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Medication Dosing for Heart Failure with Reduced Ejection Fraction:

Opportunities and Challenges: Marti: Medication Dosing for Heart Failure

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Abstract

Multiple drugs classes have shown incremental benefits in heart failure with reduced ejection fraction. Most of these trials were designed to achieve specific doses of the investigational agent. Clinical practice guidelines recommend using the same target dosing of therapies, as tolerated. However, with the increasing number of available therapies, clinicians face the challenge of simultaneously using several drugs, achieving target doses, and managing side effects that are often overlapping. Blood pressure, renal function, hyperkalemia, and other factors may impede achieving target doses of all medications, leaving clinicians with dilemmas as to how to sequence

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and dose these various classes of drugs. The guideline directed eligibility for certain drugs and devices requires stability on maximally tolerated doses of background therapies. However, significant variability exists in dosing achieved in clinical practice. We discuss the existing background data regarding the doses of heart failure medications in clinical trials and in practice, and provide recommendations on how to navigate this complex therapeutic decision-making.

Multiple drugs, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid-receptor antagonists (MRAs), and isosorbide dinitrate and hydralazine combination, are now available for the management of patients with heart failure with reduced ejection fraction (HFrEF). Recently, ivabradine and an angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan, have also shown incremental benefits. Clinical trials with these therapies tested them in addition to existing standard of care at the time the trial was being conducted, or in the case of ARNI, as a replacement for ACEi therapy. With the exception of the Systolic Heart failure treatment with the If inhibitor ivabradine (SHIFT) trial, which titrated ivabradine to a targeted heart rate, all other HFrEF trials were guided by protocols designed to achieve specific target doses of the investigational agent, or the highest tolerated dose.

Guidelines recommend and the most optimal outcomes are achieved (including lower mortality) with target dosing of HFrEF guideline-directed medical therapies. However, with the increasing number of available medical therapies for HFrEF, clinicians now face the challenge of simultaneously using several drugs, achieving target doses, and managing drug side effects, which are often overlapping. Worsening heart failure (HF) symptoms, low blood pressure, or comorbidities like chronic kidney disease, hyperkalemia, chronic lung disease, etc. may impede achieving target doses of all medications, leaving clinicians with dilemmas as to how to sequence and dose these various drugs. Furthermore, the guideline-directed eligibility for certain drugs (including ivabradine) and devices requires stability on maximally-tolerated doses of background therapies. Significant variability exists in dosing achieved in clinical practice and optimization of HF medication dosing has not received the attention it deserves. Herein, we discuss the existing data regarding the doses of HF medications in trials and in practice, and provide recommendations on how to navigate this complex therapeutic decision-making.

SELECTION OF TARGET DOSES IN PHASE II TRIALS

Although exceptions do exist, drug dosing in early phase trials is often not titrated to specific pharmacodynamics or until a particular physiological response is achieved. Rather, starting from very low doses, therapies are successively titrated to higher doses until a maximally tolerated dose is identified based on symptoms, hemodynamics (e.g. blood pressure), or toxicity. Non-specific markers of improvement such as natriuretic peptide levels or left ventricular ejection fraction (EF) are often measured at such doses to inform future development efforts. However, such biological measures are not yet considered acceptable surrogates for identifying the maximally effective dose for a therapy. This lack of targeting a specific biologic response in HF drug development contrasts with other diseases like hypertension or diabetes mellitus. While there is evidence that higher doses of some

therapies may provide modest incremental benefit, lower doses may still provide significant value compared with no therapy. Importantly, beta blockers result in left ventricular reverse remodeling in a dose-dependent manner, [1, 2] a mechanism hypothesized to mediate the mortality benefit with these agents. [3, 4] Further, similar dose-dependent benefits have been observed with higher-dose beta-blocker therapies on more definitive endpoints, such as HF hospitalizations and all-cause mortality. However, despite suggestion of modest benefits on clinical outcomes with high dose over lower dose ACEi and ARB therapy, to our knowledge no such dose-related benefits on cardiac remodeling have been shown to date with non-beta-blocker therapies. [5, 6]

DOSES OF BASELINE MEDICATIONS IN PHASE III CLINICAL TRIALS

Due to application of strict inclusion/exclusion criteria, patients in phase III drug trials are more likely to be on background evidence-based therapies than community-based populations. This may be related to the enrolled patient cohort, who tend to be younger, with fewer comorbid conditions, and/or better access to care than the HF population at large. [7–9] However, even in this setting, some patients in trials are not on all evidence-based therapies at baseline, let alone guideline-directed target doses (Table 1). In many trials, doses of baseline medications are not reported, or when reported, it is frequently not documented whether higher doses had been attempted but not tolerated. As such, the incremental value of novel drugs over ideal background therapy in every patient is almost never known. Instead, trials inform the incremental efficacy and safety over a regimen of guideline-directed medical therapy (GDMT) over a range of background therapy dosing. While it is expected that not all patients will be able to tolerate maximum doses of standard therapies prior to enrollment, trials generally recommend “optimization of HF medications” per HF guidelines prior to enrollment at the discretion of the local investigator. However, the “optimization” of background therapy called for in clinical trials is not standardized and rarely protocolized.

