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EDITORIALS/VIEWPOINTS

# Love of Angiotensin-Converting Enzyme Inhibitors in the Time of Cholera

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The highly acclaimed novel *Love in the Time of Cholera* by the Nobel Prize-winning Colombian author Gabriel García Márquez is a brilliant exploration of the complexity of love, specifically the struggle between our attraction to the ideal and depraved dimensions of love and the importance of passion and societal expectations in defining the attributes and personal rewards of love (1). Lovesickness is viewed as an illness, just as cholera is defined (from an intriguing Spanish perspective) as a passion, separate from its conventional consideration as a disease. The flow of the story (which evolves over decades) can be viewed simplistically, but that would be a mistake. The author himself has warned readers "you have to be careful not to fall into my trap" (1).

Why speak of a novel focused on the complexity of love in a medical journal devoted to heart failure? Because in 2016 the heart failure community is struggling with how to define its long-standing romance with and affection for conventional inhibitors of the renin-angiotensin system. For the past 30 years, we have assumed that angiotensin-converting enzyme (ACE) inhibitors (or alternatively, angiotensin receptor blockers) have been the cornerstone of the treatment of heart failure. However, it is not clear that this affection has been based on anything more than an ancient memory of the excitement that we experienced when ACE inhibitors led to what we then regarded (in 1987) as a dramatic effect on mortality in a small, short-term trial in patients with end-stage heart failure (2). Following that first passionate moment 3 decades ago, there has been a steady stream of positive trials of ACE inhibitors in cardiovascular disease (3–5), but viewed from the perspective of 2016, the long-term benefit of high-doses of ACE inhibitors and angiotensin receptor blockers on cardiovascular mortality in heart failure has been modest. Even under the optimal conditions of a clinical trial, target doses of conventional inhibitors of the renin-angiotensin system led to only a small relative reduction (5%-18%) (compared with placebo) in the risk of cardiovascular death in patients with chronic heart failure and a reduced ejection fraction, (compared with placebo) (6–9), and clinical trials have struggled to identify a favorable effect of these drugs on symptoms or quality of life (10–13).

Nevertheless, we are required (by both guideline and quality of care metrics) to maintain our patients on treatment with an ACE inhibitors or angiotensin receptor blocker. We generally strive to meet those expectations, but are we really doing any good? Most patients with heart failure and a reduced ejection fraction are receiving doses of an ACE inhibitor or an angiotensin receptor blocker that are far smaller than the doses that were demonstrated in clinical trials to have even a modest effect on the risk of death (14–19). The benefits of renin-angiotensin inhibitors used at currently prescribed doses have never been clearly defined, and it is certainly possible that our medical practice satisfies the needs of administrators more than it does the needs of patients.

What is a physician to do if a patient is taking low to medium doses of an ACE inhibitor or angiotensin receptor blocker? Too many prescribers are content to do nothing and continue to prescribe these drugs in doses

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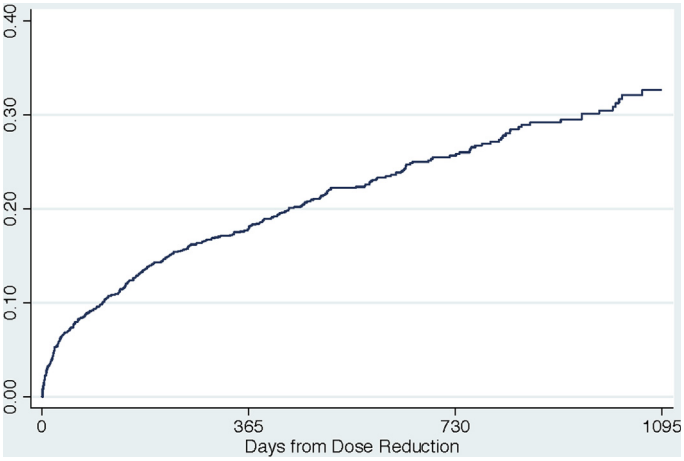
that are well tolerated but may provide little benefit. Guideline documents encourage prescribers to titrate doses of ACE inhibitors and angiotensin receptor blockers to the target doses achieved in clinical trials (20,21), but we do not do so very often. Perhaps, this lack of titration is related to the disappearing time that we spend with patients, our current emphasis on measuring rather than doing things, or perhaps, it is attributable to a potentially unjustifiable fear of side effects (especially hypotension and renal insufficiency). However, in truth, there is little clinical trial evidence that up-titration of conventional inhibitors of the renin-angiotensin system achieves our expectations of benefit from these drugs.

