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EDITORIAL COMMENT

Insulin Resistance and Risk for Incident Heart Failure*

Darren K. McGuire, MD, MHSc,
M. Odette Gore, MD, MSCS

Dallas, Texas

The association between type 2 diabetes mellitus (DM) and heart failure (HF) has been well-described for at least 4 decades (1), with DM increasing the risk of HF by 2- to 6-fold (2). Based on these observations, DM was included as 1 of the criteria for the diagnosis of Stage A HF in the revised American College of Cardiology/American Heart Association (AHA) HF classification scheme introduced in 2001 (3), identifying patients at particularly high risk of developing HF. The classification was modified in 2005 to also include the metabolic syndrome and obesity (4), underscoring the association between insulin-resistant conditions and HF risk.

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In this issue of *JACC: Heart Failure*, Vardeny et al. (5) provide further support for the incremental risk of HF observed in nondiabetic patients with insulin resistance, in this case estimated by the homeostatic model of insulin resistance (HOMA-IR) (6). Among 12,606 participants in the ARIC (Atherosclerosis Risk in Communities) longitudinal cohort study free of DM, HF, or prior myocardial infarction at baseline, and with ascertainment of 1,455 incident HF events for analysis, HOMA-IR was independently associated with incident HF over a median follow-up of >20 years. Of note, the association with incident HF was observed below the threshold of HOMA-IR most commonly used to categorize insulin resistance, and somewhat paradoxically, no further association was evident at higher HOMA-IR values. The present observations are incremental to a growing body of evidence of similar associations with other related metrics of "sub-DM" perturbations of insulin/glucose metabolism, such as impaired fasting glucose, impaired glucose tolerance, and "at risk" glycated hemoglobin (7–9).

Are the new observations true? The short answer is "most likely," based on the analytical power comprising over 1,400 incident HF events observed over >250,000 patient-years of observation; consistency with prior studies associating both type 2 DM and markers of insulin resistance with incident HF across a spectrum of complementary assessments of insulin/glucose metabolism (8); and the biologic plausibility of proposed mechanisms linking insulin resistance with compromised cardiac performance (10). As with incremental atherosclerosis risk evident well below glycemic thresholds used to diagnose type 2 DM (11,12), it is not surprising that the same "pre-diabetic" association applies to HF risk. The cardiac perturbations associated with impaired insulin sensitivity and dysglycemia, including myocardial insulin resistance, impaired myocardial substrate metabolism, coronary endothelial dysfunction, myocardial steatosis with lipotoxicity, and modification of extracellular matrix by cross-linking of advanced glycation end products, are likely all part of a pathobiologic continuum (10). In addition, other concomitants of insulin resistance, such as coronary heart disease, hypertension, and atrial fibrillation, further increase HF risk. In this context, the present observations provide additional support for the HF risk associated with perturbations of glucose/insulin regulation, although some notable limitations must be considered in addition to those discussed by the authors.

GENERAL LIMITATIONS. Although a long study duration is often a strength, it is also a weakness given the absence of interval assessment of key metrics including but extending beyond HOMA-IR, temporally dissociating the exposure from the outcome across a 20-year time horizon. Likewise, there is no ability to assess the influence of a myriad of other factors over time that are associated with both insulin resistance and with HF risk. For example, although interval myocardial infarction was included in the modeling, incident type 2 DM was not, and it is not clear if the HF risk associated with HOMA-IR was driven in part by the subset of patients who progressed to type 2 DM. In addition, hypertension incidence, prevalence, treatment, and control were not evaluated, and there are no interval assessments reported for atrial fibrillation, valvular heart disease, or cardiac function—all precluding the ability to deduce etiologic links.

The analysis strategy also has a number of notable limitations. First, it would be of interest to know the relative prognostic performance of HOMA-IR modeled to predict HF directly compared with fasting glucose (continuous), impaired fasting glucose, hemoglobin A1c, triglyceride to high-density lipoprotein cholesterol ratio (as an indirect

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From the Division of Cardiology, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas. Dr. McGuire is a consultant to Janssen, Genentech, F. Hoffman-La Roche, Takeda, sanofi-aventis, Regeneron, Boehringer Ingelheim, Merck, and Bristol-Myers Squibb; and has been involved in trial leadership for Genentech, F. Hoffmann-La Roche, Takeda, Boehringer Ingelheim, Merck, Bristol-Myers Squibb, AstraZeneca, Daiichi Sankyo, Orexigen Therapeutics, Eli Lilly, GlaxoSmithKline, Eisai, Omthera and NovoNordisk. Dr. Gore has reported that she has no relationships relevant to the contents of this paper to disclose.