DOSES OF INVESTIGATIONAL DRUGS IN PHASE III CLINICAL TRIALS

While target doses of the investigational agent are specified per protocol in phase III trials and generally achieved in the majority of patients, there are some patients who are unable to tolerate such doses (Table 2). The Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial in asymptomatic patients with an EF ≤35% targeted 20 mg but achieved only 12.7 mg daily of enalapril. [10] Inability to reach target dose was driven by dizziness, cough, and hypotension. The SOLVD Treatment trial demonstrated a significant reduction in mortality with enalapril [11] after achieving 16.6 mg daily dose while targeting 20 mg daily, a dose that was achieved in less than half the participants. Side effects were reported in 87% of the patients with enalapril, but high rates of side effects were also reported with placebo (82%). Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart failure (MERIT-HF) [12] showed a mortality reduction of 31% when targeting 200 mg/day. This was achieved in 64% of patients and the mean dose was 159 mg/day. [13] In the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) [7] trial, 4 in 5 patients were able to reach the target dose of 50mg daily. Further, side effects reported with carvedilol were actually significantly less than those reported with placebo.

In the Randomized Aldactone Evaluation Study (RALES), the MRA, spironolactone, was compared to placebo starting at 25 mg with an option to titrate up to 50 mg at 8 weeks.[14] Mean daily dose in the trial was 26 mg, and at this dose a decrease in mortality of 30% was observed compared to placebo. Titration in RALES was limited by severe hyperkalemia in only 2% of patients; however, widespread use of spironolactone following the publication of RALES led to an increase in hospitalizations for hyperkalemia shortly after the trial was published.[15] This was largely attributed to sub-optimal prescribing, laboratory monitoring, and follow-up practices; as such, detailed guidelines were developed to guide appropriate patient selection for MRA therapy and on-treatment monitoring.

The African-American Heart Failure Trial (A-HeFT) trial demonstrated improved survival among patients self-identifying as African American with the use of fixed-dose isosorbide dinitrate (20 mg) and hydralazine (37.5 mg) three times daily vs. placebo.[16] In the trial, doses were titrated to target dose in only 68% of patients with a mean number of tablets per day of 3.8. Almost 30% of patients complained of dizziness with use of the study drug. It is notable that a substantial number of patients in HF trials receiving placebo have high rates of side effects reported or are not able to achieve target dosing of placebo.

The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) compared sacubitril/valsartan (at a dose of 200 mg twice daily) to enalapril (at a dose of 10 mg twice daily) and demonstrated improved survival with ARNI as compared with ACEi.[8] Secondary analysis showed similar magnitude benefit with ARNI over ACE inhibitor for patients who achieved either low, or intermediate, or high doses.[17] [8] However, the dosing achieved in the PARADIGM-HF trial must be viewed in the context of a study design including a run-in period, in contrast to most prior landmark HFrEF trials. Specifically, 20% of patients enrolled in the trial failed the run-in period and did not receive randomized therapy, with the most common reason for run-in failure being adverse events.

The above examples highlight that oftentimes symptoms intrinsic to worsening HF and symptoms specific to a HF medication itself can be difficult to differentiate. Conceptualizing this difference is important in medication management in response to any given symptom. Greater achievement of target dosing of investigational therapies in clinical trials and routine practice may be facilitated by enhanced recognition of background adverse effects related to HF in placebo-treated patients. It is important to note that in most trials the eligibility criteria exclude patients at higher risk for side effects and intolerance, e.g. advanced age, severe comorbid conditions, hypotension, or poor renal function.

