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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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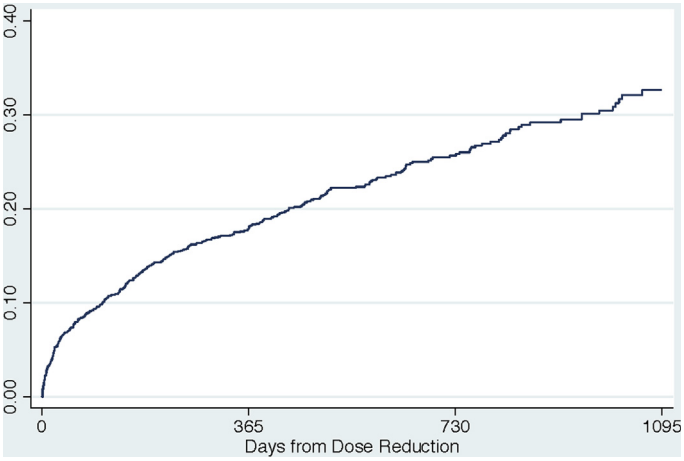
that are well tolerated but may provide little benefit. Guideline documents encourage prescribers to titrate doses of ACE inhibitors and angiotensin receptor blockers to the target doses achieved in clinical trials (20,21), but we do not do so very often. Perhaps, this lack of titration is related to 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