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EDITORIAL COMMENT

Changing the Stage Directions for Heart Failure?*

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The intrepid pilot study of Dr. Mullens and his colleagues invited us to reexamine the directions for current heart failure (HF) staging. Introduced in 2001 (1), the A-B-C-D stages provide a more stable frame of reference than the traditional New York Heart Association (NYHA) functional class I to IV symptoms that confound translation of trials to patients. The stage system also emphasizes 1-way progression of HF failure to Stage C, from which patients and their therapies can never go back—an emphasis designed to maintain the remarkable benefits of guideline-directed therapies even after symptoms are relieved. The recent TRED-HF (Withdrawal of Pharmacological Treatment for Heart Failure in Patients With Recovered Dilated Cardiomyopathy) trial of responders to medical therapy (2) and the current study of super-responders to medical therapy plus cardiac resynchronization (CRT) by Nijst et al. (3) in this issue of the *Journal* have challenged those stage directions, with different results.

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The other major impetus for the stage system was the lesson from trials of asymptomatic ventricular dysfunction that prognosis can be improved for some patients by treating them before onset of HF symptoms (4,5). Increasing distinction is being made between the population-attributable risks for Stage A and specific etiologies of asymptomatic disease that should qualify as Stage B (**Figure 1**). These now include asymptomatic relatives who share pathogenic variants with affected probands, survivors of cardiotoxic chemotherapy, and screened populations with rising natriuretic peptide levels, although not all Stage B criteria have been linked to benefit from added therapies. Perhaps some patients can now go from treated Stage C into remission as a new Stage B, with different maintenance therapy. It should be appreciated also that some patients enter Stage C directly from a newly acquired condition rather than through an asymptomatic stage B.

REVERSING THE DIRECTION OF DISEASE

It has long been recognized that some patients do appear to have clinical resolution of HF with reduced left ventricular ejection fraction (LVEF). Even before beta-blocker use, about 25% of patients with recent onset cardiomyopathy returned to a "normal" LVEF (6). For chronic HF, improvement from low LVEF to better ejection fraction (EF) is common on contemporary therapy (7) but does not necessarily represent "recovery," as biomarkers and event rates remain above normal (8).

In the recent TRED-HF trial, 50 patients were defined as "recovered" dilated cardiomyopathy after LVEF normalized on guideline-directed medications without CRT indication (2). These patients were randomized to undergo rapid sequential withdrawal of diuretics and all neurohormonal antagonists within 14 weeks. Unfortunately, relapse of LVEF, left ventricular (LV) volume, or N-terminal pro-B-type natriuretic peptide occurred in 40% of patients within 6 months. The investigators concluded that complete withdrawal of treatment should not usually be attempted in these patients, reinforcing the current 1-way Stage C direction to continue all guideline-directed medications forever. They did suggest, however, that future work might identify some subgroups with permanent recovery of myocardial function (2).

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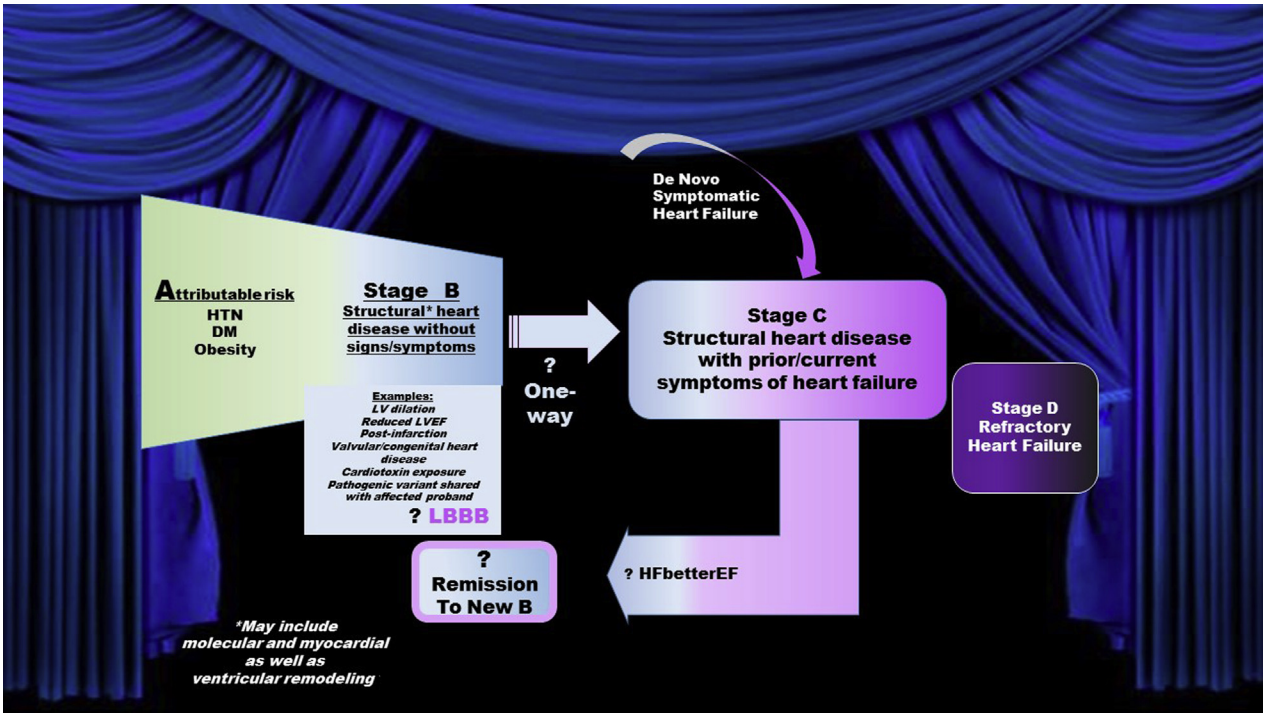
FIGURE 1 Adapted Design of the ACC/AHA HF Staging System



Adapted design of American College of Cardiology (ACC)/American Heart Association (AHA) Heart Failure (HF) staging system to focus on the question of whether some Stage C patients with potentially reversible conditions such as left bundle branch block (LBBB) can return to a new stage B with different implications for prognosis and maintenance therapies. Adapted from Hunt et al. (1).