DOSE RANGING PHASE III CLINICAL TRIALS

Randomized dose-ranging clinical trials assessing outcomes are rare in HF. The Assessment of Treatment with Lisinopril and Survival (ATLAS) trial randomized 3164 patients with EF ≤30% [5] to low- (2.5–5 mg) or high-dose (32.5–35 mg) lisinopril. There was no significant difference between the two groups for all-cause mortality, but the combined endpoint of all-cause mortality and HF hospitalization was reduced by 15% with high dose ($p<0.001$). The Heart Failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study

enrolled 3846 patients with EF ≤40% to high- (150 mg) or low-dose (50 mg) losartan. [6] High dose was not associated with improved mortality but there was a 13% reduced risk for HF hospitalizations (p=0.03). Higher doses were associated with modest increase in reversible adverse events including hyperkalemia, hypotension, and renal impairment. Based on these results, there are some benefits between low and high dose of ACEi or ARBs, especially with respect to morbidity more than mortality, and the difference in efficacy between intermediate and high doses are likely to be more modest.

A smaller trial evaluated doses of carvedilol in HFrEF. [18] [2] Target and achieved doses were similar in the three dosing groups (achieved/target: 6.25±0/6.25 mg; 12.3±1.1/12.5 mg; and 23.7±4.0/25 mg). There were dose-related improvements in EF (Figure 1a), cardiovascular hospitalizations, and mortality (Figure 1b); however, there were relatively few events in this study. In addition, the Cardiac Insufficiency Bisoprolol Study (CIBIS) I trial utilized bisoprolol 5 mg daily as a target dose, yet failed to achieve a significant mortality reduction. With CIBIS II, utilizing bisoprolol 10 mg daily as a target dose, a statistically significant 34% mortality reduction was achieved; however there are certainly limitations with cross trial comparisons.

There are no dose ranging studies with MRAs for clinical efficacy. One small study randomized patients to 1 of 5 parallel treatment groups: placebo or spironolactone at a single daily dose of 12.5, 25, 50, or 75 mg for 12 weeks for safety and tolerability assessment. Definitive clinical outcomes were not evaluated in this small study but the incidence of hyperkalemia (serum potassium ≥ 5.5 mmol/L) was 5% among patients receiving placebo, vs. 5%, 13%, 20%, and 24% for the 12.5-, 25-, 50- and 75-mg spironolactone treatment groups, respectively. [19] Due to these dose-dependent risks of hyperkalemia, clinicians tend to prefer lower-dose MRA therapy and alternative dosing strategies than employed in pivotal clinical trials. More data are needed regarding the efficacy of such low MRA doses and greater attention is needed to achieving target doses in clinical practice. Alternatively, a lower risk of hyperkalemia with ARNI therapy as compared to ACEi may allow for safer uptitration of concurrent MRA therapy. [20] Similarly, there is no significant dose ranging data evaluating hydralazine or nitrates, including use of either agent alone. [21]

DOSE RESPONSE RELATIONSHIP IN SECONDARY ANALYSIS OF CLINICAL TRIALS

Secondary analysis of clinical trials has shown benefits with high vs. low dose therapy, [22] [23] e.g. in the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, [24] higher beta blocker dose was associated with improved outcomes. However, despite multivariate modeling, such results are confounded by the clinical stability of patients who were able to tolerate higher doses. Even then, the data are inconsistent. In the PARADIGM-HF trial,[8] those needing dose reduction at some point during the trial were at higher risk of events. However, the magnitude of benefit with low, moderate, or high dose sacubitril/valsartan relative to corresponding enalapril doses were similar. [25] (Figure 2) These findings suggest that ARNI offers advantages to ACEi across

the dosing range. However, these data do not specifically address differences in efficacy and safety between lower and higher ARNI doses.

DOSES USED IN CLINICAL PRACTICE

Practice guidelines recommend the use of evidence-based medications at trial recommended doses for all HF patients, as tolerated. [26, 27] However, in clinical practice, dosing typically falls short of that achieved in clinical trials. For instance, in the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF) registry, among cardiology practices at baseline, only a third of the patients were treated at target doses of ACEi [9] and 20% at beta-blocker target doses. [28] This is in contrast with the rates of target dosing achieved in clinical trials, e.g. 59% in COPERNICUS trial, 64% in MERIT-HF, and 84% in the Valsartan Heart Failure Trial [Val-HeFT]. [29–31] In addition, data from the quality of adherence to guideline recommendations for life-saving treatment in heart failure: an international survey (QUALIFY) an international prospective observational longitudinal survey of 7,092 HF outpatients found that the proportion of patients at target dose of HF medication was low (28% for ACEi, 15% for beta-blockers, 7% for ARBs, and 7% for ivabradine). [32] Another study showed that only 7% of eligible African American outpatients with HF were actually receiving the recommended therapy with combination hydralazine/isosorbide dinitrate. [33] Furthermore, in a registry of hospitalized HF patients, only 22% of African Americans and 13% of all eligible patients were discharged on hydralazine/isosorbide dinitrate. [34] Although these findings in aggregate may be related to less effort and attention to achieving target dosing, it may also reflect the ability of “real-world” patients to tolerate GDMT achieved in clinical trials. Indeed, in practice, there are often challenges with up-titrating therapies, especially medications with potential for hypotension and renal dysfunction side effects, and in patients with co-morbid conditions such as chronic obstructive pulmonary disease (COPD). Oftentimes there is concern regarding beta-blockers in this population given the increased risk of hospitalization for COPD with beta-blocker use, especially non-selective beta-blockers such as carvedilol. [35] Studies show that patients with HF and COPD are prescribed all HF medications at a lower rate than those without COPD, however the discrepancy is most pronounced with beta-blockers. [36]

