CLOSER LOOK

MEMORANDUM

Cardiometabolic Health Congress (CMHC) 2025 October 23-26, 2025; Boston, MA; Full Report – Draft

Executive Highlights

- **The 20th Annual Cardiometabolic Health Congress (CMHC) took place in the gorgeous Boston Park Plaza.** This year's conference began with the celebration of CMHC's 20th anniversary and its continued dedication to the cardiovascular-renal-metabolic health and clinical translation. Dr. Robert Eckel (University of Colorado) encouraged clinicians to begin implementing the learnings from CMHC as soon as they returned to clinic the Monday following CMHC.
- **Drs. Eckel, Keith Ferdinand (Tulane University), and Anne Peters (USC) highlighted the latest updates from the FDA and clinical research.** On incretin-based therapies, Dr. Eckel discussed the recent FDA approval of Rybelsus (oral semaglutide) for MACE reduction, as well as new data on small molecule GLP-1 RA orforglipron and GLP-1 RA/GIP receptor antagonist maridebart cafraglutide (MariTide)**. On diabetes technology, Dr. Peters shared updates on Dexcom G7 and Abbott's Libre Plus sensors,** acknowledging persistent challenges with some while recognizing the value of having multiple 15-day sensors on the market soon. She also presented the advent of new over the counter (OTC) CGMs and Biolinq Shine, the newly approved glucose range monitor (GRM) as new technology that could be beneficial for those with prediabetes.
- **On the cardio-renal-metabolic syndrome, Duke's Dr. Jennifer Green, UCSD's Pam Taub, Hopkins' Chiadi Ndumele, and Harvard's Sylvia Rosas** shared clinical insights on CKM prevention and management. The speakers emphasized that diabetes-related mortality is driven by compounded burden of comorbidities like albuminuria, impaired eGFR, and cardiovascular disease. Notably, Dr. Taub advocated for SGLT-2 inhibitor use as a foundational therapy for protection across CKM syndrome. Similarly, Tulane's Dr. Keith Ferdinand highlighted the complementary protective mechanisms of SGLT-2 inhibitors and GLP-1 RAs, noting their additive effects in lowering albuminuria, reducing ASCVD risk, and providing renal protection through anti-inflammatory pathways. Moreover, the 2025 AHA/ACC high blood pressure guidelines, which were published just over a month ago, now endorse a lower blood pressure of 130/80 mmHg for most patients.
- **On obesity, Dr. Eckel redefined parameters to assess obesity on a clinical spectrum,** discussing the new consensus on obesity recently established by the Lancet Commission on Obesity. The Commission challenged the longstanding reliance on body mass index (BMI) as a sufficient diagnostic measure, emphasizing its inability to accurately estimate adiposity or predict related health risks at the individual level. Instead, the Commission proposed a definition of clinical obesity based on the functional consequences of excess adiposity and its effects on organs and tissues.
- **On MASH, a symposium discussed the need for earlier identification and comprehensive management of metabolic dysfunction–associated steatohepatitis (MASH).** Dr. Conan Tu (Optum), Dr. Amreen Dinani (Duke Department of Medicine), Dr. Diana Barb (University of Florida, Gainesville), and Ms. Karen Fitzpatrick (Salmon Health) highlighted the evolving guidelines, diagnostic algorithms, and emerging pharmacologic therapies that aim to slow or reverse disease progression. Importantly, **patient advocate** Ms. Fitzpatrick also highlighted the real-world challenges of diagnosis, adherence, and emotional burden.

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Top Highlights

Breaking down silos in CKM prevention and management through interdisciplinary knowledge building

During this high-impact symposium, Drs. Jennifer Green (Duke University), Pam Taub (UC San Diego), Chiadi Ndumele (Johns Hopkins University), and Sylvia Rosas (Harvard University). On theme with the rest of the congress, speakers emphasized the need to stop with siloed, fragmented care and push for interdisciplinary responsibility for risk reduction of heart failure (HF) and chronic kidney disease (CKD). Across presentations, speakers emphasized that diabetes alone is not the primary driver of mortality. Rather, it is the compounded burden of comorbidities like albuminuria, impaired eGFR, and cardiovascular disease. From risk prediction tools like the AHA PREVENT equation to emerging therapies such as aldosterone synthase inhibitors (ASIs) and implementation models like the COORDINATE-Diabetes program, the symposium underscored the urgent need to improve interdisciplinary care across cardiology, nephrology, and endocrinology.

- **Dr. Ndumele kicked off the symposium, covering CKM syndrome and the synergistic mortality risk between CKD and diabetes.** One study (n=15,046) examined 10-year cumulative mortality and found that among people with diabetes and kidney disease, standardized mortality was 31%. Despite the declining rates of coronary heart disease mortality, there is a rise in HF mortality largely as a result of CKM syndrome. The overlap between CKM diabetes and heart failure, is significant with 16% of patients with HF having comorbid diabetes and CKD. Aside from the growing list of therapies to address CKM syndrome (SGLT-2 inhibitors, finerenone, and GLP-1 RAs). Dr. Ndumele highlighted the AHA's Predicting Risk of cardiovascular disease EVENTs (PREVENT) equation. This helps calculate risk and direct conversation with care teams to prevent or slow CKM. Importantly, Dr. Ndumele underscored the need to repair the fragmented care structure for

treating CKM, urging the need for interdisciplinary models.

