[AN HCG OPINION PIECE]

AMERICAN HEART ASSOCIATION

November 16–18, 2024

Revving the engine on cardiometabolic health

Learnings from the European Society of Cardiology (ESC) meeting highlighted the critical role of fat distribution and inflammation in cardiometabolic health. These insights set the stage for the growing prominence of incretin therapies in the fight against cardiometabolic diseases at the American Heart Association (AHA) conference. This evolving knowledge promises to drive significant advancements beyond the scope of just obesity and weight management to truly impact these diseases where they interconnect. At ESC we looked under the hood of what may be driving cardiometabolic health, and at the recent AHA conference we saw signals that cardiologists may be ready to "rev the engine" and explore the full scope of GLP-1 and GIP benefits.

> The spotlight on research that highlights the distribution of incretin receptors throughout the body marks a clear path for impact beyond weight loss

/ Signal 1

A mechanism begins to emerge for incretin therapies

From keynote lectures to cardiology fellow presentations, the connection of inflammation and its attenuation by incretin therapies (GLP-1 RAs and GIPs) was made several times. In support of this leap from ESC speculation to heightened receptivity at AHA was the spotlight on research that highlighted the distribution of incretin receptors throughout the body. This marks a clear path for impact beyond weight loss and

>

> This interplay of visceral fat, kidney and cardiovascular effects—with inflammation at the center—was referenced multiple times... as cardiologists begin to adopt a new mindset in the treatment of HFpEF

the mechanical influence that reduction has on organs like the heart and kidney.

While the presence of incretin receptors in various tissues was explored, the central role of fat deposition was also prominent at AHA, as it was at ESC. However, a clearer picture was coming into focus—heart failure with preserved ejection fraction (HFpEF).

/ Signal 2

A convergence on HFpEF

While evidence has long been established (and continues to grow) for the benefits of incretin therapies on cardiovascular health, specifically for major adverse cardiovascular events (MACE), it was the role in HFpEF where clinicians and researchers began to expand on how visceral fat, inflammation, and heart failure come together. Increases in visceral fat lead to an altered synthesis of adipocytokines, which have antinatriuretic (kidney) and proinflammatory (heart) effects.

These combined effects lead to increased filling pressure while at the same time reducing the ability of the heart to tolerate increased filling, leading to heart failure. This interplay, with inflammation at the center, was referenced multiple times throughout the remaining days of the conference as cardiologists began to adopt a new mindset in the treatment of HFpEF.

> Where end-stage disease is often a key driver for clinical decision making, these end stages are not created equal in all patients

/ Signal 3

Beyond the heart: cardiometabolic health

While there was a convergence on HFpEF, the interconnectedness of the mechanisms described could not be ignored, and while the heart was front and center (as one would expect at AHA), nephrologists, diabetologists, and obesity specialists also had their say. As these clinicians came together to better define the road for cardiometabolic health management, they discussed central drivers of disease, insulin resistance and obesity.

Explored at ESC and now expanded at AHA, clinicians and researchers stressed the level of support for managing these central disease drivers with gliflozins (SGLT2is) and incretin therapies. Key to this management was understanding the patient profile; where end-stage disease is often a key driver for clinical decision making, these end stages are not created equal in all patients.

Consider the patient with diabetes, for whom incretin and gliflozin medications are proven therapies (demonstrating reduced MACE, decreased macroalbuminuria and slowed eGFR decline). This is where patient stratification is most important. With the competing risk of