In dedicated HF disease management programs and studies utilizing standardized protocol for medication dosing, it has been suggested a majority of patients can achieve target dosing. [37] Without systematic approaches to care for these challenging patients it may be more difficult to reach target doses GDMT [9] for many reasons. Yet, such effort is worthwhile; in the Coreg (carvedilol) Heart Failure Registry (COHERE) study, despite enrolling older patients with substantial comorbidities, most patients were able to achieve target doses of beta-blockers with a focused effort. [37]

TRADEOFFS WITH TARGET DOSES OF DIFFERENT MEDICATION CLASSES

Though many patients can tolerate target doses of GDMT, there are many for which this may not be the case. Nonetheless, even in these circumstances, achievement of target dosing

for at least 1 therapeutic class of medication may be possible. For example, patients on low doses of ACEi in the MERIT-HF trial were able to tolerate higher doses of beta-blockers in modestly higher proportion. [38] The mortality benefit of combined beta-blocker and ACEi therapy was apparent in both the low- and high-dose ACEi groups (Figure 3). [38] Similar analysis from COPERNICUS showed that the outcomes improved to a similar degree with carvedilol in patients receiving various doses of ACEi. [39]

BIOMARKER GUIDED MEDICATION TITRATION

The natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP), have demonstrated both diagnostic and prognostic value in patients with HF. [40, 41] A decrease in natriuretic peptide levels over a period of follow-up has been associated with improved outcomes, including morbidity and mortality. [42, 43] Importantly, HF therapy guided by natriuretic peptides has not been shown to improve outcomes in HF patients [44] [45] Beta-blockers have been shown to substantially decrease natriuretic peptide levels in the long run, [46] as have ACEi/ARBs [47] and MRAs. [48] One recent study demonstrated improved outcomes with patients who attained a significant reduction in NT-proBNP <1000; importantly, treatment with sacubitril/valsartan was nearly twice as likely as enalapril to achieve reductions in NT-proBNP to this level. [49] More data are needed regarding doses of medications and their interaction with natriuretic peptides, or other biomarkers, and clinical outcomes; and importantly if doses should be specifically titrated to achieve specific biomarker levels rather than the current recommendation for maximally tolerated dosing.

PRACTICAL OPTIONS TO MAXIMIZE TARGET DOSING

While there is little to no evidence on what specific strategies work best, given the benefits of target dosing highlighted above, we propose practical considerations for providers. Although these strategies are largely empiric and require prospective validation, they hold promise. Every effort to maximize target dosing of HF therapy should be made as evidence suggests that target doses of at least select components of GDMT may reduce mortality and morbidity. [26, 27] Furthermore, more structured implementation and employment of a dedicated nurse facilitator may improve guideline-directed dose titration. In a small, randomized clinical trial, target dosing of beta-blockers was achieved to a greater extent over a median of 12 months in the nursing facilitator group compared with routine clinical practice. [50] Although this study did not find utility of clinical reminders to patients and providers, new algorithms leveraging natural language processing in the electronic health records may allow for specific targeting of patients at suboptimal dosing regimens. [51] In many cases, nurse- or pharmacist-driven dosing protocols can result in faster up-titration with more frequent visits and greater number of medication changes. This may partly relate to developing better patient rapport, improving recognition of common adverse drug-related effects, and appropriately responding to patient symptom reporting.

