#ItsPossible

with Diet, Stride & Tirzepatide

BEYOND WEIGHT LOSS

Emerging Insights in Metabolic and Cardiorenal Care — A Cardiac Perspective

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The World is Getting **Heavier..**

1.3
BILLION
The number of people around the world that will be living with obesity in 2030.

$3.23
TRILLION
The estimated global economic impact of overweight and obesity in 2030.

115%
INCREASE
Adult obesity is expected to increase by 115% between 2010 and 2030.

2 in 3
PEOPLE
It is expected that 2 in 3 of us will be living with overweight or obesity by 2030.

1.6
MILLION
Premature NCD deaths annually are due to overweight and obesity

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The Additional Weight Of IRRESPONSIBILITY...

Self Care Behaviors among Pakistani Population

- 51% Healthy Diet
- 35% Physically Active
- 50% Medication Adherence

- International Diabetes Federation. IDF Diabetes Atlas, 10th edn. International Diabetes Federation, 2021
- Paudel G, Vandelanotte C, Dahal PK, Biswas T, Yadav UN, Sugishita T, Rawal L. Self-care behaviours among people with type 2 diabetes mellitus in South Asia: A systematic review and meta-analysis. J Glob Health 2022;12:04056.

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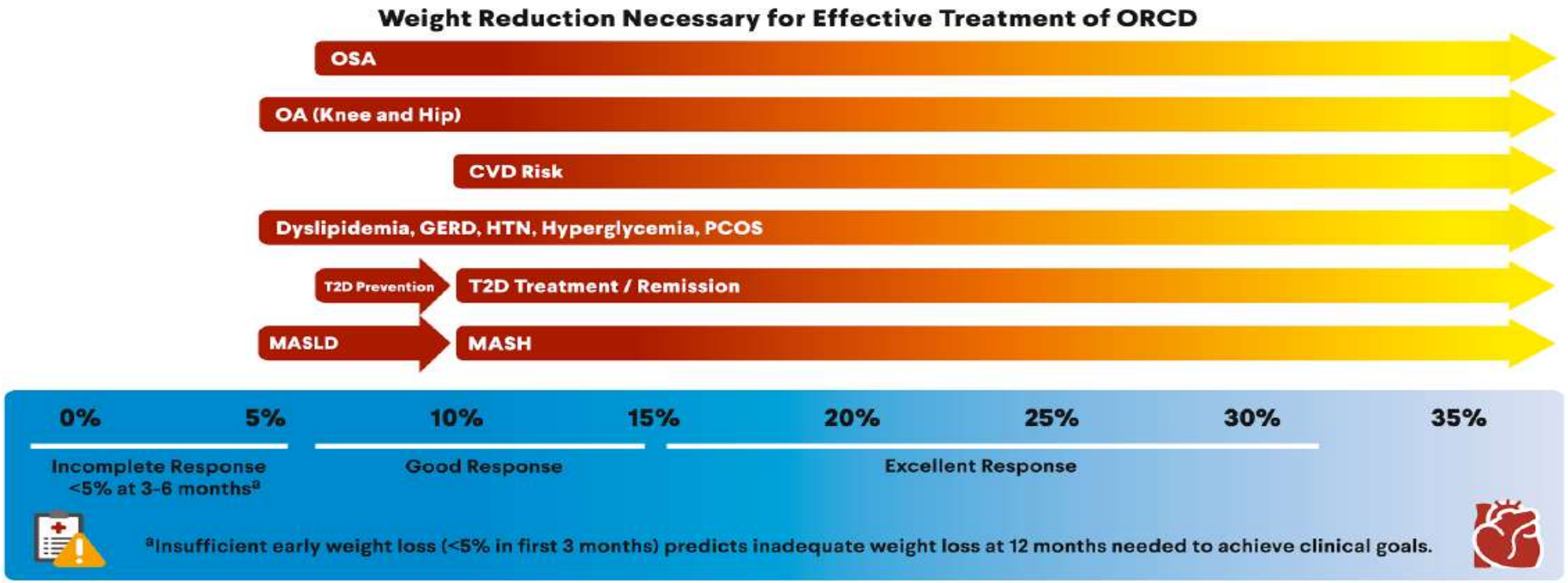
RESPONSE TO THERAPY AND WEIGHT-LOSS TARGETS FOR PEOPLE WITH ABCD



