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Review

Inferential characterization of the dose-response relationships of neurohormonal antagonists in chronic heart failure: A novel approach based on large-scale trials with active comparators

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ABSTRACT

Background: Current guidelines for the treatment of heart failure strongly recommend the use of inhibitors of the renin-angiotensin system and sympathetic nervous system in all patients with a reduced ejection fraction who can tolerate these drugs. Yet, there is no consensus about the efficacy of low doses of these drugs or the likely shape of the dose-response relationship for these agents.
Methods: Inferences were made by examining the effects of drugs in placebo-controlled trials before the protocol-specified opportunity for uptitration and by reassessing the results of large-scale trials with active comparators that inadvertently produced different intensities of neurohormonal blockade.
Results: In the case of inhibitors of the renin-angiotensin system, low starting doses appear to be effective in many patients, and 3–5 fold increases in dose do not have a mortality advantage over low doses. By contrast, in the case of beta-adrenergic blockers, although low starting doses appear effective in improving outcomes, achievement of target doses may yield substantial incremental mortality benefits, even such doses are accompanied by only small additional decreases in heart rate.
Conclusion: When treating patients with heart failure to reduce mortality, the totality of evidence supports a relatively flat dose-response relationship for inhibitors of the renin-angiotensin system but a steep dose-response relationship for beta-adrenergic receptor blockers.

Current guidelines in the US and Europe strongly recommend the use of inhibitors of the renin-angiotensin system and sympathetic nervous system to prolong life in patients with chronic heart failure and a reduced ejection fraction [1,2]. These recommendations suggest that both classes of drugs be initiated at low doses and that the drugs be progressively uptitrated in a timely manner until patients are receiving the target doses that were shown to be effective in the large-scale randomized trials that demonstrated a survival benefit [3].

However, in clinical practice, most patients with heart failure are not receiving target doses, and instead, they are commonly treated with low-to-moderate doses, even if they are able to tolerate higher doses [4–9]. Are these low doses effective at all? Do higher doses provide worthwhile incremental benefits? Must physicians make all reasonable efforts to achieve target doses for maintenance therapy if patients are doing well? Most physicians assume that little is known about the dose-response relationships for neurohormonal antagonists, and therefore, they have considerable latitude in selecting a dose for individual patients in a manner that is in compliance with current guidelines. Yet, we actually know more about dose-response relationships for the use of inhibitors of the renin-angiotensin and sympathetic nervous systems in chronic heart failure than most physicians realize.

1. Inferential characterization of dose-response relationships

The classical approach to determining the dose-response relationship for any drug is to conduct a multiple-arm, parallel-group clinical trial, ideally with a placebo comparator, which would evaluate a wide range of different doses of the same drug for periods of time long enough to assess the impact on major adverse clinical events. Such a design is commonly used for drugs in early phase development, but typically, early trials are short-term studies that focus on a biomarker as the primary endpoint. The clinical outcomes that are collected in these early-phase trials are difficult to interpret because of the small numbers of events. By contrast, large-scale placebo-controlled outcomes trials in heart failure generally examine the effects of only a

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single target dose. When trials have been conducted to evaluate the effects of several doses of the same drug in a single study, they have often compared doses at extreme ends of the dosing range and have not included a placebo comparator. Hence, these trials have yielded little useful information about the efficacy of low doses or about the shape of the dose-response relationships.

Nonetheless, it is possible to make reasonable inferences regarding dose-response relationships from the trove of available evidence, using two novel approaches. *First*, in certain large-scale placebo-controlled trials, one can estimate the efficacy of low starting doses of drugs by focusing on the relatively brief period of time that follows randomization but before the study protocol provides an opportunity for uptitration. This window is typically about 1–2 months in duration and yields only a small number of events; yet, its reliability is enhanced because it is interpreted in the context of the effects seen over the entire duration of follow-up. *Second*, one can examine the results of large-scale long-term trials that were designed to compare two different drugs that have substantially overlapping mechanisms of action. These trials may have been originally designed with the belief that the active comparators produced pharmacologically equivalent effects. Yet, when this assumption was not fulfilled, the trials inadvertently provided evidence about the relative efficacy of higher-intensity versus lower-intensity neurohormonal blockade, and thus, allowed for inferences about the dose-response relationships.

Importantly, neither of these inferential approaches relies on observational methods or cross-study comparisons, which are plagued by unmeasured confounders. When these methodological approaches are used, the analysis maintains the protection of randomization, and thus, allows for reasonably unbiased conclusions, as long as the comparisons can be interpreted in a clinical context. In contrast, observational methods that rely on comparisons of groups that are defined by a dose that is achieved post-randomization are often difficult to interpret. Nevertheless, when such biases can be shown to be minimal, these methods can yield information that supports a framework that has been built primarily on evidence from randomized controlled trials.

