
High-sensitivity C-reactive protein level ≥2 mg/dl	1607 (61.8)	1589 (61.0)
Stage 3 chronic kidney disease	418 (16.1)	393 (15.1)
Elevated coronary calcium score	29 (1.1)	28 (1.1)
Previous testosterone use — no. (%)	5 (0.2)	10 (0.4)

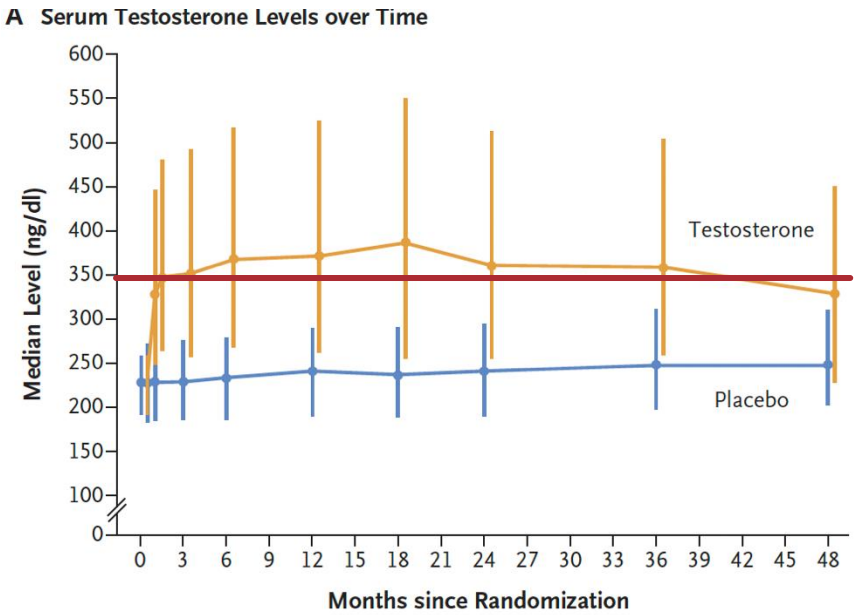
As expected from the inclusion criteria, men with obesity and the metabolic syndrome, with median TT 7.8 nmol/L