- **Dr. Rosas discussed screening strategies for CKD, emphasizing it isn't enough to know the numbers, but that they must also be applied.** She highlighted that diabetic kidney disease (DKD) is the most common cause of CKD in the US and is rising worldwide. She emphasized that diabetes itself is not the main driver of mortality but instead its comorbidities. One study (15,046) found that 10-year standardized mortality risk reached 47% when both albuminuria and impaired GFR were present – more than double the risk seen with impaired GFR alone (23.9%) or albuminuria alone (17.8%). Dr. Rosas urged that microalbuminuria is an important marker for risk, especially for patients that might be overlooked with normal GFR levels. She highlighted the PREVENT-HF phase 3 trial (n=11,300), which is currently recruiting, for people with T2D, CVD, and a history of hypertension to determine if baxdrostat and dapagliflozin is better at reducing mortality than dapagliflozin alone.
- **Dr. Taub followed by diving into SGLT-2 inhibitors as foundational therapies for cardio-renal-metabolic protection.** She reiterated that physicians cannot operate in silos, with the heart, kidney, and endocrine system intricately linked. She highlighted the EMPA-REG trial (n=7,064) which showed that treatment with empagliflozin conferred a 33% reduction in hospitalizations for HF when compared with placebo. Despite these benefits, residual risk remains, prompting her to spotlight aldosterone as a key driver of cardio-renal damage. She introduced aldosterone synthase inhibitors (ASIs), which reduce plasma aldosterone exposure and potentially mitigate organ damage. ASIs in combination with SGLT-2 inhibitors are currently being investigated in the EASI-PROTKT trial (n=6,000) and aforementioned PREVENT-HF trials.
- **Dr. Green closed the session looking more closely at clinical implementation of risk reduction for CKD and CVD.** She highlighted one study which estimated the economic impact of using SGLT-2inhbotors in patients with T2D, CKD, and/ or CVD. Ultimately, the study found that government investment of $1 billion over 10 years in SGLT-2 inhibitors treatments would result in 7,450 fewer deaths and almost $5 billion in cost savings. She also highlighted the KDIGO guidelines which call for integrated cardio-renal-metabolic care, including early CKD screening via both eGFR and albuminuria, and use of SGLT-2 inhibitors and finerenone to address the compounded risk of diabetes, CKD, and HF. She closed by discussing the COORDINATE-diabetes program which showed that a multifaceted intervention in cardiology clinics more than doubled the rate of patients with T2D and ASCVD receiving all three guideline-directed therapies (statins, antithrombotic, and glucose-lowering agents with CV benefit) rising from 15.4% under usual care to 37.9% with intervention.

Ms. Davida Kruger on the role of GLP-1 RAs in T2D management, especially in context of CKD

In a Novo Nordisk-sponsored breakfast symposium, Ms. Davida Kruger (Henry Ford Health) reflected on the evolving management of T2D over her 44-year career thus far. Despite the early hour, Ms. Kruger brought great energy. She shared that early in her career, there were not many treatment options for T2D, so patients were allowed to be "sweet" (remain in hyperglycemia). T2D is now recognized as a complex multisystem disease associated with cardiovascular disease (CVD) and chronic kidney disease (CKD), and treatment guidelines have shifted in response to this. In her talk, Ms. Kruger emphasized: (i) the escalating prevalence of T2D and its comorbidities; (ii) the lack of universal, guideline-based CKD screening; and (iii) the importance of a comprehensive cardiorenal risk management approach, including GLP-1 RAs and other incretin therapies.

- **Ms. Kruger cited data showing that 40% of adults in the US with T2D also have CKD,** yet fewer than one in four receive guideline-recommended screening for renal impairment, despite KDIGO and ADA recommendations for annual UACR and eGFR testing. She emphasized that patients with concurrent T2D and CKD face a five-fold greater risk of cardiovascular death than of kidney failure, underscoring the imperative for early detection and intervention. Moreover, the 2025 ADA Standards of Care now recommend GLP-1 RAs or SGLT-2 inhibitors for patients with T2D and CKD regardless of A1c level, reflecting a paradigm shift toward organ protection as a therapeutic goal.
- **Ms. Kruger reviewed evidence from major clinical trials recently showing the impact of incretin therapies beyond weight management**, notably FLOW and SUSTAIN-6. The FLOW trial demonstrated a 24% relative risk reduction in major cardiorenal events among adults with T2D and CKD, independent of weight loss effects, while SUSTAIN-6 reported a 26% reduction in major adverse cardiovascular events

(MACE) in high-risk patients with established CVD.

Dr. Anne Peters on the last few decades of clinical guidelines in T2D

In an engaging morning presentation, Dr. Anne Peters (USC) reviewed guidelines on T2D management. She began with a slide shared by Dr. John Buse (UNC) in 2006, entitled, "The elephant in the room: Traditional therapies fail to address important issues in T2D management." Nearly 20 years later, the slide remains prescient and relevant today. Dr. Peters traced the field's early preoccupation with beta cell burnout and the phenomenon of secondary failure, as demonstrated in the ADOPT and UKPDS trials. She discussed the emergence of thiazolidinediones (TZDs), which "really did help slow progression [of T2D]" despite their complicated reputation. She candidly reviewed early CVOTs with "stupid endpoints," which Dr. Peters said obscured early signs of cardioprotective benefits. She recounted the historical tension between the conservative ADA/EASD consensus algorithm and Dr. Ralph DeFronzo's (UT San Antonio) model advocating for early, aggressive combination therapy of TZDs, metformin, and incretin agents immediately following T2D diagnosis.

- **Following this important historical context,** Dr. Peters then showed how clinical practice guidelines have evolved from rigid, tiered frameworks to the more nuanced, physiology-based approaches that are the standard of care today. She joked that previous standards were also written with Dr. Buse and herself at the helm, though clinical recommendations have become more comprehensive as more clinical evidence is available. While lauding the impact of CGM and current anti-obesity medications, Dr. Peters said that lifestyle changes still need to be at the core of any obesity management guidelines, given that "you can out-eat any therapy." As various clinical trial results are posted, these guidelines will continue to be updated.

Evolving landscape of HFpEF care dominated by SGLT-2 inhibitors, with GLP-1 RAs emerging as key therapy

In this afternoon session, Dr. Biykem Bozkurt (Baylor University) delivered an overview of current and emerging therapies for heart failure with preserved ejection fraction (HFpEF). She began with a study (n=39,982) that showed that people with HFpEF face a 76% five-year mortality, emphasizing the urgent need for prevention and management strategies. She highlighted that the therapeutic landscape for HFpEF is changing rapidly, led by SGLT-2 inhibitors, mineralocorticoid receptor antagonists (MRAs), and incretin-based therapies.