Abbreviations: **ABCD**, adiposity-based chronic disease; **BMI**, body mass index; **CVD**, cardiovascular disease; **GERD**, gastroesophageal reflux disease; **HLD**, hyperlipidemia; **HTN**, hypertension; **MASH**, metabolic dysfunction-associated steatohepatitis; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **OA**, osteoarthritis; **ORCD**, obesity-related complications and diseases; **OSA**, obstructive sleep apnea; **PCOS**, polycystic ovary syndrome; **T2D**, type 2 diabetes

Algorithm Figure 6 - Response to Therapy and Weight-Loss Targets

AACE

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WHY RISK REMAINS

Diabetes-related CV risk is driven by an interconnected disease system

Atherosclerotic Pathway

- Hyperglycemia, dyslipidemia, hypertension, inflammation, and endothelial dysfunction promote vascular injury. [14]
- Excess adiposity amplifies insulin resistance and several traditional and non-traditional risk factors. [14]
- Risk remains even when a single biomarker reaches target. [1,14]

Heart Failure and Kidney Pathway

- Diabetes, obesity, CKD, and HF frequently cluster as cardiovascular-kidney-metabolic syndrome. [14]
- Volume stress, renal dysfunction, inflammation, and altered cardiac structure contribute to HF events. [7,14]
- Treatment therefore combines lifestyle and organ-protective therapies with standard CV care. [1,13]

[1] American Diabetes Association PPC. (2026). Diabetes Care, 49(Suppl. 1), S216–S245. | [7] Packer, M., et al. (2025). New England Journal of Medicine, 392, 427–437. | [13] Marx, N., et al. (2023). European Heart Journal, 44, 4043–4140. | [14] Ndumele, C. E., et al. (2023). Circulation, 148, 1606–1635.

MECHANISM

Tirzepatide is one molecule with dual GIP and GLP-1 receptor activity

GIP receptor

Glucose-dependent insulin secretion and integrated metabolic signaling. [3,15]

GLP-1 receptor

Glucose-dependent insulin secretion, lower glucagon, delayed gastric emptying, and reduced food intake. [3,15]

Clinical phenotype

Lower glucose and body weight, with improvements in several cardiometabolic risk markers. [3,18]

Mechanistic plausibility supports—but does not replace—clinical outcome evidence. [4,15]

[3] National Library of Medicine. (2026, August). Mounjaro US prescribing information. DailyMed. | [4] Nicholls, S. J., et al. (2025). New England Journal of Medicine, 393(24), 2409–2420. | [15] Willard, F. S., et al. (2020). JCI Insight, 5(17), e140532. | [18] Frías, J. P., et al. (2021). New England Journal of Medicine, 385, 503–515.

PATHOPHYSIOLOGY: THE CARDIO-METABOLIC AXIS

- Adiposopathy (Sick Fat): Visceral and epicardial fat depots undergo chronic hypoxia, macrophage infiltration, and secrete pro-inflammatory adipokines.
- Endothelial Dysfunction: Systemic inflammation directly impairs nitric oxide bioavailability, accelerating atherosclerosis and vascular stiffness.
- Myocardial Remodeling: Lipotoxicity and insulin resistance drive adverse myocardial fibrosis, diastolic dysfunction, and arrhythmogenesis.

"Cardiologists must transition from treating downstream hemodynamic consequences to targeting upstream metabolic drivers."