Appropriate blood pressure and heart rate targets need to be clearly defined, targeting symptomatic blood pressure and heart rate reduction as indications for stopping uptitration as opposed to arbitrary asymptomatic thresholds. However, this does require close patient

monitoring and careful history taking.[7, 12] If symptomatic hypotension prevents adequate uptitration of GDMT, providers should consider potential hypovolemia (with concomitant reduction in diuretics, if appropriate), or discontinuation of any medications that lower blood pressure without proven outcomes benefits in HFrEF patients (e.g. calcium channel blockers). Patients should be counseled on the importance of their medication, the concept of “target doses” (to mitigate resistance to frequent titration), and how to manage minor side effects with lifestyle changes, e.g. avoidance of sudden changes in posture to attenuate orthostatic symptoms. Switching agents within a drug class may also improve tolerance to GDMT. [52] Splitting of dosing regimens over a 24-hour period and avoiding intake of all vasoactive medications at once may limit blood pressure swings. Furthermore, referral to a cardiologist or HF program for assistance can often help if patients are unable to reach target dosing in the primary care setting. [53] (Table 3)

PRACTICAL CONSIDERATIONS FOR MANAGEMENT OF OVERLAPPING MEDICATION SIDE EFFECTS

Challenges achieving target dosing are particularly germane in patients with borderline blood pressure or renal function. Many patients with HFrEF are elderly or have concomitant diabetes mellitus, which further exaggerates these risks. [54] For patients with borderline blood pressure, it is uncertain whether to use higher doses of ACEi/ARB/ARNI and lower doses of beta blockers, or vice versa. A similar conundrum exists for the use of MRAs and ACEi/ARB/ARNI for those at risk for hyperkalemia or renal dysfunction. [55] In some cases, using moderate to higher doses of one class of agents may completely preclude the use of other medication altogether.

For the broader HFrEF population, there are four biologic targets that have been shown to improve outcomes, including angiotensin II, norepinephrine, aldosterone, and vasoactive peptides. [56, 57] In general, it is the best practice to target all of these pathways and not leave one unattended. Ivabradine is a special case targeting elevated heart rate but only in patients who are in sinus rhythm on maximally-tolerated beta-blocker doses. [58] For African American patients who have persistently limiting class III and IV symptoms despite achieving optimal therapy otherwise, addition of hydralazine and isosorbide dinitrate is further recommended.

Data suggests that achieving high doses of one therapy and not focusing on other therapies is less beneficial. The CIBIS III trial [59–61] randomized patients to either an initial strategy of ACEi or beta-blockers. Whichever drug was started first, either the ACEi or the beta-blocker, ended up achieving higher relative doses than the medication started second. While there were no differences in outcomes overall with either strategy, a strong predictor of outcome was whether the patient was on monotherapy for 6 months before the second class of drug was initiated. Thus, these data suggest targeting all relevant pathways is more important than achieving higher doses of one and ignoring other drugs. [59–61] This is especially important considering the fact that other than beta-blockers, the dose response data with other agents is less robust.

Recently, the American College of Cardiology Expert Consensus Pathway for HF Therapies addressed some of the issues of dosing of various medications (Figure 4)[62]:

1. In all patients, it is best to achieve maximum doses of all four biologic targets including angiotensin II modulation, beta blockade, aldosterone antagonism, and neprilysin inhibition.
2. If this is not possible, then the second-best option is to use lower doses of all drugs rather than higher doses of one and omitting another.
3. If the patient is able to tolerate higher doses of one but lower doses of the other therapy due to blood pressure, then preferences should to be given to beta blockers over angiotensin II modulation based on better dose response data with adrenergic blockade. [1] [18] [2]
4. If concerns are related to renal function or hyperkalemia, then higher doses of angiotensin II modulating drugs should be preferred, with lower doses of MRA used. [5] [6] Secondary analyses from PARADIGM-HF suggest that there may be less hyperkalemia with ARNI vs. ACEi, therefore sacubitril/valsartan may have an advantage in these settings. [8]

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FUTURE RESEARCH AND CLINICAL CONSIDERATIONS

Given the general lack of biologically-guided therapeutic targets in HF, the priority should be to conduct phase II trials with more focus on dose identification based on pharmacodynamics profile rather than tolerability, through either molecular imaging or soluble biomarkers as targets. In phase III trials, increased focus should be placed on investigating the safety and efficacy of HF medications in a randomized, controlled manner. Post-approval quality improvement and education efforts should focus on achieving doses targeted in clinical trials (Table 4), recognizing that in real life, relatively fewer patients achieve target doses for a variety of reasons. Available evidence suggests existence of dose-response curves for many HF medications with improved outcomes at higher doses, with beta-blockers having the strongest such relationship. As such, strong emphasis is warranted on maximally targeting each pathway known to improve HF outcomes, including angiotensin II, beta-blockade, aldosterone, and vasoactive peptides. If a patient is unable to tolerate maximal doses of all medications, lower doses of all medications are preferred over a high dose therapy of one and no coverage of other pathways. Side effects and tolerability are emerging as major concerns in contemporary HF drug development. [63] While the magnitude of benefit may be debated, lower doses are nevertheless associated with benefit. *It is critical for clinicians to recognize the important contribution of each targeted pathway in the HF armamentarium and to maximize each of these therapies to the highest tolerated dose. Combining practical approaches with sound clinical judgment to optimize this important aspect of HF patient care is the key to improving outcomes for HF patient*