ARE THERE REVERSIBLE CAUSES OF CARDIOMYOPATHY? Once the ventricle has dilated, does it ever return to normal molecular and cellular structure? Peripartum cardiomyopathy and alcoholic cardiomyopathy are often cited as reversible diseases, but these conditions are increasingly associated with genetic mutations in structural proteins such as truncating titin variants (9). Can abnormal rhythms cause fully reversible cardiomyopathy? Left bundle-branch block (LBBB) in otherwise healthy people confers a 3- to 4-fold higher risk of future HF (10), which could reflect causality of HF by LBBB, or a triangulated association with myocardial disease causing both LBBB and HF. Similar causality questions apply to cardiomyopathy attributed to atrial fibrillation or to frequent premature ventricular contractions, after which neural remodeling may persist, as shown in a canine model (11).

The current study identified 80 patients in whom EF improved after CRT and guideline directed therapies to ≥0.50 with normal LV volumes and no recent hospitalizations, after CRT for LBBB on a background of guideline-directed medications (3). The primary endpoint of LV dilation and secondary endpoint composite of events were rarely reached whether therapies were continued or withdrawn. However, beta-blockers or angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were restarted in 21 of 60 patients, most commonly for hypertension or arrhythmias. It is not known whether or when the left ventricle after "successful" medication withdrawal might eventually redilate. However, these results do suggest that there are patients with dilated cardiomyopathy and successful CRT for intrinsic LBBB in whom monitored withdrawal of one or both recommended medications may be "safe" for at least 2 years. As the investigators suggest, this data supports feasibility of a larger trial.

DESIGNING A RELEVANT WITHDRAWAL TRIAL

LOOK FOR BENEFIT BEYOND FEASIBILITY? The endpoints of both the current trial and the TRED-HF trial were "safety" endpoints of LV structure and function. Why would we accept risk without seeking benefit? It is unlikely that normalized EF or volume

would be further improved by withdrawal of recommended therapies. What could be the positive outcomes of withdrawal? Exercise capacity might improve for some after withdrawal of medications that can decrease heart rate response and inhibit redistribution of blood flow to exercising muscle, but this would not be common or easy to demonstrate.

Patients clearly must have reasons to ask so often whether they can stop their medications, even when cost is not an issue. It is not known how often this reflects patient perception of side effects, most commonly with beta-blockers. Any complex medical regimen may suspend an unwelcome cloud that reminds patients of their illness and mortality. Patient-reported outcomes have high face validity if collected thoughtfully (12). If there is benefit of withdrawal, it may be detected by patient-reported outcomes of specific side effects, quality of life, and self-efficacy.

IDENTIFY THE PATIENTS WHO PERCEIVE A POTENTIAL BENEFIT. Patients in whom withdrawal could be considered would have EF, cardiac dimensions, and neurohormones close to normal levels, off diuretics. The ethics of withdrawal trials have been questioned. Both in the TRED-HF trial and the current study, investigators describe carefully informed consent. Patients willing to accept the risks presumably sought some gain from withdrawal of therapy. Subjects for a new trial should be explicitly selected for their preference to discontinue medications. Surveying and quantitating these reasons would identify not only the appropriate subjects but also the relevant benefits to be measured.

SELECT A THERAPY TO WITHDRAW. This protocol and the TRED-HF protocol both deviate markedly from experienced clinical practice, in which at most 1 neurohormonal antagonist might be withdrawn within 6 to 12 months, except perhaps for women planning pregnancy. In view of the complexity and relevance to clinical practice, it would seem simplest to agree upon just 1 agent to withdraw in a trial, rather than the accelerated sequential design that was tested in these pilot trials, but will not likely translate into practice.

HOW WOULD RESULTS TRANSLATE INTO HEALTH SYSTEMS? Health care for common chronic conditions reflects a trade-off between modest benefit of a fixed intervention multiplied over a large population and larger individual benefits multiplied over an elite patient group fortunate to access personalization of therapies. The former would favor continuation of inexpensive therapies. Personalization to withdraw therapy would increase staff time in busy clinics and costs for repeated monitoring, but could save costs of more expensive medications as long as hospitalizations do not increase later. The calculated financial impact would vary according to how the costs are shared and how patient-reported outcomes are valued.

CONCLUSIONS

Nijst et al. (3) should be commended for piloting this challenge to our current HF stage directions for CRT super-responders. We should continue to probe for specific etiologies that may allow remission from Stage C to a new Stage B, with different considerations for maintenance therapy. Current practice should maintain recommended therapies, however, in patients who become asymptomatic, while considering adjustment if they report persistent side effects. As HF survival increases and new interventions restructure the disease, it will be ever more important to refine our understanding of the different stages and the directions for each.

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