- **SGLT-2 inhibitors emerged as a foundational therapy for heart failure across the ejection fraction spectrum,** with the EMPEROR-Preserved (n=5,988) and DELIVER (n=6,263) trials demonstrating early and sustained reductions in the composite of cardiovascular death or HF hospitalization. EMPEROR-Preserved showed 415 events with empagliflozin versus 511 in placebo. DELIVER showed 512 events with dapagliflozin versus 610 in placebo. These highlight SGLT-2 inhibitors as a foundational, first-line therapy in guideline-directed HF care to reduce HF hospitalizations and burden.
- **Outside of SGLT-2 inhibitors, Dr. Bozkurt highlighted the emerging roles of MRAs and GLP-1 RAs in HFpEF.** In the FINEARTS-HF trial (n=6,016), there were 1,083 cardiovascular deaths or worsening HF events in the finerenone arm versus 1,283 in the placebo arm. Dr. Bozkurt noted that steroidal MRAs are more effective at lower ejection fractions. There are different levels of evidence across ejection fractions, extending benefit into HFmrEF and HFpEF subgroups.
    - She highlighted GLP-1 RAs in the STEP-HFpEF trial (n=529), which evaluated the efficacy of semaglutide on Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) – a patient-reported measure of quality of life, HF-related symptoms, and social and physical functioning – and change in body weight. Semaglutide demonstrated a 16.6-point change in KCCQ versus 8.7 points in placebo, reflecting significant improvement in quality of life. She also highlighted the SELECT trial (n=17,604), which showed that semaglutide reduced composite CV death, non-fatal MI or nonfatal stroke by 20% over five years in adults with overweight or obesity without diabetes. In the SUMMIT trial (n=731), tirzepatide (GIP/GLP-1 RA) reduced the risk of CV deaths or worsening HF by 38% in participants with HFpEF and led to 19.5-point increase in KCCQ-CSS in the tirzepatide group, compared to 12.7-point increase with placebo.

- **Currently, there is no real-world evidence to support the use of beta-blockers in HFpEF.** In all, Dr. Bozkurt emphasized that clinicians should prioritize symptom management, while adopting SGLT-2 inhibitors that have wealth of data, as well as adding MRAs and considering GLP-1/GIP RAs. She emphasized the need to individualize therapy by mechanism and trajectory rather than ejection fraction number alone.

Modifiable risk factors for CVD: Opportunities for earlier intervention in disease progression

Dr. Keith Ferdinand (Tulane University) reviewed modifiable cardiovascular risk factors and various treatment options for overlapping cases of hypertension, CKD, and T2D. High blood pressure, elevated BMI, non-HDL cholesterol, smoking, and diabetes are key modifiable drivers of CKD- and CVD-related morbidity. Dr. Ferdinand highlighted the complementary protective mechanisms of SGLT-2 inhibitors and GLP-1 RAs, noting their additive effects in lowering albuminuria, reducing atherosclerotic cardiovascular disease (ASCVD) risk, and providing renal protection through anti-inflammatory pathways. The 2025 AHA/ACC hypertension guidelines, which were published just over a month ago, endorse a lower blood pressure of 130/80 mmHg for most patients, encouraging tighter management and lower thresholds for intervention.

- **Dr. Ferdinand expanded on evidence from large-scale meta-analyses and landmark trials** (n=344,000+) such as SPRINT, which confirmed that intensive blood pressure reduction reduces total mortality and major cardiovascular events. He also cited emerging data from a Chinese cohort study of nearly 34,000 individuals demonstrating that effective hypertension management can not only extend life expectancy but also preserve cognitive function by reducing dementia risk.
- **Advances in technology** have also benefited CVD management. Clinical-grade heart monitors are now available in the home, which allow for better disease tracking; as Dr. Ferdinand described, "What we do in the clinic is not enough for a biomarker that a person lives with 24/7." By enabling patients to access this data in their homes, there are more opportunities to identify potential problems and intervene earlier.
- **In closing,** Dr. Ferdinand stressed that health equity must remain both a moral and clinical imperative, calling for targeted interventions to close persistent gaps in hypertension control across demographic and socioeconomic groups.

Impact of lifestyle and behavioral health on obesity management

To open his presentation, Dr. Robert Eckel (CU Anschutz School of Medicine) emphasized the dramatic rise in state-specific obesity prevalence over the past two decades and the need to contextualize obesity within the framework of metabolic syndrome. Since 2005, definitions of this syndrome have been harmonized to include central obesity, dyslipidemia, hypertension, and insulin resistance. Dr. Eckel discussed the central role of insulin resistance as the pathological core of obesity-related complications, connecting decades of clinical insight to current public health trends. He also reflected on pivotal nutritional discoveries, particularly the cardiovascular risks of trans fats, which raise LDL and lower HDL cholesterol levels. Dr. Eckel then delved into the scientific and therapeutic evolution of obesity management, from early pharmacologic efforts to the current era of incretin-based treatments. He reviewed drug approvals, from phentermine in 1959 through orlistat and sibutramine in the late 1990s to the emergence of GLP-1 RAs, dual agonists, and the anticipated tri- and quad-agonists now in development. These newer agents, he argued, have fundamentally transformed obesity treatment by addressing underlying metabolic dysfunction rather than merely suppressing appetite. Dr. Eckel concluded with a call to prioritize dietary quality alongside pharmacotherapy, urging clinicians to educate patients on interpreting food labels, particularly regarding trans fats and hydrogenated oils, which remain key contributors to metabolic risk.