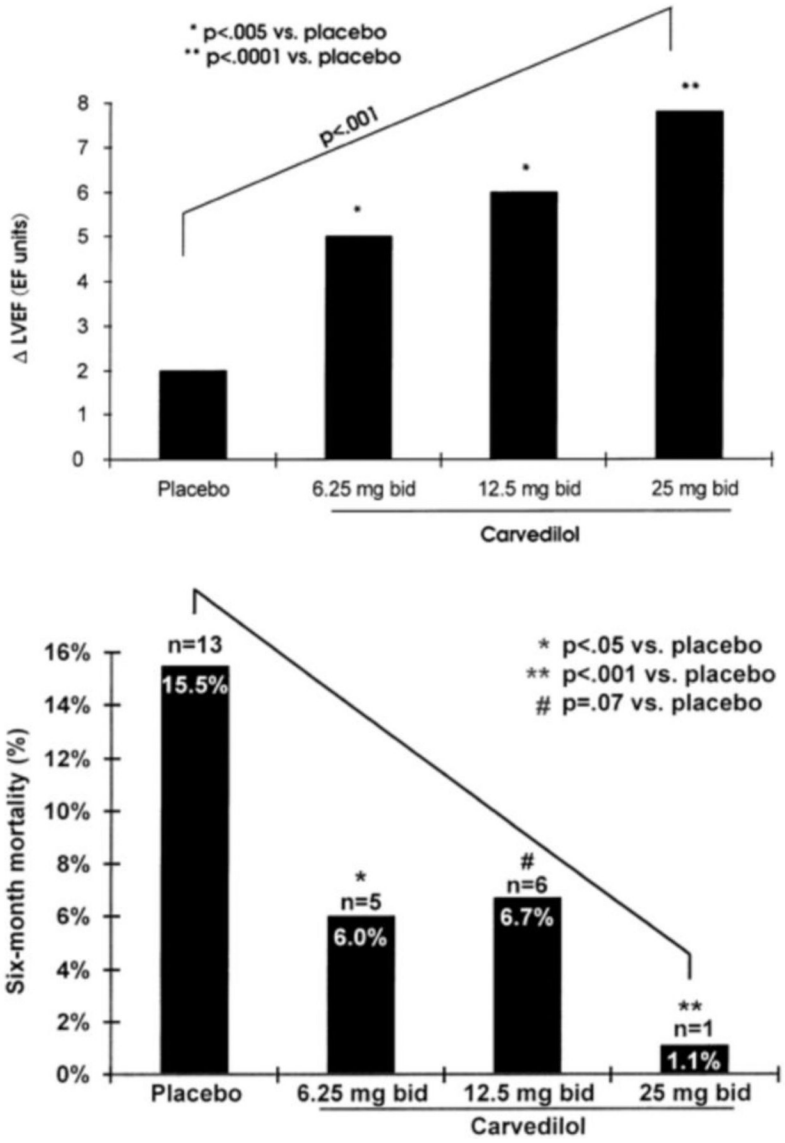

Figure 1: Dose ranging effect of carvedilol.

Ejection fraction **(2a)**, and 6-month mortality **(2b)**.