In the ATLAS (Assessment of Treatment with Lisinopril and Survival) trial (22), an 8-fold increase in the dose of the ACE inhibitor lisinopril failed to provide important incremental benefits with respect to all-cause or cardiovascular mortality. Such substantial increases in dose were accompanied by only an insignificant 7% relative decrease in the risk of death but were associated with a meaningful increase in the risk of hypotension, renal insufficiency, and hyperkalemia (22,23). In the HEAAL trial (Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan) (24), a 3-fold increase in the dose of the angiotensin receptor blocker losartan failed to provide important incremental benefits with respect to all-cause or cardiovascular mortality. Again, such marked increases in dose were accompanied by only an insignificant 6% relative decrease in the risk of death but were associated with a meaningful increase in the risk of hypotension, renal insufficiency, and hyperkalemia. These disappointing results are consistent with the finding that the intensification of inhibition of the renin-angiotensin system by the addition of angiotensin receptor blockers or direct renin inhibitors to ACE inhibitors produces few incremental benefits (7,25). Despite the drumbeat of encouragement to get clinicians to achieve maximal inhibition of the renin-angiotensin system, we have given them few evidence-based reasons to follow such advice. The addition of beta-blockers and mineralocorticoid receptor antagonists have served us well, entirely because of their own effects to reduce mortality in heart failure, but ironically, their benefits has probably allowed us to ignore the limitations of current approaches to inhibiting the renin-angiotensin system.

**FIGURE 1** Rate of Cardiovascular Death After Reduction of Enalapril Dose




Kaplan-Meier time-to-event plot is shown for the occurrence of cardiovascular death following a reduction in dose of the ACE inhibitor enalapril to a level <20 mg daily in 1,755 patients with mild-to-moderate symptoms of heart failure enrolled in the PARADIGM-HF trial. All patients were receiving diuretics; nearly all patients were receiving beta-blockers, and the majority were receiving mineralocorticoid receptor antagonists. ACE = angiotensin-converting enzyme; PARADIGM-HF = Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure.

Why should we care about the disappointing results seen in trials where we have made a major effort to up-titrate the doses of inhibitors of the renin-angiotensin system? Recent experience indicates that cardiovascular mortality in heart failure remains unacceptably high, even in patients who are clinically stable and have only mild symptoms (26). In particular, patients in the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) trial with only mild-to-moderate symptoms who could not sustain target doses of ACE inhibitors had an 18% annual risk of cardiovascular death following dose reduction, even when they were being concurrently treated with beta-blockers and mineralocorticoid antagonists (**Figure 1**). (This author was 1 of the 2 co-principal investigators and served as a consultant to Novartis for the study.) Interestingly, most of these deaths were sudden deaths, and many occurred in patients already treated with an implantable cardioverter-defibrillator (27). Therefore, it makes little sense to continue to prescribe low doses of inhibitors of the renin-angiotensin system to such individuals in the hope that these will be sufficient to achieve our therapeutic goals, and it makes even less sense to encourage physicians to utilize higher doses that they do not readily prescribe and that we have little evidence to support.

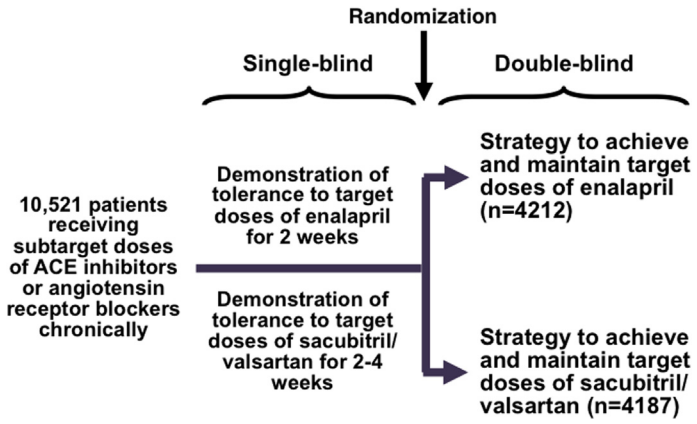
Recent studies and analyses indicate that there is new hope for resolution to our current confused love

affair with ACE inhibitors and angiotensin receptor blockers. In the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) (26), patients who had been largely treated with subtarget doses of inhibitors of the renin-angiotensin system for long periods of time but were shown to be able tolerate target doses of the ACE inhibitor enalapril for 2 weeks were randomized to receive long-term treatment with target doses of enalapril or to be switched to the angiotensin receptor neprilysin inhibitor sacubitril/valsartan for periods of up to 5 years (**Figure 2**).

