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EDITORIAL COMMENT

Gated SPECT Myocardial Perfusion Imaging for the Prediction of Incident Heart Failure

An Old Dog Learns a New Trick*

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In the most recent revision of the guidelines for the evaluation and management of chronic heart failure (HF) in adults, the American College of Cardiology and the American Heart Association identified a pre-clinical stage of HF, stage A, which encompasses clinical conditions associated with a high risk of developing HF (1). Examples of such conditions, provided in the guideline document, are systemic hypertension, coronary artery disease (CAD), diabetes mellitus, history of cardiotoxic drug therapy or alcohol abuse, personal history of rheumatic fever, and family history of cardiomyopathy. This staging system, including the pre-clinical stage A, stage B (patients in whom structural heart disease has developed that is strongly associated with the development of HF but who have never shown signs of symptoms of HF), stage C (patients who have current or prior symptoms of HF associated with underlying structural heart disease), and stage D (advanced HF), reflects the clinical progression of HF and implies the potential for specific therapies to be applied to individual stages with the goal of prevention of progression. The inclusion of a pre-clinical stage emphasizes the preventive philosophy in that the identification and treatment of conditions highly likely to progress to overt clinical HF may impact the natural history of HF favorably. It is also important to note that once clinical HF develops, the prognosis for patients remains worse than that of many commonly encountered malignancies despite the many therapeutic advances the field has seen in the past decade (2).

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However, conditions included in stage A are relatively common, and a strikingly large number of individuals could be included in this stage. For example, the estimated total number of adults worldwide with hypertension alone was 957 to 987 million in 2000, and predicted to increase to 1.54 to 1.58 billion in 2025 (3). Thus, strategies to better identify patients with the greatest risk of developing clinical HF are necessary to direct the focused application of preventive strategies.

In this issue of *iJACC*, Nakata et al. (4) report on a subanalysis of the J-ACCESS (Japanese Assessment of Cardiac Events and Survival Study by Quantitative Gated Single-Photon Emission Computed Tomography) database that was designed to determine the value of myocardial perfusion imaging using single-photon emission computed tomography myocardial perfusion scintigraphy (MPS) for predicting major cardiac events in Japanese patients with known or suspected CAD. This subanalysis explored the utility of MPS for predicting the incidence of overt clinical HF in patients with known or suspected CAD. This approach is conceptually quite appealing, because MPS is ubiquitously available and widely used for the assessment of CAD. Furthermore, CAD is currently the most common underlying etiology of HF (5).

The patients included in the J-ACCESS database were age 20 years or older and referred for MPS for known or suspected CAD. Patients with an acute coronary syndrome, valvular or idiopathic cardiomyopathy, New York Heart Association functional class III or IV HF, and notably severe

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liver or kidney disease were excluded. Also excluded from the final analysis were the 223 (4.8%) patients lost to follow-up, and the 375 (8%) patients censured for early (<60 days after MPS) coronary revascularization. In addition, 196 patients with prevalent HF at the time of the initial MPS were also excluded from the subanalysis, leaving 3,835 patients available for analysis. For the outcome measure, the authors chose refractory HF, loosely defined as HF requiring admission and aggressive medical therapy. As is the common, albeit imprecise, practice in HF clinical trials, the diagnosis of HF was established by a combination of clinical symptoms and signs and laboratory and imaging data. It is important to note that the MPS results were unblinded to treating physicians who made the decision to hospitalize the patient. During the follow-up period of 3 years (or until the first event), 71 new-onset (incident) HF admissions occurred. On univariate analysis, patients in whom HF developed were older, with a higher prevalence of hypertension, diabetes mellitus, chronic renal insufficiency, peripheral vascular disease, and prior myocardial infarction (MI) than those in whom HF did not develop. Patients in whom HF developed also had more myocardial perfusion defects (quantitated by summed stress scores [SSS]), lower (but not necessarily abnormal) ejection fraction, and larger left ventricular volumes by gated imaging. Based on the frequency of the primary outcome, the authors appropriately included only the 7 strongest univariate predictors in a Cox proportional hazards regression model. This analysis found chronic renal dysfunction, end-systolic volume index, and SSS to be independent predictors of incident HF. Chronic renal dysfunction was the strongest predictor, with a hazard ratio of 6.22 (95% confidence interval: 2.92 to 13.27). When categorized into tertiles of severity, patients with a higher SSS and larger end-systolic volumes had more incident HF.

These findings are not surprising. They are biologically tenable, and consistent with our current understanding of the interplay between CAD, left ventricular volumes, and incident HF (6). They are also consistent with the increasing recognition of the adverse effect of chronic kidney disease on cardiovascular outcome (7,8). The novel point of great interest in this report relates to the prognostic value of combining data on myocardial perfusion and function (simultaneously assessed by gated single-photon emission computed tomography MPS) with data on renal function in a large cohort of subjects. However, before these results can be put into clinical perspective, some limitations have to be recognized.

First, it is important to note that the original J-ACCESS database recruited patients based on referral for diagnostic stress testing. Although patients with New York Heart Association functional class III and IV HF patients were excluded from the parent study, and this subanalysis further excluded patients with a prior history of HF, the retrospective selection of patients for data analysis results in the inclusion of a population sample whose characteristics are not entirely clear. There is no information on the proportion of subjects whose ejection fraction was abnormal at baseline. It is not clear whether this is a sample of consecutive patients assessed at these many centers, or whether the consented and enrolled patients represent all of the referred patients. These characteristics are important to assess the strength of the database as well as the robustness and generalizability of the results. It is also noteworthy that many of these patients already had structural heart disease in the form of prior MI, left ventricular chamber enlargement, and so on, and therefore fall into stage B of the American College of Cardiology/American Heart Association classification. Thus, therapy, some of which may have preventive effects on the development of HF, was already indicated.

Secondly, some important methodological and analytical issues were present. Because the treating physicians were not blinded to the MPS results, they may well have influenced the physicians' decisions to make the HF diagnosis and hospitalize patients. It is also not clear how the investigators dealt with competing risks of death, MI, and HF. Because only the first event was used as the end point of follow-up, patients who had an MI were no longer followed up for HF. The confounding effect of competing risks is one reason why composite end points are used in clinical trials.

Finally, the term refractory HF is generally reserved for end-stage disease and not for first hospitalization for HF. What the investigators predicted was the occurrence of incident (new-onset) HF, resulting in hospitalization. This was the only HF end point included among the primary end points of the parent study, and the investigators most likely did not have data on the development of all new-onset HF, which is perhaps the more clinically relevant end point, although challenging to capture. Hospitalization for HF is certainly important in clinical and economic terms and has been used as an end point in large clinical trials (9).

Despite these limitations, the context of this analysis, that is, the utility of MPS findings along with renal function data for the prediction of incident HF, with the implicit potential for preventive intervention, is novel and exciting. It provides a signal of yet another potential application of MPS, which despite being a mature imaging modality, continues to be applied to HF and other cardiac patients in new and innovative ways (10). Although the prediction of cardiac death and nonfatal MI in patients with known or suspected CAD is a well-established strength of MPS, its use for the prediction of new-onset HF has not been extensively explored. Although being far from conclusive, the current data from Nakata et al. (4) have at the very least set the stage for future prospective investigation in this area. The clinical implications are important for the possibility of focused preventive strategies. With recent studies exploring its use for measurement of indexes such as left ventricular dyssynchrony (11) and left ventricular shape indexes (12), the potential applications of MPS continue to evolve. Indeed, the old dog continues to learn new tricks.

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