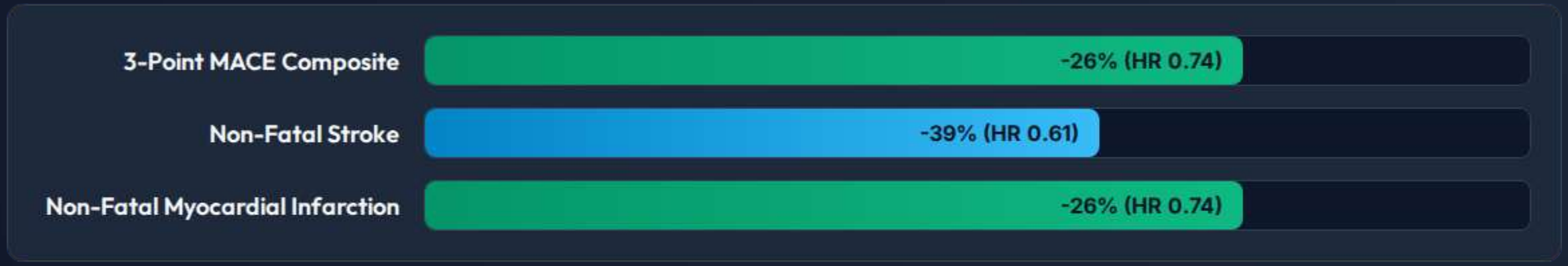
LANDMARK CVOTS & FOLLOW-UP DURATIONS

Trial / Agent	Population	Follow-Up Period	Primary Hard Outcome
LEADER (Liraglutide)	T2D, High CV Risk	**3.8 Years** (Median)	**-13% MACE** (HR 0.87, p=0.01; -22% CV Death)
SUSTAIN-6 (Semaglutide)	T2D, High CV Risk	**2.1 Years** (Median)	**-26% MACE** (HR 0.74; -39% Stroke)
REWIND (Dulaglutide)	T2D, Primary/Secondary	**5.4 Years** (Median)	**-12% MACE** (HR 0.88; Longest CVOT)
SURPASS-CVOT (Tirzepatide)	T2D, Established ASCVD	**4.0 Years** (Median)	**Non-inferior to Dulaglutide** on MACE; Superior on Expanded MACE

LEADER TRIAL: LIRAGLUTIDE OUTCOMES (3.8 YRS)

LEADER (N=9,340, Follow-up: 3.8 years): *Liraglutide reduced primary 3-point MACE by 13% (p=0.01), driven predominantly by a highly significant* ***22% reduction in cardiovascular death*** *in T2D.*

SUSTAIN-6: SEMAGLUTIDE SC OUTCOMES (2.1 YRS)



SUSTAIN-6 (N=3,297, Follow-up: 2.1 years): *Once-weekly subcutaneous semaglutide showed a striking* ***39% reduction in non-fatal stroke****, demonstrating robust cerebrovascular protection alongside anti-atherosclerotic effects.*

REWIND TRIAL: DULAGLUTIDE OUTCOMES (5.4 YRS)

REWIND (N=9,901, Follow-up: 5.4 years): *The longest CVOT to date. Approximately 69% had risk factors without established CVD (primary prevention), proving consistent benefit across diverse cohorts.*

SELECT TRIAL: PROTECTION WITHOUT DIABETES (3.4 YRS)

20%

RELATIVE RISK REDUCTION IN MACE

Semaglutide 2.4mg vs. Placebo

Follow-Up Duration: Mean 3.4 years (104 weeks evaluation period).

Evaluated **17,604 patients** with pre-existing CVD and overweight/obesity, explicitly *without diabetes*.

Key Takeaway: Cardioprotection is driven by treating adiposopathy and vascular inflammation independently of glycemic status.