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reflection of insulin resistance), and metabolic syndrome, as this information is commonly available in routine clinical care whereas fasting insulin required for HOMA-IR assessment is not. Second, a number of key factors previously associated with incident HF are absent from the multivariable modeling, such as atrial fibrillation, prevalent coronary heart disease, and valvular heart disease (2). Importantly, factors published from prior analyses of this same dataset that independently predict incident HF were not included, such as those in the ARIC HF risk score, with present analyses omitting systolic blood pressure, heart rate, former smoking, prevalent coronary heart disease, and N-terminal pro-brain natriuretic peptide from that model (13), troponin T (14), and numerous others (15–19). Last, to determine the utility of such novel metrics for prognostic use, in addition to demonstrating independence of association in the "best possible" multivariable model, it would be useful to evaluate the incremental prognostic performance of models with versus without HOMA-IR, using assessments of discrimination (e.g., changes in C-statistic) and of accuracy (e.g., reclassification, or net reclassification index) as prescribed in a scientific statement from the AHA (20).

SPECIFIC LIMITATIONS OF HOMA-IR. As discussed by Vardeny et al. (5), there is variability in the literature with regard to the association between HOMA-IR and incident HF, both within studies where other metrics of insulin/glucose metabolism were shown to independently predict HF but HOMA-IR did not (21), and between studies with some demonstrating associations (22) and others not (23). With reported variability of the measure by older age and male sex and with the present loss of association at the higher HOMA-IR levels, 1 possible explanation for such variability of association with HF may be competing risk, as other more potent contributors to HF risk cluster by age, sex, and worsening glycometabolic state.

Although it is not that surprising that HOMA-IR values lower than the threshold associated with DM predict HF risk, the lack of a graded association across the continuum of HOMA-IR values from intermediate to the most abnormal is more challenging to understand. It remains unclear whether this is a limitation of HOMA-IR per se, whether it is a manifestation of competing risk as discussed in the previous text, or whether it may be attributable to limitations of the study and analysis. Introduced in 1985 (6), HOMA-IR is 1 of several derived metrics intended to characterize the glucose/insulin axis. The advantage of HOMA-IR is its relative simplicity compared with insulin/glucose clamp studies and frequently-sampled glucose tolerance tests, requiring only a single blood sample for fasting insulin and glucose for calculation. However, it is a static measurement of a dynamic hormonal system, its mathematical derivation may not perform precisely across populations, and it primarily reflects hepatic insulin sensitivity that most commonly but not always tracks with systemic insulin sensitivity and alterations of glucose disposal (24). Ultimately, it remains to be determined whether any of the methods to estimate insulin resistance will improve prognostication added to or replacing the more conventionally available measures of fasting glucose and hemoglobin A1c.

If true, are the study observations generalizable? The short answer is "probably not," at least not clinically, based almost entirely on the fact that fasting insulin is not commonly measured in usual clinical practice. However, this is not to say that the present study is not valuable. First, the information is an important addition to prior studies, confirming some and extending the observations across a longer time horizon and in an ethnically-diverse contemporary cohort, a bit younger on average than several of the prior studies published. Second, the nexus of dysglycemic states and risk for HF, as highlighted by the American College of Cardiology/AHA Stage A HF classification for over a decade, remains an important public health issue, and studies such as this one maintain and amplify academic and clinical awareness of the problem. Importantly, such awareness may inform focused intensification of therapeutic lifestyle interventions with intent for primary/primordial prevention of HF—a proposition worthy of confirmation in prospective clinical trials of intervention.

Reprint requests and correspondence: Dr. Darren K. McGuire, Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Room E5.726, Dallas, Texas 75235-8830. E-mail: darren.mcguire@utsouthwestern.edu.

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