During the course of follow-up, approximately one-half of the patients had their doses of study medication reduced for reasons similar to why patients fail to be up-titrated to target doses of inhibitors of the renin-angiotensin system in the first place: hypotension, renal insufficiency, hyperkalemia, and cough. As expected, the trial's requirement of having patients take target doses of the study drugs was achieved only temporarily in a substantial proportion of patients, but did the decision to reduce the dose of study medication influence the finding that sacubitril/valsartan was superior to enalapril on reducing the risk of cardiovascular death? Vardeny et al. (28) recently showed that the advantages of sacubitril/valsartan over those of enalapril were maintained in patients requiring a dose reduction. As shown in **Figure 3**, patients whose dose of study medication was reduced during the trial had a risk of cardiovascular death that was increased compared with those who were able to sustain target doses of the study medications; however, that risk was reduced more when patients were treated with lower doses of sacubitril/valsartan than with lower doses of enalapril. The magnitude of the superiority of sacubitril/valsartan compared to that of enalapril with respect to cardiovascular death in patients with a dose reduction was similar to those without a dose reduction (20% reduction in risk with $p < 0.01$ in both subgroups). An intriguing benefit was the ability of sacubitril/valsartan to reduce the risk of sudden death in clinically stable patients with only mild symptoms, including those with an existing implantable cardioverter-defibrillator (27).

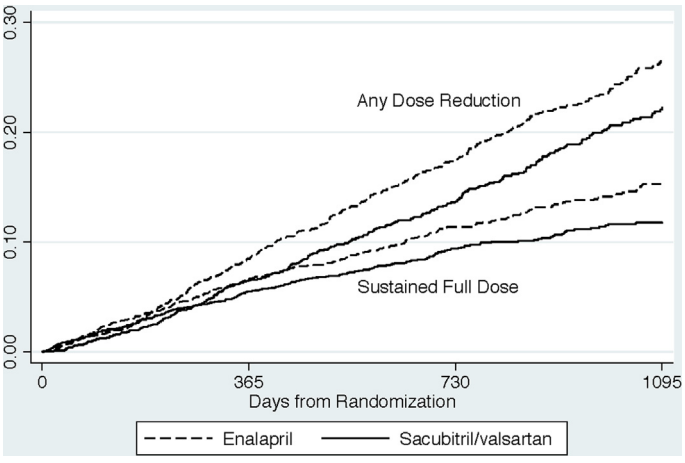
Did patients who were switched to sacubitril/valsartan experience more frequent adverse events than those maintained on enalapril? As reported by McMurray et al. (26), patients switched to sacubitril/valsartan were more likely to report hypotension requiring dose reduction but were less likely to experience meaningful degrees of renal insufficiency and hyperkalemia requiring discontinuation of study medication. These findings are in contrast to the

**FIGURE 2 Design of PARADIGM-HF**




A total of 10,521 patients with heart failure treated long-term with subtarget doses of ACE inhibitors or angiotensin receptor blockers were enrolled with the intent that one-half be up-titrated to target doses of an ACE inhibitor and that the other one-half be treated with target doses of sacubitril/valsartan. Randomization was preceded by a run-in period, during which patients were shown to tolerate target doses of each study medications for a few weeks. Abbreviations as in **Figure 1**.

**FIGURE 3 Cardiovascular Death**




In the PARADIGM-HF (Efficacy and Safety of LCZ696 Compared to Enalapril on Morbidity and Mortality of Patients With Chronic Heart Failure) trial, Kaplan-Meier time-to-event curves were constructed for the occurrence of cardiovascular death, using a time-varying covariate, updated when a dose change occurred from the maximum dose to any other lower dose level. Participants were categorized according to whether or not they received the target dose of study drug for the entire duration of the double-blind portion of follow-up; >40% of the patients in both arms of the trial received less than target doses (shown in upper 2 curves identified as **Any Dose Reduction**). The risk of a cardiovascular death was 20% lower in patients who received less-than-target doses of sacubitril/valsartan than in those who received less-than-target doses of enalapril and 20% lower in patients who received target doses of sacubitril/valsartan than in those received target doses of enalapril for the duration of follow-up ($p < 0.01$, comparison between sacubitril/valsartan and enalapril in both analyses). Abbreviations as in **Figure 1**.

results of the ATLAS and HEAAL trials, which showed that up-titration to very high doses of ACE inhibitors was associated with more renal insufficiency and hyperkalemia, a particularly disconcerting finding, as these high doses did not meaningfully reduce the risk of cardiovascular death (compared with low doses) (22–24).