>

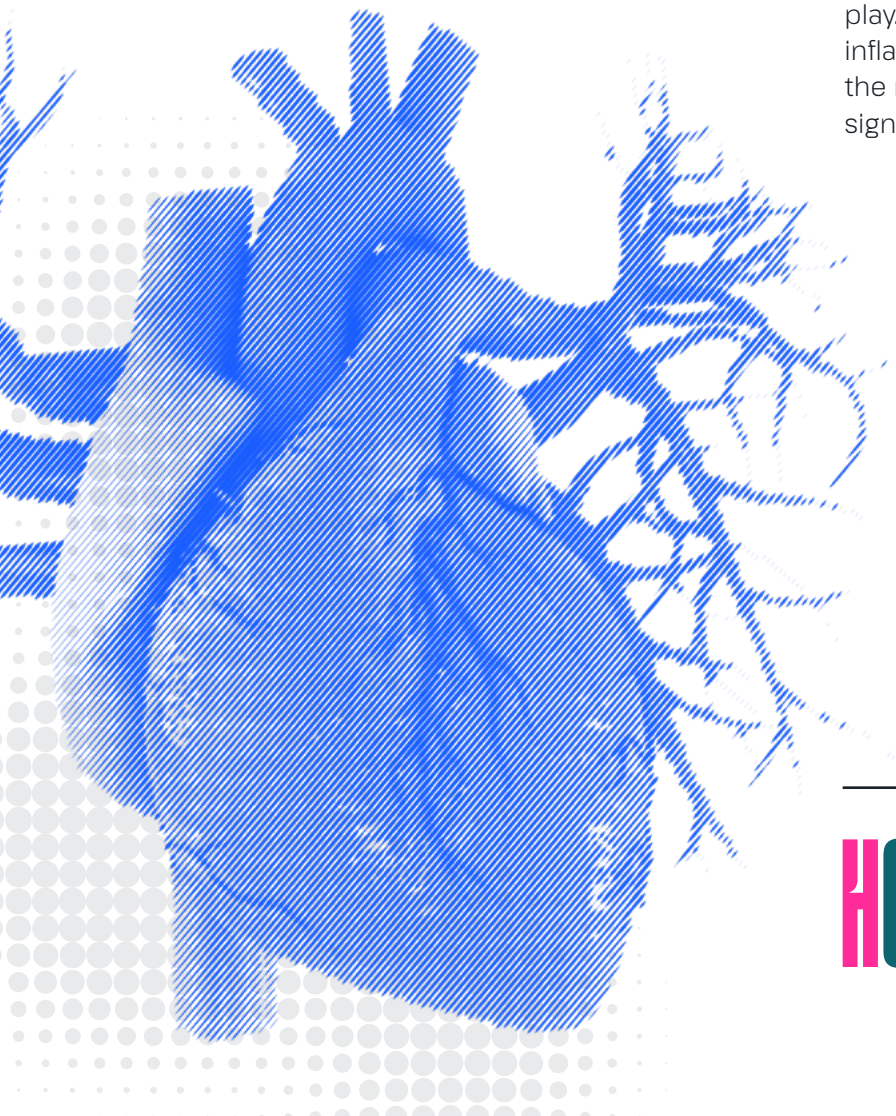
cardiovascular issues and kidney failure in diabetes, patients with normal eGFR levels have a far higher likelihood of death due to a CV event before they progress to kidney failure.

In key gliflozin treatment trials that were enriched with chronic kidney disease patients, it was demonstrated that participants were first afforded better cardiovascular outcomes, which allowed them to see better kidney outcomes.

/ Signal 4

Clarity in the obstacles ahead

Broached at ESC, global inequities in access to treatments were also discussed at AHA, especially in reference to gliflozin and incretin therapies. Highlighted at the conference were search data, where there were fewer searches in low- and middle-income countries for the latest therapies. The search data suggest that those with access are more likely to search for these drugs, and those without access are not bothering to explore.



Some of the barriers cited at ESC were also mentioned at AHA and include financial constraints, differential referrals by race and socioeconomic status, limited health literacy, as well as barriers that may be more specific to the United States (eg, high healthcare costs, suboptimal insurance). Efforts to increase access were discussed and focused on policy solutions like limiting co-pays, increasing rebates, negotiating prices, and public production. Optimism exists among the attendees for affordable options, such as generic medications and reduced costs for insulin.

/ Our insights

Speeding into the sunset

As we peered under the hood just a few short months ago and now are primed and revving our engines, we turn our attention to the horizon. The insights gained from both the ESC and AHA conferences have provided a robust foundation for understanding the intricate mechanisms at play. With a clearer picture of how fat distribution, inflammation, and innovative therapies intersect, the medical community is poised to make significant strides. ■