Trial Intervention

Titration to maintain serum TT 12.1-26 nmol/L and avoid Hct >54%

Mean **treatment duration 22 months** and follow-up 33 months

Treatment discontinued in 61% of patients in both groups

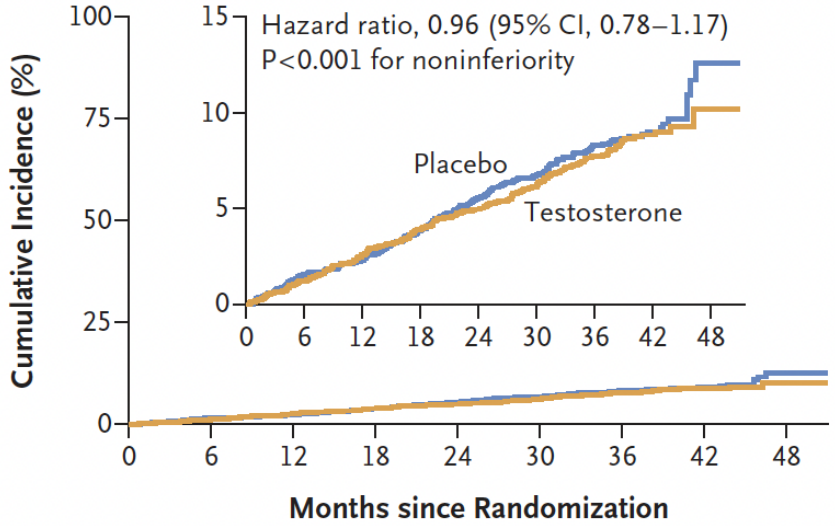


Increase in serum estradiol 21 to 32 pg/mL

Noninferiority for adjudicated primary CV safety endpoints

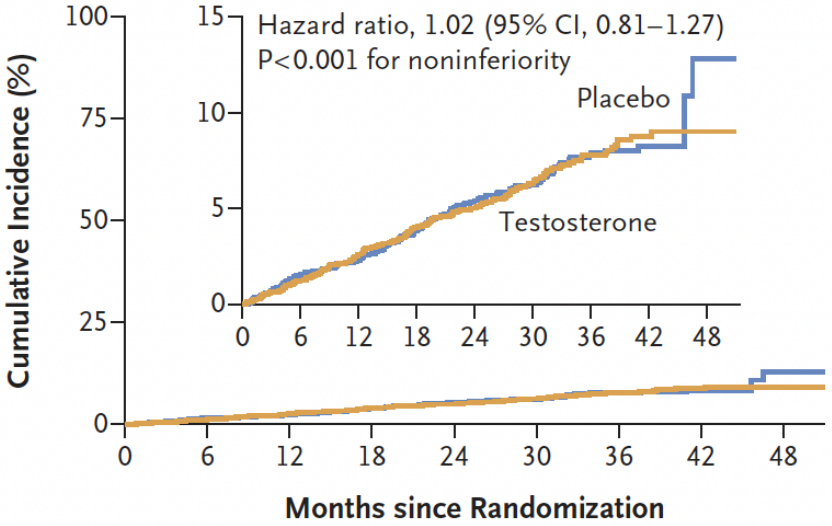
Death from Cardiovascular Causes, Nonfatal MI, or Nonfatal Stroke

A Primary Cardiovascular Composite Safety End Point: Safety Population



No. at Risk									
Placebo	2602	2507	2323	2088	1792	1568	1337	598	33
Testosterone	2596	2504	2339	2120	1829	1605	1380	653	39

B Primary Cardiovascular Composite Safety End Point: Principal Sensitivity Analysis Population



No. at Risk									
Placebo	2602	2507	2323	1842	1390	1070	829	347	16
Testosterone	2596	2504	2339	1850	1408	1089	850	370	20

Summary of results for all endpoints

Table 2. Adjudicated Cardiovascular End Points in the Safety Population.*

End Point	Testosterone Group (N = 2596)	Placebo Group (N = 2602)	Hazard Ratio (95% CI)†
	number of patients (percent)		
Primary cardiovascular composite end point: major adverse cardiac events‡	182 (7.0)	190 (7.3)	0.96 (0.78–1.17)
Secondary cardiovascular composite end point§	269 (10.4)	264 (10.1)	1.02 (0.86–1.21)
Components of primary and secondary composite end points			
Death from cardiovascular causes	87 (3.4)	103 (4.0)	0.84 (0.63–1.12)
Nonfatal myocardial infarction	68 (2.6)	62 (2.4)	1.10 (0.78–1.56)
Nonfatal stroke	36 (1.4)	38 (1.5)	0.94 (0.60–1.49)
Coronary revascularization	144 (5.5)	121 (4.6)	1.20 (0.95–1.53)
Tertiary end points			
Death from any cause	144 (5.5)	148 (5.7)	0.98 (0.78–1.23)
Hospitalization or urgent visit for heart failure	55 (2.1)	50 (1.9)	1.11 (0.76–1.62)
Peripheral arterial revascularization	30 (1.2)	33 (1.3)	0.92 (0.56–1.51)
Venous thromboembolic events¶	44 (1.7)	30 (1.2)	1.46 (0.92–2.32)
Components of venous thromboembolic events‖			
Pulmonary embolism	24 (0.9)	12 (0.5)	—
Deep venous thrombosis	16 (0.6)	13 (0.5)	—
Other peripheral venous thrombosis	11 (0.4)	12 (0.5)	—

Adverse events

- Increased incidence in testo group
  - **Nonfatal arrhythmia** warranting intervention: 5.2% vs 3.3% (P=0.001)
  - **Atrial fibrillation**: 3.5% vs 2.4% (P=0.02)
  - **Acute kidney injury**: 2.3% vs 1.5% (P=0.04)
- High-grade prostate cancer similar: 0.5% vs 0.4%