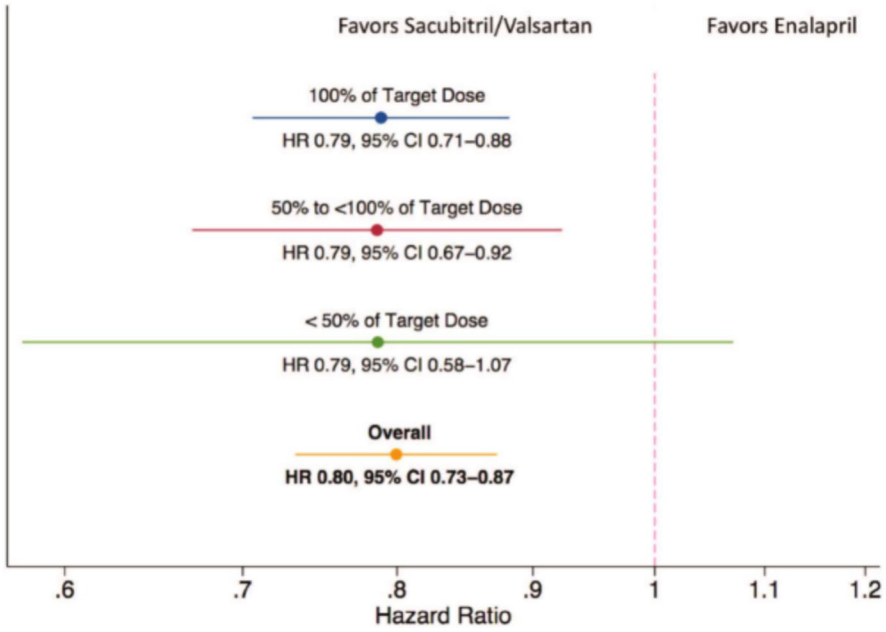

Figure 2: Outcomes with sacubitril/valsartan relative to enalapril.

Participants taking lower than target sacubitril/valsartan doses had a lower risk of the primary event compared with those taking similar doses of enalapril.

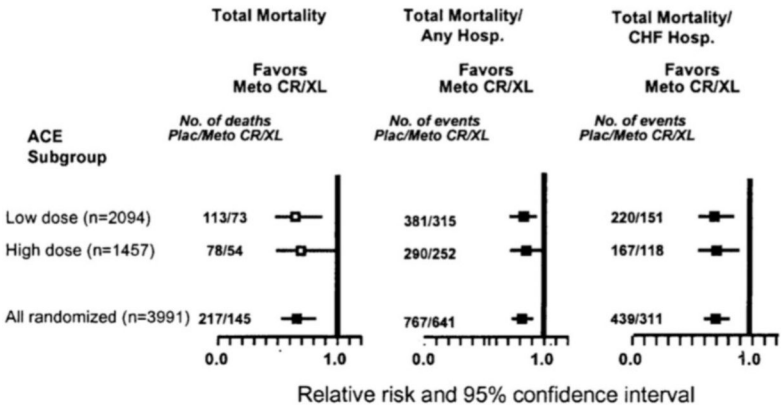

Figure 3: Benefit with high vs. low dose ACE inhibitor on top of beta-blocker therapy.
Point estimates of relative risk and 95% confidence intervals in the two angiotensin-converting enzyme inhibitor dose groups for various outcomes.

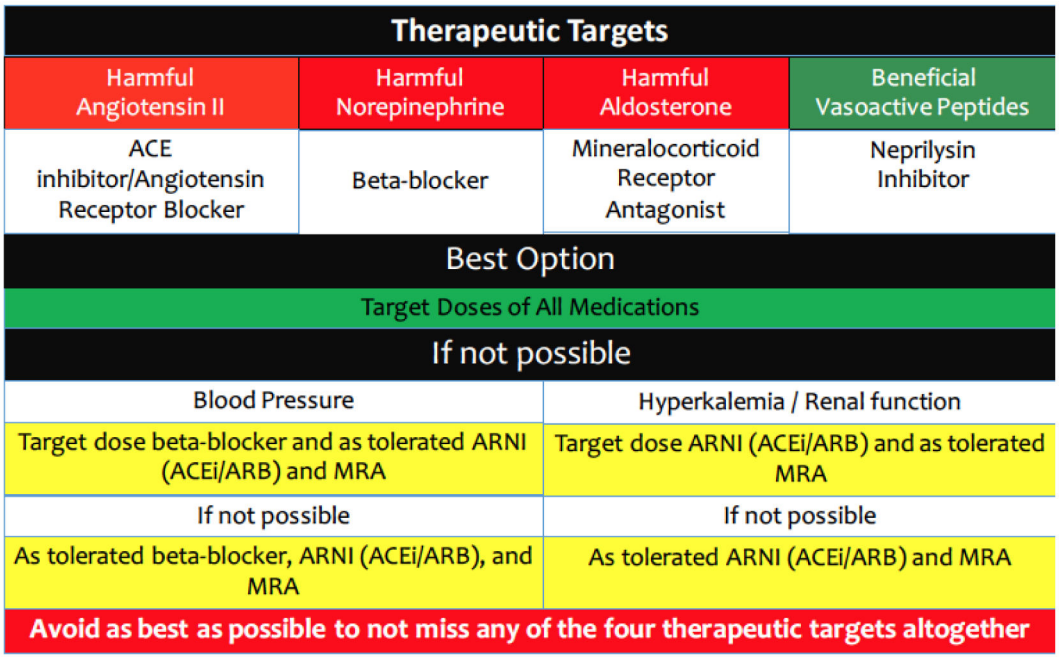

Figure 4:

Suggested hierarchy of medication titration in heart failure.