Updates on GLP-1 RAs in cardiovascular risk reduction and tailored treatment with metabolic phenotyping

Dr. Robert Eckel emphasized that new scientific findings should translate directly into clinical practice as soon as possible. His ideal timeline was one in which attendees would learn about evidence-based recommendations today at CMHC, and by this upcoming Monday, already be implementing these changes in their respective clinics. He discussed the expanding role of oral GLP-1 RAs in diabetes and obesity management, highlighting the FDA's recent approval of Rybelsus (oral semaglutide) for cardiovascular risk reduction. Dr. Eckel reviewed emerging therapies including small

molecule GLP-1 RA orforglipron and GLP-1 RA/GIP receptor antagonist maridebart cafraglutide (MariTide). Beyond incretin therapies, Dr. Eckel encouraged clinicians to anticipate next-generation oral and peptide-based obesity treatments, including cannabinoid receptor inhibitors, glucagon agonists, tri-agonists, and myostatin antibodies. He also presented new research on metabolic phenotyping and gene-based prediction of weight-loss responsiveness, suggesting that integrating deep phenotyping and machine learning could help tailor anti-obesity medications based on individual "calories-to-satiation" profiles.

The promise of ongoing CGM innovation, including OTC and glucose range monitoring

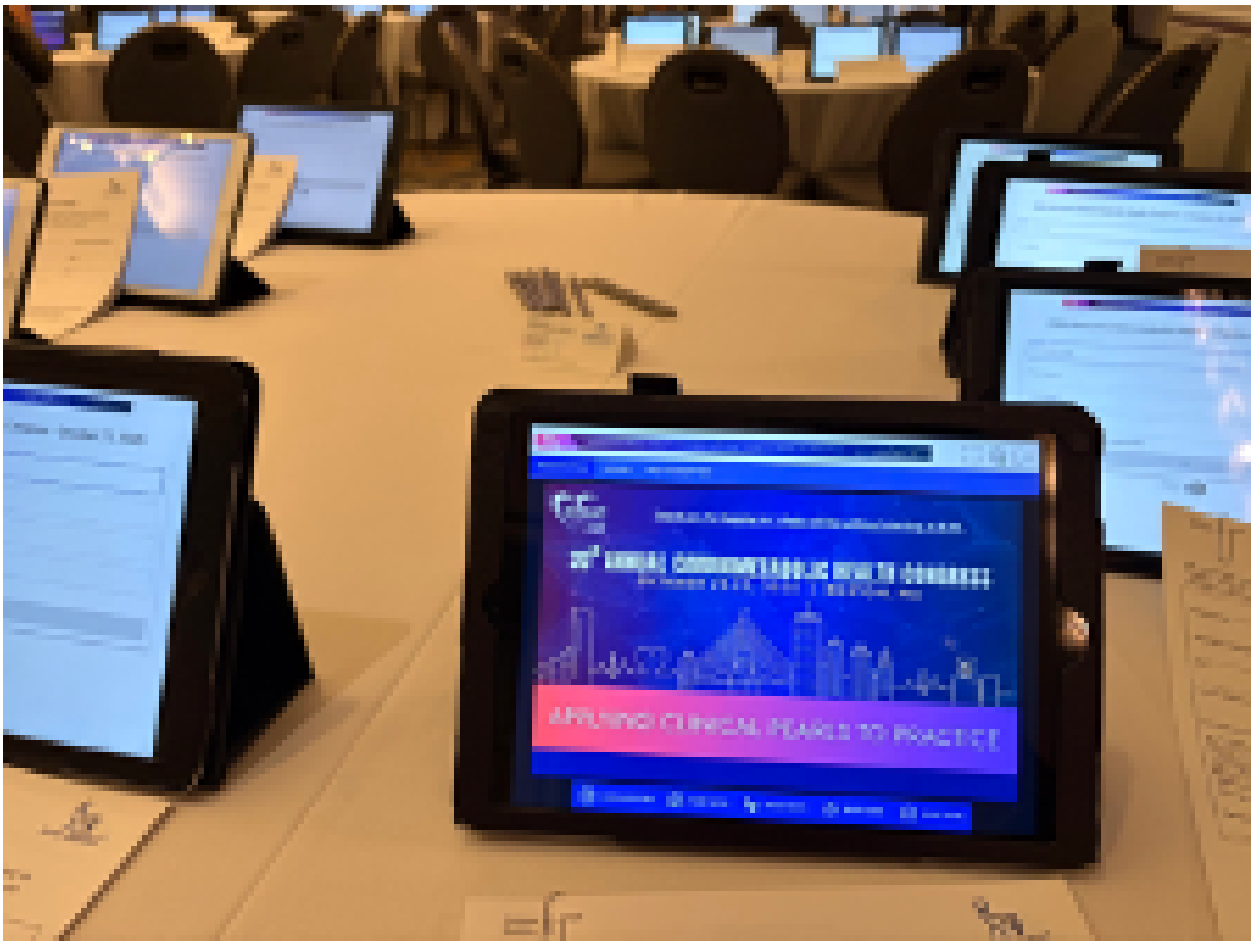
Dr. Anne Peters provided a pragmatic update on diabetes technology and therapeutic developments. She voiced strong criticism of the Dexcom G7, describing it as the "buggiest sensor" she has encountered due to manufacturing inconsistencies between U.S. and Malaysian facilities. On a positive note for Dexcom users, however, Dr. Peters announced that a debugged, US-produced 15-day G7 sensor is expected soon, while also noting that Libre Plus sensors now share the same extended wear time. She discussed the advent of over the counter (OTC) CGMs, which may appeal to individuals with prediabetes, and the Biolinq Shine, the newly approved glucose range monitor (GRM), which tracks metabolic data without displaying numerical glucose values. Regarding therapy updates, Dr. Peters mentioned the recent FDA approval of semaglutide for MASH with liver fibrosis. She concluded with a sober assessment of islet cell transplantation for T1D, noting that while several patients have achieved insulin independence with Vertex's zimislecel, high rates of immune-related complications and mortality demonstrate that this therapy remains experimental and not yet viable for routine care.