Conclusions on this study

- In middle-aged and older men with low TT with or at high risk of CVD, **androgen replacement for 2 years**:
  - No increased risk of major CVD events
  - **Higher incidence of pulmonary embolism**, **nonfatal arrhythmia** requiring intervention, **AF** and **acute kidney injury**
- Limitations
  - Treatment discontinuation high: small benefits perceived?
  - Median TT levels on-treatment 11.3-12.7 nmol/L: same results if higher levels?
  - Withdrawal rates: outcome data on 82% of patients in both groups
  - Short treatment duration

Breaking News: The TRAVERSE Fracture Trial

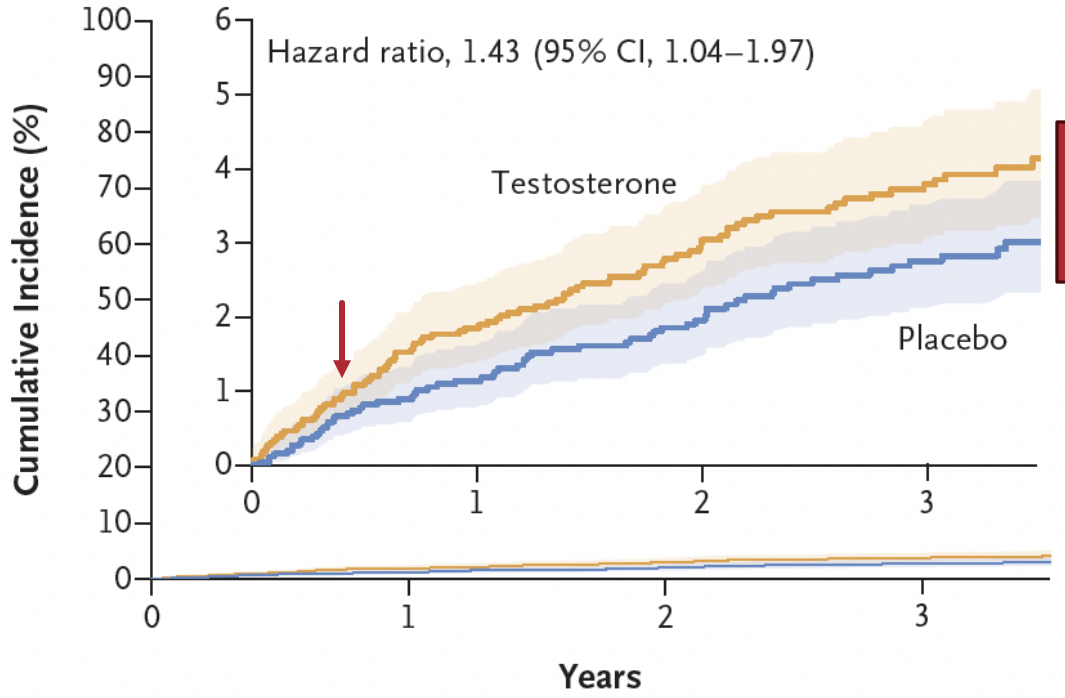
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 18, 2024 VOL. 390 NO. 3

Testosterone Treatment and Fractures in Men with Hypogonadism

Peter J. Snyder, M.D., Douglas C. Bauer, M.D., Susan S. Ellenberg, Ph.D., Jane A. Cauley, Dr.P.H., Kevin A. Buhr, Ph.D., Shalender Bhasin, M.B., B.S., Michael G. Miller, Pharm.D., Nader S. Khan, M.D., Xue Li, Ph.D., and Steven E. Nissen, M.D.

