LETTERS TO THE EDITOR

Is the Tolerability of Long-Term Thiazolidinedione Therapy Overstated?

The study by Tang et al. (1) concluded that their retrospective chart review demonstrated the tolerability of long-term thiazolidinedione (TZD) therapy in a diabetic population with established chronic heart failure (HF). Although we applaud their efforts to study this important topic, we believe the data presented are not so clear, and that their conclusions that a large majority of chronic HF patients tolerate these agents are overstated.

First, we believe the definition of TZD-related fluid retention, as a 10-pound weight gain from baseline, in addition to signs or symptoms of volume overload, is far too exclusive of important levels of fluid retention. By using this cut-off, we can be sure that those patients had severe fluid retention. However, we do not know the number of other patients who had important levels of weight gain or edema and who were missed by the investigators’ likely insensitive criteria. Heart failure guidelines recommend action when weight increases by 2 to 4 pounds depending on how quickly it occurs.

Second, we disagree that the reported incidence of fluid retention of 17.1% is an overestimate due to selection bias. In fact, it is probably an underestimate. Obtaining data from a chart review can only lead to under-reporting the true incidence of fluid retention and adverse events. Furthermore, the majority of patients had stable New York Heart Association functional class I or II heart failure where TZD therapy is not contraindicated. (The incidence of edema [with or without weight gain] in TZD randomized controlled trials ranged between 2% and 15% [2,3].)

Third, the intolerability of these agents in this population is further illustrated by the fact that 31% discontinued TZD therapy within one year of initiation (most due to fluid retention), whereas the rate of discontinuation was far <0.1% in randomized controlled trials (2,3). Also of concern is that 26% of patients who met the criteria for fluid retention were hospitalized. Finally, we are concerned that both the data and the discussion regarding the incidence of fluid retention and characteristics of the non-TZD control group were very limited. This data would likely provide more insight into the true tolerability of these medications in this population.

In summary, we agree that further studies are needed to examine the relationship between TZD-related fluid retention and patient cardiac status. We believe this study and its conclusions should be interpreted very carefully, as the true risks of adverse effects related to volume expansion are likely understated.

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REPLY

We appreciate the comments by Dr. Malone and his colleagues regarding our recent report on the characteristics of fluid retention after initiation of thiazolidinedione (TZD) therapy in diabetic patients with established chronic heart failure (HF). In our report, we fully acknowledged that fluid retention does occur with TZD use in patients with established HF, and until we have more experience with this drug class “there is little doubt that TZDs...should be avoided in highly symptomatic patients with HF who are already having difficulty maintaining a balanced volume status” (1). Although we recognize that the definition of fluid retention is arbitrary, there is currently no gold standard for “important levels of fluid retention.” We chose the 10-pound limit to account for the long-term, nonedematous weight gain associated with TZD use that has been previously reported in the literature (2). It is noteworthy that 68% of patients received 12 months of TZD therapy without demonstrating significant fluid retention. Also, 20% of patients in our cohort had TZD discontinued owing to reasons other than edema. Until we have more objective measures to quantify the degree of fluid retention (such as sequential plasma volume analyses or surrogate markers like plasma B-type natriuretic peptide levels), observations of this nature can only rely on “insensitive” clinical criteria.

The selection bias in this retrospective observational study originated from the referral nature of the specialized HF clinic, where a large number of patients are seen specifically because of fluid retention following TZD initiation. Meanwhile, the non-TZD user “control” group in our study was used in a nested case-controlled manner to illustrate the discrepancy in clinical presentation between TZD-related fluid retention and what we commonly consider to be HF exacerbation independent of TZD use. As stated in our discussion, the incomplete nature of retrospective data collection precludes any statistical comparisons between groups (including drug tolerability) so as to avoid false inferences. Although we agree that any association between TZD-related fluid retention and patient’s cardiac status should be interpreted with caution, we argue against the proscription of this drug class in patients with HF simply by equating fluid retention with HF exacerbation. What is more alarming to us is the paucity of published reports in this area (limited to sporadic case reports) over the past few years despite widespread recognition of the metabolic syndrome and the potential benefits of this class of drugs in such patients. The true incidence of TZD-related fluid retention and TZD tolerability in patients with HF can only be determined by well-designed prospective studies specifically addressing patients with HF.
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Is Diastolic Heart Failure Synonymous With Heart Failure With Preserved Ejection Fraction?