2. Dose-response relations for inhibitors of the renin-angiotensin system

Two randomized placebo-controlled trials (the CONSENSUS and SOLVD Treatment trials [10,11]) have demonstrated a favorable effect of an angiotensin converting-enzyme (ACE) inhibitor on survival in patients with chronic heart failure, and both trials were carried out with a single agent — enalapril. The achieved doses in the two trials were approximately similar (16–18 mg daily), and thus, it would seem reasonable that patients with chronic heart failure be treated with enalapril at 20 mg daily. Although higher doses can be prescribed, they are generally poorly tolerated in severely ill patients, and there is little controlled clinical trial experience with such high doses for durations exceeding six months [10]. Many believe that high doses of angiotensin receptor blockers provide mortality benefits that are equivalent to those of high doses of ACE inhibitors, but it should be noted that the active comparator trials (e.g., VALIANT and ONTARGET [12,13]) that demonstrated such comparability were not carried out in patients with chronic heart failure.

Are low doses of inhibitors of the renin-angiotensin system effective in the treatment of heart failure if patients are not subsequently uptitrated to target doses? An analysis of the effects of enalapril in the SOLVD Treatment trial during the first 1–2 months following randomization has not been carried out. However, an estimate of the effects of low doses in the trial has been provided by an observational analysis that focused on patients who were not uptitrated to target doses at the time that was specified for uptitration in the protocol [14]. As a result, a large group of patients received subtarget doses of enalapril (mean dose 8.8 mg daily) for the duration of the trial, and they could be compared to patients who received subtarget doses of placebo. Such an approach does not ensure comparability of the treatment groups (since it relies on a post-randomization event), but the investigators provided evidence that the analyses were not markedly confounded. According to these analyses, when compared with their placebo-treated counterparts, patients receiving half-target doses of enalapril had a 10% lower risk of death ($P = 0.057$) during the 4-year follow-up period. The magnitude of this effect should be viewed in the context that the mortality risk reduction seen in the entire trial (including patients at target doses) was 16% (when compared with placebo) [11]. These findings suggest that the use of low-to-moderate doses of ACE inhibitors is likely to be accompanied by survival benefits that are not substantially different than those seen in a population that includes many patients who are titrated to high target doses.

If a patient is doing well on subtarget doses of an inhibitor of the renin-angiotensin system, is it worth increasing the dose to target doses? This question has been evaluated in two large-scale active-comparator trials that compared different doses of the same drug (the ATLAS and HEAAL trials) [15,16], Table 1. In these trials, exceptionally high doses of lisinopril (35–40 mg daily) and losartan (150 mg daily) were more effective than very low doses of the two drugs (i.e., lisinopril 2.5–5.0 mg daily and losartan 50 mg daily) with respect to hospitalizations for heart failure. However, all-cause mortality was only 6–8% lower in patients randomized to high doses as compared with low doses; these differences were not statistically significant. It should be noted that the high doses of lisinopril and losartan that were studied in these trials are rarely prescribed in clinical practice; indeed, the use of losartan 150 mg daily is beyond the dosing range approved for the drug in the US. Nevertheless, these findings are consistent with findings of the observational analysis of the SOLVD trial [14], which reported that little was gained by increasing the dose of enalapril, when the drug is prescribed within the conventional dose range.

Interestingly, such a conclusion is strongly supported by the findings of two large-scale active comparator trials that compared (inadvertently) treatment regimens that yielded different intensities of inhibition of the renin-angiotensin system. In the ELITE II and OPTIMAAL trials [17,18], captopril was compared with losartan in patients with chronic heart failure and in high-risk patients who had survived an acute myocardial infarction, typically with heart failure or left ventricular systolic dysfunction. In both trials, captopril was used at the target dose that has been shown to reduce mortality (150 mg daily) [19], whereas losartan was used at a dose that is often used for initiation of treatment (50 mg daily). Captopril may exert some pharmacological effects beyond angiotensin II suppression; however, given the comparability demonstrated in the VALIANT and ONTARGET trials [12,13], these two studies can be viewed as testing the comparative efficacy of higher-intensity versus lower intensity inhibition of the renin-angiotensin system. It is therefore noteworthy that in both trials, mortality was 13% lower with captopril when compared with losartan, without a difference in the risk of hospitalizations for heart failure; these differences were not statistically significant. These modest between-group differences are fully consistent with the modest between-group differences observed in the ATLAS, HEAAL and SOLVD trials.

The totality of evidence suggests that low starting doses of inhibitors of the renin-angiotensin system may be effective in reducing the risk of major adverse cardiovascular events in patients with chronic heart failure and a reduced ejection fraction, and that aggressive efforts to achieve target doses are not likely to yield meaningful incremental benefits with respect to mortality reduction. The dose-response relationship for survival with conventional inhibitors of the renin-angiotensin system appears to be shallow, and these drugs do not have large effects to reduce mortality in most patients, even when utilized in an optimal manner [11]. To achieve meaningful incremental decreases in the risk of death, it may be necessary to prescribe a neprilysin inhibitor in conjunction with an angiotensin receptor blocker; this combination yields survival benefits that cannot be achieved by aggressive uptitration of an ACE inhibitor to target levels [20].

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