The latest and greatest in hypertension and CKD management

Dr. Keith Ferdinand presented a session overviewing of hypertension and CKD-related innovations, as outlined in the 2025 AHA guidelines. He discussed recent recommendations to avoid antihypertensive therapy in adults over 80 years old when systolic blood pressure remains near 130 mmHg, balancing benefits and risks in frail populations. Dr. Ferdinand highlighted the CONFIDENCE trial, which demonstrated that combined therapy with finerenone (a nonsteroidal mineralocorticoid receptor antagonist) and empagliflozin significantly reduced albuminuria (UACR) in patients with CKD and T2D compared with either therapy alone. Additional late-breaking studies included FINEARTS-HF, showing benefit of finerenone in HFpEF, leading to its 2024 FDA approval for heart failure with preserved ejection fraction (LVEF >40%). He concluded by emphasizing the ongoing investigation of APOL1 genetic variants in CKD among individuals of West African ancestry, reflecting the growing recognition of precision medicine in hypertension and renal disease management.

Exhibit Hall opens with exhibitors spanning CVD risk assessment and glycemic management – An ode to interdisciplinary care

CMHC's Exhibit Hall opened Thursday morning and showcased a variety of exhibitors (as well as snack offerings, ranging from fruit salad to cookies and cakes). The Exhibit Hall also featured raffles for bags, pens, AirPods, and more! The ballroom filled quickly, with clinicians and attendees across cardiometabolic health drawn to visually striking posters and digital displays. The Siemens Healthineers booth highlighted the uptick of metabolic disease prevenance and its suite of tests to help assess risk. Novartis's messaging highlighted elevated Lp(a) uncovered as testing rates rise nationwide. We also enjoyed seeing Abbott's FreeStyle Libre booth, truly showcasing CMHC's commitment to an interdisciplinary approach to cardiometabolic health. The atmosphere of the hall certainly generated excitement for the rest of the conference, giving attendees the chance to mingle and discuss the tools that ameliorate the delivery of cardiometabolic care. If you are in Boston for the Congress and have not stopped by yet, the Exhibit Hall is a must-see and will be open until 2 pm on Friday!



Lancet Commission on Obesity: Redefining parameters to assess obesity on a clinical spectrum

In an early morning, well-attended session, Dr. Robert Eckel (CU Anschutz School of Medicine) discussed the new consensus on obesity recently established by the Lancet Commission on Obesity. *The international effort* brought together 54 global experts and 79 endorsing organizations to reframe the medical understanding of obesity. The Commission challenged the longstanding reliance on body mass index (BMI) as a sufficient diagnostic measure, emphasizing its inability to accurately estimate adiposity or predict related health risks at the individual level. Instead, the Commission proposed a definition of clinical obesity based on the functional consequences of excess adiposity and its measurable effects on organs, tissues, and overall physiological function. This approach established objective diagnostic criteria to support clinical decision-making, inform public health strategies, and prioritize therapeutic interventions. As Dr. Richard Horton, *The Lancet*'s Editor-in-Chief, summarized, this represents "a sharp before and after moment" in how obesity is conceptualized in modern medicine.

- **While earlier medical traditions** dating back to Hippocrates and Galen recognized only some forms of obesity as pathological, the modern view positions obesity as a **clinical spectrum** rather than a uniform disease. Dr. Eckel likened p*reclinical obesity,* characterized by excess body fat without demonstrable organ dysfunction or limitation of daily activities, to prediabetes or HIV. He described this state as an *at-risk* position with opportunity for early intervention and prevention. C*linical obesity*, on the other hand, has been redefined by the Commission as a chronic disease with direct evidence of organ or tissue impairment (e.g., reduced mobility, hyperglycemia, elevated triglycerides, or low HDL cholesterol).
- **The implications of this reconceptualization are wide-ranging** for clinical care, health policy, and research. Recognizing *preclinical obesity* as a state of elevated but reversible risk prioritizes preventive and behavioral interventions aimed at reducing future morbidity. In contrast, *clinical obesity* necessitates evidence-based therapeutic management focused on reversing or mitigating organ dysfunction. The proposed diagnostic

model allows for an objective, standardized classification across global health systems. By distinguishing between preclinical and clinical forms, the Commission's framework introduces a more ethically and medically meaningful approach to obesity management.

Screening, prioritization, and treatment of MASH

In a symposium sponsored by Novo Nordisk, Boehringer Ingelheim, and the Global Liver Institute, Dr. Conan Tu (Optum) moderated a panel to discuss the need for earlier identification and comprehensive management of metabolic dysfunction–associated steatohepatitis (MASH). Panelists included Dr. Amreen Dinani (Duke Department of Medicine), Dr. Diana Barb (University of Florida, Gainesville), and Ms. Karen Fitzpatrick (Salmon Health). The speakers explained that MASH, driven by adiposity and metabolic dysfunction, is a progressive liver disease with significant mortality risk, particularly among individuals with T2D and/or obesity. Panelists touched on evolving guidelines, diagnostic algorithms, and emerging pharmacologic therapies that aim to slow or reverse disease progression. Importantly, patient advocate Ms. Fitzpatrick also highlighted the real-world challenges of diagnosis, adherence, and emotional burden.