In his excellent Editorial Comment, Dr. Zile states that “heart failure with a preserved ejection fraction” and “diastolic heart failure” are synonymous (1). Respectfully, I must disagree. Not all patients with diastolic heart failure have left ventricular hypertrophy. Therefore, the general applicability of the study cited supporting the equivalency of the two terms might be limited because all patients in that study had echocardiographic evidence for left ventricular hypertrophy, and diastolic dysfunction is generally accepted to precede hypertrophy. In our early experience about one-third of patients with heart failure with a preserved ejection fraction had explanations for the signs and symptoms of failure other than diastolic dysfunction, predominately right heart failure due to pulmonary disease and regurgitant valvular heart disease (2). The nonspecific nature of the symptoms of heart failure and iatrogenic volume overload were also noted. It is unclear to what extent stricter diagnostic criteria for heart failure would affect these findings, and I believe that our initial criteria would still lead most clinicians to the diagnosis of heart failure. Furthermore, a patient with heart failure due to chronic, severe mitral regurgitation with an ejection fraction of 40% or even 50% has predominately systolic, not diastolic, heart failure. Therefore, I believe it is best to conclude that patients with “diastolic heart failure” form a subgroup of patients with “heart failure with a preserved ejection fraction.”

Until a uniformly accepted and therapeutically meaningful measure of diastolic dysfunction is defined, diastolic heart failure is in many ways a diagnosis of exclusion. The value of initially using the term “heart failure with preserved, or normal, ejection fraction” underscores the need to define left ventricular function in virtually all patients with heart failure (3) as well as the need to carefully eliminate other cardiac and noncardiac possibilities from the patient’s signs and symptoms. After eliminating other possibilities, I agree that the term “diastolic heart failure” seems most appropriate, and I hope, as Dr. Zile does, that accepting the term promotes the investigative efforts that are long overdue for these patients.

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REPLY

One of the first, if not the first, study to use the term “diastolic heart failure” was by Dr. Kessler in 1988 (1). His report was truly innovative and showed remarkable insight into a difficult clinical problem. I enthusiastically agree with Dr. Kessler’s point of view and I am grateful to receive his support. In his letter to the editor of the JACC, he raises three important issues: 1) some patients with diastolic heart failure do not have left ventricular (LV) hypertrophy; 2) the diagnosis of diastolic heart failure should exclude patients with noncardiac (such as pulmonary disease) and other cardiac (such as mitral stenosis, regurgitant valve disease) causes of heart failure; and 3) left ventricular (LV) function must be measured in every patient with heart failure.

In the study that Dr. Kessler refers to in his letter (2), only about one-third of the patients had LV hypertrophy defined as LV mass ≥125 g/m². However, all patients had concentric hypertrophic remodeling characterized by a decreased LV end diastolic volume/mass ratio or LV end diastolic dimension/wall thickness ratio or an increased relative wall thickness. I believe that a majority of patients with diastolic heart failure in fact have either concentric remodeling or some other evidence of myocardial or cardiac structural alterations such as an enlarged left atrium. With or without concentric remodeling, if a patient truly has objective signs and symptoms of heart failure and noncardiac and other cardiac causes have been ruled out, then heart failure with a normal ejection fraction (EF) is caused by diastolic dysfunction and the appellation “diastolic heart failure” should be applied.

Dr. Kessler correctly points out that in patients with primary right heart failure (caused by chronic lung disease, pulmonic stenosis, tricuspid regurgitation) or mitral stenosis or left-sided regurgitant valvular disease, this can result in heart failure with a normal EF. I am grateful that Dr. Kessler emphasized this point because our previous publications (2,3) did not make it explicitly clear that we had in fact excluded patients with noncardiac and other cardiac causes of heart failure in this study patient cohort.