Even if these down-titration data were ignored, it is important to understand the design and implications of the PARADIGM-HF trial from a clinical practice perspective. When viewed from the start of the trial (i.e., the time that patients provided informed consent) (**Figure 1**), the results of the study indicated that, in patients treated chronically with subtarget doses of ACE inhibitors and angiotensin receptor blockers, long-term treatment aimed at achieving target doses of sacubitril/valsartan was superior to treatment aimed at achieving target doses of enalapril, with respect to both all-cause mortality and clinical disease progression (26,29). Accordingly, patients currently taking a subtarget dose of an ACE inhibitor or an angiotensin receptor blocker should be switched to comparable doses of sacubitril/valsartan followed by target doses of the drug (rather than be up-titrated to target doses of only an inhibitor of the renin-angiotensin system). Doing so provides substantial incremental survival benefits, and this advantage is accompanied by a lower risk of discontinuation due to adverse events related to inhibition of the renin-angiotensin system. With respect to the occurrence of renal insufficiency and hyperkalemia, patients appear to tolerate higher doses of a renin-angiotensin system inhibitor when it is combined with a neprilysin inhibitor than when it is used alone (30).

Does this mean that we are now prepared to end our decades-long love affair with ACE inhibitors? Some have suggested that the results of PARADIGM-HF will force writers of guidelines to abandon their current class 1A recommendation for ACE inhibitors and angiotensin receptor blockers, but such a position fails to appreciate the fact that sacubitril/valsartan is simply a new approach to inhibiting the renin-angiotensin system. The question is not whether the new drug completely replaces ACE inhibitors and angiotensin receptor blockers; the question is when is it appropriate to use current inhibitors of the renin-angiotensin system and when is it appropriate to switch patients to angiotensin receptor neprilysin inhibition? We are not in the midst of an existential dilemma; instead, we now have sufficient evidence to grant our highest level of recommendation to all approaches we have of inhibiting the renin-angiotensin system.

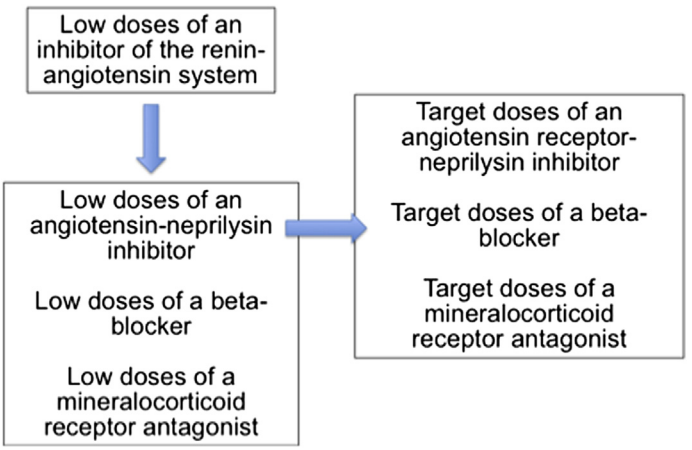
In a patient with newly diagnosed heart failure who has never taken an ACE inhibitor or angiotensin receptor blocker, we have insufficient data to recommend initiation of treatment with sacubitril/valsartan. The early responses to initiation of treatment with an inhibitor of the renin-angiotensin system remain unpredictable; some patients demonstrate a marked hypotensive effect even with the lowest dose of the shortest-acting agent. Therefore, it is always prudent to initiate treatment cautiously with a very low dose of a renin-angiotensin inhibitor, and some may argue that there is no reason to complicate matters by adding the hypotensive actions of a neprilysin inhibitor during the commencement of treatment. In any case, once we have established that the patient can tolerate a low dose of an ACE inhibitor or angiotensin receptor blocker, we need to define our next steps. Before we had the results of the PARADIGM-HF trial, the available evidence supported titrating the inhibitor of the renin-angiotensin system to the target doses studied in clinical trials, even though the reasons for doing so was primarily to reduce the risk of hospitalization for heart failure (22,24). Now, in light of the findings of PARADIGM-HF, it seems best to switch the patients on a low dose of an ACE inhibitor or angiotensin receptor blocker to a comparable low dose of sacubitril/valsartan. Once neprilysin inhibition is added, we can then move forward toward our goal of achieving evidence-based target doses of the drug; the reasons for doing so are to reduce both the risk of cardiovascular death as well as the risk of hospitalization for heart failure (26). If a patient cannot be switched to low doses of sacubitril/valsartan because of symptomatic hypotension, then continued treatment with only an ACE inhibitor or angiotensin receptor blocker seems justified. A serious risk of life-threatening angioedema in African-American patients (which characterized the experience with earlier neprilysin inhibitors in hypertension [31]) was not seen in the PARADIGM-HF trial, even though a large proportion (26%) of the patients enrolled in the United States were black; further studies concerning this risk are under way.

