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EDITORIAL COMMENT

A New Frontier in Heart Failure

Promise and Pitfalls of Primary Prevention

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In this issue of *JACC: Heart Failure*, Sayed et al[1] model how modern cardiometabolic therapies—sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide-1 receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists—might alter projected incident heart failure (HF) in the United States. Using the AHA (American Heart Association) PREVENT (Predicting Risk of cardiovascular disease EVENTs) equations to estimate baseline risk, the investigators project that complete implementation of these agents across eligible populations could yield 10-year numbers needed to treat ranging from 9 to 27 to prevent a single incident HF event.

Although these drug classes have revolutionized management in established HF and high-risk cardiometabolic disease, applying their trial-derived treatment effects to primary prevention at a population level introduces critical methodological assumptions. The effect sizes used in this modeling study draw heavily from secondary prevention trials where primary endpoints centered on HF hospitalizations in symptomatic, high-risk patients. Asymptomatic individuals with stage A HF (or low-risk stage B) exhibit substantially lower baseline event rates. Assuming identical relative risk reductions across lower-risk cohorts inflates projected absolute benefits and yields overly optimistic numbers needed to treat. Validating whether these agents truly prevent incident HF and evaluating their cost-effectiveness demand dedicated randomized controlled trials focused on primary prevention, much like the landmark trials that historically established the foundation for antihypertensive and lipid-lowering therapies.[2,3]

Furthermore, relying on NHANES (National Health and Nutrition Examination Survey) cross-sectional data presents inherent epidemiologic constraints. NHANES lacks longitudinal clinical details that are necessary to operationalize strict medication eligibility even in a hypothetical population health model. To accurately project disease trajectories, investment in a new generation of contemporary and well-phenotyped prospective cohort studies is essential. Such cohorts would allow researchers to measure true incident HF risk in the context of modern guideline-directed background therapies.

There is no doubt that expansion of cardiometabolic options represents a monumental shift. By targeting upstream drivers such as obesity, insulin resistance, and systemic inflammation, these therapies hold genuine promise for reshaping population cardiovascular health. However, translating theoretical efficacy into meaningful population-level risk reduction requires overcoming substantial real-world hurdles, including drug costs, insurance coverage barriers, and persistent health care inequities. Expanding pharmacologic prevention to lower-risk populations also shifts the risk-benefit equation, where minor adverse effects, off-target risks, and long-term financial costs loom far larger than in secondary prevention.

So, can we prevent incident HF today? Unquestionably—yes. Decades of epidemiologic data demonstrate that modifiable risk factors and health behaviors account for more than 80% of cardiovascular mortality and incident disease.[4] Yet, despite all we have learned since the early Framingham cohorts,

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population-level control of hypertension and dyslipidemia remains disappointingly suboptimal. Before assuming that novel pharmacotherapy will single-handedly solve the HF epidemic, we must double down on delivering established, low-cost class 1 primary prevention strategies. Newer cardiometabolic therapies may well mark the dawn of a new era in primary prevention, but realizing that potential requires rigorous clinical trial evidence, precise risk modeling, and a firm foundation built on traditional risk factor control.

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