- **Dr. Tu open the session by framing MASH** as part of a broader disease continuum that begins with metabolic dysfunction-associated steatotic liver disease (MASLD) before progressing to MASH, potentially resulting in fibrosis and cirrhosis. He emphasized that liver fibrosis, rather than elevated liver enzyme levels, is the most powerful predictor of both liver-related and all-cause mortality, citing data that only a quarter (or fewer) of cases with fibrosis also see elevated liver function tests. The root cause of MASH lies in systemic metabolic dysfunction, which triggers inflammation and organ injury across multiple body systems, reinforcing the need to view MASH as a metabolic, rather than purely hepatic, disease.
- **Dr. Dinani focused on screening and diagnosing MASH,** advocating for early identification to prevent disease progression. She presented a stepwise diagnostic algorithm beginning with the FIB-4 score for initial risk assessment, followed by imaging-based noninvasive tools such as vibration-controlled transient elastography (VCTE) or magnetic resonance elastography (MRE) for secondary evaluation. Dr. Dinani emphasized that screening should target high-risk groups: individuals with T2D, obesity, or a family history of MASLD-related cirrhosis. She also reviewed evidence showing that fibrosis stage directly correlates with mortality risk, noting that even moderate fibrosis (F2-F3) increases liver-related mortality up to 17-fold. Her key message was that noninvasive testing, guideline adherence, and multidisciplinary referral are critical to intervening in the MASH continuum before irreversible liver damage occurs.
- **Dr. Barb provided an in-depth overview of current and emerging treatments for MASLD and MASH,** stressing the importance of individualized, multidisciplinary care. She also discussed the use of noninvasive tests (FIB-4, VCTE, MRE) for ongoing risk assessment and outlined therapeutic goals focused on achieving weight loss greater than 10%, optimizing glycemic and cardiovascular control, and addressing underlying metabolic dysfunction. Dr. Barb reviewed key pharmacologic advances, including the thyroid hormone receptor-beta agonist *resmetirom*, which has shown significant improvements in fibrosis and steatohepatitis resolution, and incretin-based therapies such as *semaglutide* and *tirzepatide*, which have demonstrated MASH resolution and fibrosis improvement in clinical trials. She also described novel investigational agents targeting pathways such as FGF21, GLP-1/glucagon dual agonism, and pan-PPAR activation, all showing promising early results. Her remarks emphasized that the management of MASH requires integration across primary care, endocrinology, and hepatology, scaling in intensity as fibrosis advances.
- **Ms. Fitzpatrick shared her perspective as a patient advocate.** She described her journey from an incidental liver function test that was elevated to an eventual MASH diagnosis and the emotional challenges of dealing with this unexpected diagnosis. Ms. Fitzpatrick urged clinicians to prioritize communication, persistence, and empathy. She said what helped her the most was understanding what drives her disease and feeling empowered to take ownership of her care. She encouraged providers to "help patients find their why," as motivation is key to sustaining behavior change and adherence, and urged clinicians in the audience to not give up on their patients who might seem unengaged or resistant to treatment. She shared her story to help emphasize the importance of connecting patients with educational resources, multidisciplinary care, and clinical trial opportunities.

Dr. Anne Peters on the complexity of diagnosing adult-onset T1D in diverse, real-world populations

In this afternoon session, Dr. Anne Peters (USC) discussed adult-onset T1D as continually difficult to diagnose due to "homogenous guidelines for a heterogenous disease." She stressed that the ADA/EASD 2021 consensus report for the management of T1D in adults, which she helped formulate, can aid diagnosis when features suggest T1D but lacks full sensitivity and specificity. She highlighted that much of the guideline data derive from white European cohorts with limited generalizability to diverse populations such as the predominantly Hispanic patients she treats in East Los Angeles.

- **Dr. Peters highlighted one framework that was published just last week in *The Lancet* which urges a shift toward risk-stratified, pragmatic glycemic management for adults found to be islet autoantibody positive.** Instead of reflexive initiation of lifelong insulin, clinicians should place patients on a pathway to early longitudinal monitoring. Dr. Peters emphasized that this allows clinicians to avoid overtreatment, a focused use of resources (CGM, repeat biomarkers, and genetic testing) and personalized therapy based on evolving physiology rather than a single diagnostic label.
- **Through two instructive cases, Dr. Peters showed that autoantibody positivity does not always equal immediate lifelong insulin dependence.** Some patients with longstanding autoimmune markers can be managed off insulin using noninsulin therapies. One case involved a 58-year-old male patient who had been hospitalized with an A1c of 9.5% and very high islet autoantibodies. Nevertheless, he had preserved C-peptide levels of 2.7 ng/mL and received a brief basal insulin trial. With close CGM monitoring showing average glucose values of approximately 112 mg/dL and a Time in Range (TIR) of up to 97%, clinicians de-intensified insulin therapy and continued their surveillance of his A1c values, C-peptide levels, and symptoms. This illustrated that high antibody titers do not automatically mandate lifelong insulin use.
- **She also broadened the treatment differential beyond T1D and T2D by explicitly discussing other etiologies** such as type 3c (pancreatogenic) and type 5 (undernutrition-associated) diabetes. She noted that structural pancreatic disease, chronic pancreatitis, prior pancreatectomy, or a life-course undernutrition phenotype require different diagnostic tests and management strategies and should not be forced into a binary of T1D or T2D. Her practical message was to treat current metabolic needs safely, reassess diagnosis longitudinally, and redesign diagnostic pathways to reflect real-world diversity and clinical complexity.

Overview of the obesity landscape from Dr. Donna Ryan

Dr. Donna Ryan (Pennington Biomedical Research Center) provided an update on the rapid evolution of obesity treatment, marked by the increasing use of both approved and off-label medications by obesity specialists. Incretin therapies, such as semaglutide and tirzepatide, have achieved robust and clinically meaningful weight loss (15-22% from baseline). Despite high costs, both payers and patients have embraced their use, with growing trends in out-of-pocket purchasing. For individuals unable to access these drugs, Dr. Ryan suggested alternative options including sympathomimetics (phentermine), naltrexone/bupropion, and topiramate. A recent randomized comparison of 751 adults reaffirmed tirzepatide's superior efficacy (21.6% weight loss) compared with semaglutide (15.4%) at 72 weeks, though she suggested that uptake tends to rely on insurance coverage.