The approach of initiating treatment with a low dose of an ACE inhibitor followed by an early switch to low doses of an angiotensin receptor neprilysin inhibitor, followed by up-titration of sacubitril/valsartan to target doses is consistent with the totality of evidence we currently have for the use of neurohormone blockers in the management of chronic heart failure. During the past 3 decades, we have learned that interfering with multiple systems as early as possible has important advantages and that the addition of a low dose of a new

neurohormone inhibitor is superior to the decision to delay the start of inhibition of an enzyme or system until an already prescribed inhibitor is titrated to target doses (**Figure 4**). We start low doses of a beta-blocker or mineralocorticoid antagonist, even in patients receiving low dose of an inhibitor of the renin-angiotensin system, because such a strategy provides immediate benefits that cannot be replicated by up-titration of an ACE inhibitor (32,33); we certainly do not delay the start of treatment with a beta-blocker until we have achieved target doses of the ACE inhibitor. Furthermore, the magnitude of the benefits of new pharmacological interventions is not optimized by previous titration of neurohormone antagonists to target doses (34–36). Now that the PARADIGM-HF trial has demonstrated the need to inhibit neprilysin, we should do so as early as possible and not delay until we have achieved target doses of a conventional inhibitor of the renin-angiotensin system. Differences in outcome are apparent within 30 days of initiation of neprilysin inhibition (29). A decision to prescribe target doses of an ACE inhibitor or angiotensin receptor blocker before initiating treatment with a neprilysin inhibitor ignores the fact that the early addition of neprilysin inhibition is accompanied by greater benefits on cardiovascular death (especially sudden death) and fewer discontinuations due to renal insufficiency and hyperkalemia.

In *Love in the Time of Cholera*, the female protagonist is enticed to choose between 2 types of love, the need to decide between a socially lauded relationship that is disloyal to her and a passionate relationship that carries its own significant limitations. Some cardiologists may think that the advent of sacubitril/valsartan forces us to make a similar choice for our patients, but the available evidence suggests that the conflict actually does not exist. Over the past 3 decades, we have learned how to choose the appropriate inhibitor of the renin-angiotensin system for our patients when our only choices were ACE inhibitors and angiotensin receptor blockers. Now that we have 3 ways of inhibiting the renin-angiotensin system, we can learn how to initiate therapy with 1 approach with the understanding that we need to move rapidly to a new third approach in order to optimize clinical outcomes for our patients. Unlike the choices we often need to make in adult relationships, at least with respect to the treatment of heart failure, we do not need to abandon our long-standing comfort with our traditions; we just need to understand how to move the relationship to a happier ending.

**FIGURE 4 Approach: Low-Dose ACE Inhibitor Then Angiotensin-Neprilysin Inhibitor Plus Neurohormone Modulators**




Approach of initiating treatment with a low dose of an inhibitor of the renin-angiotensin system (ACE [angiotensin-converting enzyme] inhibitor or angiotensin receptor antagonist) followed by an early switch to low doses of an angiotensin-neprilysin inhibitor and the addition of low doses of other neurohormone modulators, followed by up-titration of all neurohormone modulators to target doses. The decision to initiate treatment with a low dose of a new neurohormone inhibitor was superior to a decision to delay the start of inhibition of an enzyme or system until an already prescribed inhibitor was titrated to target doses. Such a strategy provides benefits that cannot be replicated by first up-titrating the dose of an ACE inhibitor to a target dose.

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**KEY WORDS** angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, heart failure, neprilysin, sacubitril/valsartan