Table 1:

Baseline therapy in heart failure clinical trials

Trial	Beta blockers	ACEi/ARB	MRA	ISDN	Digoxin	Loop diuretic
V-Heft [64]	35%	93%	-	-	67%	85%
CONSENSUS [65]	3%	-	52%	46%	93%	98%
SOLVD Treatment Trial [11]	8%	-	-	51%	67%	-
MERIT-HF [13]	-	96%	-	-	64%	90%
COPERNICUS [66]	-	97%	20%	-	66%	99%
COMET [67]	-	92%	11%	33%	59%	99%
RALES [14]	11%	95%	-	-	74%	100%
CHARM-Alternative [68]	55%	-	24%	43%	45%	85%
A-HeFT [16]	74%	87%	39%	-	60%	90%
EMPHASIS [69]	87%	93%	-	-	27%	85%

ACEi/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; ISDN: Isosorbide dinitrate

Table 2.

Doses of various interventions in heart failure clinical trials

Trial	Drug	Target Daily Dose	Percent Reaching Target	Mean Daily Dose
V-HeFT [64]	Hydralazine/Isosorbide dinitrate	112.5/160mg	55%	270mg/136mg
CONSENSUS [65]	Enalapril	40mg	-	18.4mg
SOLVD Treatment [11]	Enalapril	20 mg	-	16.6mg
MERIT-HF [13]	Metoprolol CR/XL	200mg	64%	159mg
COPERNICUS [66]	Carvedilol	50mg	80%	45mg
COMET [67]	Metoprolol tartrate/ carvedilol	100/50mg	75%/78%	85mg/42 mg
RALES [14]	Spironolactone	25mg	-	26mg
CHARM-ALTERNATIVE [68]	Candesartan	32mg	-	23mg
A-HeFT [16]	Hydralazine/Isosorbide dinitrate	225/120 mg	68%	143mg/76mg
EMPHASIS [69]	Eplerenone	50mg	60.2%	39.1 mg

Table 3:

Practical considerations for maximal medical therapy in heart failure

Concern	Solution
Clinical time constraints	• Multidisciplinary heart failure disease management program • Nurse- or pharmacy-directed medication titration clinic • Nurse-directed titration schedule via phone
Low blood pressure to add new medications	• Decrease unnecessary blood pressure lowering medications not known to benefit heart failure outcomes • Space out medications throughout day • Assess for hypovolemia
Orthostatic symptoms	• Decrease diuretics • Space out medications throughout day • Counsel on behavior modification (e.g., standing slowly, etc.)
Low enough blood pressure/heart rate to titrate medications	• Ensure appropriate blood pressure and heart rate targets • Track patient's symptoms rather than absolute hemodynamic numbers
Fatigue	• Move beta-blocker dosing to nighttime • Counsel on importance of medication and need to "power through" potentially manageable symptoms

Table 4:

Target doses of heart failure medications from clinical trials [70]

	Starting dose (mg)	Target dose (mg)
ACE Inhibitors		
Captopril	6.25 mg thrice a day	50 mg thrice a day
Enalapril	2.5 mg twice a day	10–20 mg twice a day
Fosinopril	5–10 mg daily	40 mg daily
Lisinopril	2.5–5.0 mg daily	20–40 mg daily
Ramipril	1.25–2.5 mg daily	10 mg daily
Quinapril	5 mg twice a day	20 mg twice a day
Trandolapril	1 mg daily	4 mg daily
Angiotensin receptor blockers		
Candesartan	4–8 mg daily	32 mg daily
Valsartan	20–40 mg twice a day	160 mg twice a day
Losartan	25–50 mg daily	50–150 mg daily
Angiotensin receptor neprilysin inhibitor		
Sacubitril/valsartan	49/51 mg twice a day	97/103 mg twice a day
Beta-blockers		
Bisoprolol	1.25 mg daily	10 mg daily
Carvedilol	3.125 mg twice a day	50 mg twice a day
Metoprolol succinate	12.5–25 mg daily	200 mg daily
Nebivolol	1.25 mg daily	10 mg daily
Mineralocorticoid-receptor antagonists		
Eplerenone	25 mg daily	50 mg daily
Spironolactone	12.5–25 mg daily	25 mg daily/twice a day
If-channel blocker		
Ivabradine	5 mg twice a day	7.5 mg twice a day
Isosorbide dinitrate and hydralazine		
Hydralazine	25–50 mg thrice a day	100 mg thrice a day
Isosorbide dinitrate	20–30 mg thrice a day	40mg thrice a day