- **Beyond efficacy,** Dr. Ryan emphasized that GLP-1 RAs have reshaped the clinical landscape by expanding their indications beyond obesity to encompass diabetes, cardiovascular disease (CVD), metabolic dysfunction-associated steatohepatitis (MASH), and obstructive sleep apnea (OSA). The pleiotropic effects of GLP-1 and GIP hormones include not only insulin secretion and improved glycemic management but also cardiometabolic and anti-inflammatory benefits. GLP-1 RAs lower blood pressure, improve renal function, reduce coagulation and postprandial lipids, and attenuate systemic inflammation, independent of weight loss.
- **Dr. Ryan concluded that GLP-1 RAs should be regarded as *chronic disease medications*** rather than simple weight-loss agents given their demonstrated capacity to reduce mortality and modify obesity-related comorbidities. The expansion of generic competition within the United States is expected to improve accessibility and affordability, further driving adoption, while the advent of dual and triple agonists has the potential to increase the already impressive benefits seen with monotherapies. Collectively, these

advancements signify a paradigm shift: obesity treatment is evolving from symptomatic management toward disease modification, offering new opportunities to improve cardiometabolic health on a population scale.

Diabetic neuropathy: Global burden, diagnostic limitations, and treatment tradeoffs

During this afternoon session, Dr. A. Gordon Smith (Virginia Commonwealth University) framed diabetic neuropathy as one of the world's largest neurological problems. He cited a Global Burden of Disease finding which showed that 37 common nervous-system conditions account for 443 million disability-adjusted life-years (DALYs) and affect 3.4 billion people, placing diabetic neuropathy as one of the five highest-burden neurological conditions worldwide. He emphasized that epidemiology has shifted, driven by rising T2D prevalence worldwide as well as an aging global population. He issued a "call to arms" to prioritize prevention and early detection of diabetic neuropathy.

- **Dr. Smith reviewed the broad clinical spectrum and diagnostic challenges of diabetic neuropathy.** One study (n=195) showed that neuropathic pain prevalence rose from 7% in a control group to 28 % in people with diabetes. He stressed the limitations of routine testing – while clinicians have a large toolbox of tests available, choosing the right one can difficult. Different neuropathies preferentially affect either large, small myelinated, or unmyelinated nerve fibers. Most routine tests detect large-fiber dysfunction, while small-fiber and autonomic injury require less-available, specialized diagnostics. In a study of 458 new distal symmetric polyneuropathy patients, nerve conduction studies or electromyography (EMG) testing were able to alter neuropathy cause or management plan in only two cases, neurologist diagnostic testing changed management in 15%, and treatment plans were modified in 63% of patients.
- **Dr. Smith contrasted effective disease modification via glycemic management in T1D and T2D, emphasizing the need for more targeted intervention.** One study (n=1,441) found a 78% relative risk reduction for complications in T1D with effective glycemic management versus another study (n=10,251) which found only a 5–9% benefit for T2D. He also reviewed recent interventional efforts including the TopCSPN randomized trial (n= 211) of topiramate, an anti-epileptic therapy that calms overactive nerves. While the TopCSPN trial did not show benefit in the primary intent-to-treat analysis, a per-protocol analysis suggested that topiramate improved neuropathy-related quality of life (NQOL) with an estimated annual improvement of 3.69 points.
    - **Turning to practical insights, Dr. Smith cautioned that rapid A1c reductions can trigger treatment-induced neuropathy,** where a 4.0% decrease in A1c is associated with an 80% increased risk of neuropathy. Importantly, he highlighted an August 2025 study reporting large increases in neuropathic attacks from 2020–2024, with a 700% increase in diabetic lumbosacral radiculoplexus neuropathy and a 900% increase in common fibular neuropathy events that coincides with increased GLP-1 RA use. Given the efficacy of GLP-1 RAs for glycemic management, this underscores the need for clinicians to balance aggressive metabolic management with staged, evidence-based symptom management.

Ms. Davida Kruger on difficult-to-manage T2D as a marker of hypercortisolism

In this informative afternoon presentation, Ms. Davida Kruger (Henry Ford Health) reviewed hypercortisolism as an under-recognized contributor to difficult-to-manage T2D. When patients have poor glycemic management despite optimized therapy, escalating insulin needs, resistant hypertension, rapid central weight gain, unexplained hypokalemia, osteoporosis, or treatment-resistant depression, she emphasized that clinicians should test for hypercortisolism. While Cushing Syndrome has typical markers like proximal myopathy and easy bruising , many patients also present atypically, so relying only on classical signs risks overlooking many cases.

- **She recommended the 1-mg overnight dexamethasone suppression test as a practical, sensitive initial screen that can be performed in primary care**. A post-DST cortisol >1.8 µg/dL reading would then prompt further evaluation. She noted that late-night salivary cortisol testing and 24-hour urinary free cortisol are useful adjuncts but are less sensitive for ACTH-independent disease. Following a positive screening result, measurement of plasma ACTH and DHEA-S would help distinguish ACTH-dependent from ACTH-independent causes, guiding imaging and specialist referral for management.

- **Ms. Kruger highlighted CATALYST trial (n=1,057) data showing a substantial prevalence of hypercortisolemia among patients with A1c values >7.5% despite the use of optimal therapy**. Additionally, data showed that the prevalence of hypercortisolism was 24% in the overall population versus 35% in those taking three or more antihypertensives. She emphasized that early identification and treatment – including surgical when appropriate, or individualized medical therapy when surgery is not possible – reduce morbidity and mortality and frequently improve glycemic management. She emphasized that early treatment lowers risks of fractures, cardiovascular events, and death. As such, she urged clinicians to screen for hypercortisolism rather than assume treatment nonadherence when cardiometabolic disease is in fact treatment-resistant.