SURPASS-CVOT: TIRZEPATIDE MACE & MACCE DATA

SURPASS-CVOT (N=13,299, Median Follow-up: 4.0 years): *Tirzepatide (GIP/GLP-1 dual agonist) achieved strict noninferiority on 3-point MACE vs dulaglutide while delivering superior metabolic weight loss (-11.6%) and a significant reduction in expanded hard endpoints.*

EXECUTIVE SYNTHESIS

The cardiovascular case rests on three distinct evidence pillars

PIVOTAL CVOT

0.92

SURPASS-CVOT MACE-3 HR vs dulaglutide; non-inferior, not superior. [4]

The compliant conclusion: benefit statements depend on population, comparator, endpoint and label. [2–4,7]

HFpEF OUTCOMES

0.62

SUMMIT CV death or worsening HF HR vs placebo in obesity-related HFpEF. [7]

Defined obesity-related HFpEF population.

REGULATORY

FDA 2026

US indication: MACE risk reduction in adults with T2D at high risk. [2,3]

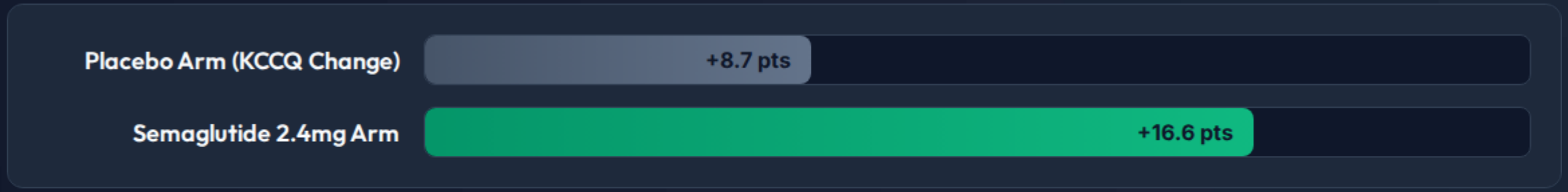
US approval does not automatically apply in Pakistan.

[2] U.S. FDA. (2026, August 27). NDA 215866/S-044 and S-045 approval letter. | [3] National Library of Medicine. (2026, August). Mounjaro US prescribing information. DailyMed. | [4] Nicholls, S. J., et al. (2025). New England Journal of Medicine, 393(24), 2409–2420. | [7] Packer, M., et al. (2025). New England Journal of Medicine, 392, 427–437.

SUMMIT TRIAL: TIRZEPATIDE IN HFPEF

SUMMIT Trial (Obesity-driven HFpEF): *Tirzepatide not only radically improved heart failure symptoms and KCCQ clinical scores by nearly 20 points, but also significantly reduced the composite risk of urgent heart failure visits or CV death.*

STEP-HFPEF: SEMAGLUTIDE IN HEART FAILURE (52 WKS)



STEP-HFpEF (Follow-up: 52 weeks / 1 year): *Among obese patients with HFpEF, Semaglutide delivered nearly double the improvement in heart failure symptoms, physical limitations, and 6-minute walk distance.*

MECHANISMS: EPICARDIAL FAT & VASCULAR PROTECTION

- Epicardial Adipose Tissue (EAT): EAT shares a microcirculation with the myocardium. Incretin RAs natively bind EAT receptors, shrinking volume and suppressing local inflammatory cytokine secretion.
- Arrhythmogenic Substrate Mitigation: By reducing EAT and atrial stretch, incretin-based therapies lower structural atrial remodeling and Atrial Fibrillation burden.
- Renal Hemodynamics: Attenuates progression of albuminuria and stabilizes glomerular hyperfiltration across cardiorenal cohorts.

THE CARDIAC MANDATE FOR IMPLEMENTATION

1. Screen

Identify BMI >27, insulin resistance, and subclinical cardiorenal decline across all established CVD cohorts.

2. Prescribe

Initiate GLP-1 RAs or dual GIP/GLP-1 agonists early alongside SGLT2is as core cardiovascular disease-modifying therapies.

3. Titrate

Follow slow titration schedules to ensure optimal gastrointestinal tolerability and long-term compliance.

4. Own

Cardiologists own cardiovascular risk; therefore, we must own the prescription of metabolic risk-reducers.

Thank You

Questions & Discussion

BEYOND WEIGHT LOSS • THE CARDIAC PERSPECTIVE