Increased risk of all clinical fractures in testosterone group



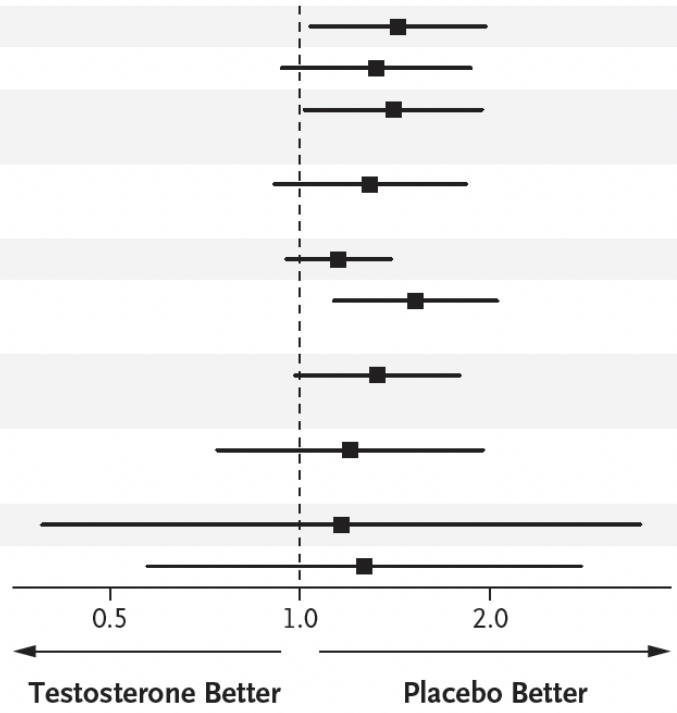
3-year cumulative incidence: 3.8% vs 2.8%

No. at Risk

Testosterone	2601	2332	1812	1369
Placebo	2603	2335	1812	1354

Fracture risk: subgroup analyses

Subgroup	Testosterone	Placebo	Hazard Ratio for Fracture (95% CI)
	no. with fracture/no. at risk (%)		
All clinical fractures	91/2601 (3.50)	64/2603 (2.46)	1.43 (1.04–1.97)
Non–high-impact clinical fractures	75/2601 (2.88)	57/2603 (2.19)	1.32 (0.94–1.86)
Clinical fractures in participants not taking osteoporosis medication	88/2588 (3.40)	63/2592 (2.43)	1.41 (1.02–1.94)
Non–high-impact fractures in participants not taking osteoporosis medication	72/2588 (2.78)	56/2592 (2.16)	1.29 (0.91–1.83)
Fracture-free survival	226/2601 (8.69)	198/2603 (7.61)	1.15 (0.95–1.39)
All clinical fractures, including those that had been excluded	109/2601 (4.19)	72/2603 (2.77)	1.52 (1.13–2.05)
All clinical fractures including uncertain and insufficient documentation	99/2601 (3.81)	75/2603 (2.88)	1.33 (0.98–1.79)
Major osteoporotic fractures: hip, wrist, humerus, and clinical spine	36/2601 (1.38)	30/2603 (1.15)	1.20 (0.74–1.95)
Hip fractures	7/2601 (0.27)	6/2603 (0.23)	1.16 (0.39–3.46)
Clinical vertebral fractures	14/2601 (0.54)	11/2603 (0.42)	1.26 (0.57–2.79)



Consistency of associations among subgroups
No increased risk of MOF

Conclusions on this study

- **Early increase in all clinical fractures but not MOF** with androgen replacement
- Unanticipated, mechanism unclear
  - Adverse effect of T on bone? Seems unlikely.
  - Behavior change: physical activities that increase fracture risk?

Grossmann M et al. *NEJM*, Jan 2024.

What does this study add to the discussion of risks and benefits with our patients?

Benefits

- Moderate improvement in sexual function
- Some benefit on mood
- Increase in walking distance
- Reduced incidence or amelioration of unexplained anemia[1]

Potential Risks

- Erythrocytosis, clinical implications unclear
- Suppression of endogenous testosterone production and spermatogenesis
- **Higher incidence of pulmonary embolism, nonfatal arrhythmia requiring intervention, AF and acute kidney injury**[2]
- **Higher risk of all clinical fractures**[3]
- **No increased risk of major CVD events up to 2 years**[2]
- **No worsening of urinary symptoms**[4]
- **No increased risk of de novo prostate cancer**[4]

[1]Pencina KM et al. *JAMA Netw Open*. 2023; [2]Lincoff AM et al. *NEJM*, 2023; [3]Snyder PJ et al. *NEJM*. Jan 2024; [4]Bhasin S et al. *JAMA Netw Open*. 2023.

Discussion

Join at **slido.com** with **#1803685**

Please put your questions in the Q&A

Wrap Up

Accreditation

This activity is an accredited group learning activity under Section 1 as defined by the Royal College of Physicians & Surgeons of Canada for the Maintenance of Certification program.

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https://csem-scem.bespokeav.ca/yir/y-2023/

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