Quick Take: The role of GLP-1 RAs in addressing substance use disorders, addiction, and Alzheimer's disease

Dr. Ziyad Al-Aly (VA St. Louis Health Care System) discussed the potential for GLP-1 RAs to confer broader neuropsychiatric and neuroprotective benefits. He first cited a large discovery study comparing over 215,000 GLP-1 RA users with more than two million control patients, which found reduced risks of substance use disorders (SUDs), suicidal ideation, psychosis, and Alzheimer's disease (AD) with use of the therapies. Clinical trials thus far have provided mixed but overall encouraging findings; he referenced a 14% reduction in cognitive decline with the use of dulaglutide seen in the REWIND study as well as liraglutide's slowing of metabolic deterioration in mild Alzheimer's disease in the ELAD trial. He expressed great interest in the pending results of the phase 3 semaglutide trials in AD (EVOKE and EVOKE+), both of which are currently underway. He said that clinical studies report associations between the use of incretin therapy and reductions in alcohol consumption, particularly among individuals with obesity. While these findings are preliminary, Dr. Al-Aly suggested that they position GLP-1 RAs as promising therapeutic candidates for neurodegenerative, addictive, and mood disorders, warranting further investigation through large-scale randomized and longitudinal studies.

Residual inflammatory risk and anti-inflammatory strategies in cardiometabolic disease

As the final presentation at CMHC, Dr. Paul Ridker (Harvard University) discussed inflammation as an equal clinically actionable driver of atherosclerotic risk alongside LDL cholesterol. He illustrated how standard high-intensity statin therapy lowers both LDL and hsCRP from an elevated baseline but frequently leaves a persistent inflammatory signal that independently predicts events. He emphasized that "clinicians will not treat what they do not measure" and recommended routine hsCRP assessment alongside LDL-C in both primary and secondary prevention settings.

- **Dr. Ridker reviewed a study (n=15,494) showing that hsCRP strongly predicts cardiovascular death and MACE.** The study showed that patients with residual inflammatory risk had a 1.8-fold higher risk for MACE compared with those with no residual cholesterol or inflammatory risk, with elevated hsCRP conferring increased risk regardless of achieved LDL-C. He discussed the clinical phenotype "SMuRF-Less but Inflamed," which he initially presented at ESC 2025, to describe patients lacking standard modifiable risk factors yet carrying elevated hsCRP and measurable long-term CHD risk. On the JUPITER trial-derived SMuRF-less analysis (n=8,278), statin therapy reduced major cardiovascular events by 38%, with MI reduced by 69%, stroke 47%, and revascularization 39%, supporting treatment of the "SMuRF-Less but Inflamed" phenotype.
- **Turning to therapeutics, Dr. Ridker summarized randomized-trial evidence for targeted anti-inflammatory strategies.** In the CANTOS trial (n=10,066) of canakinumab, 150 mg or 300 mg given every three months significantly reduced major adverse cardiovascular events versus placebo. These benefits occurred without LDL-C lowering and correlated with 35-40% reductions in IL-6 and hsCRP. He also highlighted various ongoing studies targeting the IL-6 inhibition (ZEUS for ziltivekimab, ARTEMIS recruiting for ziltivekimab, and more) and framed these as the next wave of precision anti-inflammatory therapy for residual inflammatory risk.
- **Dr. Ridker closed with a call to action for clinicians and guideline committees.** He urged the universal implementation of one-time hsCRP screening with LDL-C as part of global risk assessment, while emphasizing that diet and lifestyle changes are still critical in reducing the inflammation characteristic of the

Western diet. He highlighted the need to reclassify and consider targeted therapy for SMuRF-less but inflamed patients and use biomarker-driven decision rules to choose intensified lipid lowering versus specific anti-inflammatory approaches.

Benefits of genetic testing and polygenic risk scores in the early detection of cardiometabolic disease

On day #3 of CMHC, Dr. Pradeep Natarajan (Harvard University) reviewed the expanding role of genetic evaluation across cardiometabolic medicine. He began with genetic counseling and the legal context of genetic testing under the Genetic Information Nondiscrimination Act (GINA, 2008), which prohibits health insurers and employers from using an individual's genetic information for coverage, premium, hiring, or firing decisions. He emphasized that growing population-based sequencing has increased uptake of testing by reducing diagnostic uncertainty and addressing patient fears around discrimination, while also clarifying who benefits from intensified prevention and cascade screening.

- **Familial hypercholesterolemia (FH), a genetic condition that affects ~1 in 250 people, was a focal point of Dr. Natarajan's presentation.** He highlighted that carriers of pathogenic FH mutations have greater CAD risk at any given LDL-C level compared with noncarriers. One study (n=20,485) showed that carriers with LDL-C ≥190 mg/dL face a six-fold higher CAD risk, and those with both LDL-C ≥190 mg/dL and a pathogenic FH mutation face a 22-fold higher risk. Not every phenotypic FH has a single-gene mutation, and Dr. Natarajan noted that many LDL-raising pathways (PCSK9, ABCG5/8, etc.) act through LDL-C, reinforcing LDL-lowering as the principal therapeutic aim.
- **Dr. Natarajan also covered other monogenic conditions and risk tools** including sitosterolemia, affecting ~1 in 200,000 people and often presenting in young people. He discussed how sitosterolemia can be unresponsive to statins or PCSK9 inhibitors. He noted that it responds to ezetimibe and targeted dietary restriction of plant sterols with dietitian involvement. He also covered familial chylomicronemia syndrome, affecting ~1 in 300,000 people, which has promising new agent approvals and late-stage candidates, including olezarsen and which received FDA approval in December 2024 and plozasiran which is under FDA review.
- **Dr. Natarajan pointed to polygenic risk scores (PRS) as complementary to monogenic testing, with their ability to materially improve early identification and stratification.** He highlighted one study (n=134,765) which showed that genomic models outperform clinical risk alone for early-life risk recognition and that combining genomic and clinical data increases case prediction across ages 40–75. PRS importance declines with age (HR 3.58 at age 19 vs. ~1.51 at age 70), emphasizing the need for early genetic testing.

--by Kayla Mathieu, Monica Oxenreiter, Jeremy Alkire, Nour Khachemoune, and Kelly Close