

Guideline-directed medical therapy for heart failure does not exist: a non-judgmental framework for describing the level of adherence to evidence-based drug treatments for patients with a reduced ejection fraction

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Received 2 March 2020; revised 9 April 2020; accepted 21 April 2020; online publish-ahead-of-print 20 May 2020

Numerous guideline documents have issued recommendations to clinicians concerning the treatment of chronic heart failure and a reduced ejection fraction. However, guidelines do not describe what constitutes an acceptable standard of care, and thus, practitioners who adhere to only a small fraction of the recommendations might claim that they are treating patients 'in accordance with the guidelines'. As a result, <1% of patients with heart failure are receiving all life-prolonging treatments at trial-proven doses. A major impediment to the widespread adoption of trial-based treatments is a lack of any existing framework that would allow physicians to describe the adequacy of care. To address this deficiency, we propose a novel simple approach that would ask practitioners if a patient had been treated using the dosing algorithm that had been shown to be effective for each drug class. The proposed framework recognizes that all landmark survival trials in heart failure were 'strategy trials', i.e. the studies mandated a standardized forced-titration treatment plan that required timely uptitration to specified target dose unless patients experienced clinically meaningful, intolerable or serious adverse events, which persisted or recurred despite adjustment of other medications. Adherence to trial-proven regimens might be improved if physicians were asked to describe the degree to which a patient's treatment adhered to or deviated from the strategies that had been used to demonstrate the survival benefits of neurohormonal antagonists. The proposed framework should also promote practitioner self-awareness about the lack of evidence supporting the current widespread use of subtarget doses that are non-adherent with trial-proven forced-titration strategies.

Keywords Optimal medical therapy • Heart failure guidelines • Guideline-directed medical therapy

The care of patients with chronic heart failure with a reduced ejection fraction should be determined by the evidence from large-scale randomized controlled trials that form the basis of accepted standards of practice. Numerous guideline documents have issued recommendations to clinicians.^{1,2} These describe the treatments that should be prescribed (class I); those that are appropriate but are not mandated (class II); and those that should not be used (class III). However, guidelines typically do not describe what constitutes an acceptable standard of care. As a result of this uncertainty, practitioners who adhere to only one or two

recommendations could contend that they are treating patients with heart failure 'in accordance with the guidelines'.

Current challenges in describing the adequacy of treatment regimens

Authors often claim that patients enrolled in clinical studies were receiving optimal medical therapy as background treatment. In

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clinical practice, practitioners commonly state that their treatment plan is 'guideline-directed medical therapy'. What do these statements mean? Actually, there exists no standardized framework to describe the degree to which a patient's medical regimen adheres to, or deviates from, the strategies that were used in clinical trials to demonstrate the benefits of specific drugs and devices.

There should be no doubt that most patients are not receiving target (or the highest tolerated) doses of all essential drugs, even when patients are treated by clinical investigators with considerable expertise in heart failure. Critical (class I) elements are often missing, and most eligible patients are never prescribed target doses of essential drugs at any point in time during follow-up.³⁻⁵ In one prospective study, only 23% of patients were receiving $\geq 50\%$ of target doses of beta-blockers, renin-angiotensin inhibitors and mineralocorticoid receptor antagonists.⁴ In a second survey, target doses of angiotensin receptor-neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists were prescribed in $< 1\%$.⁵

Even if an expert panel were formed to critically examine the treatment of individual patients, such oversight does not necessarily improve physician adherence to crucial recommendations. For example, the COAPT trial established a compulsory review of drug treatments for patients with heart failure prior to enrolment. Yet, only 60% to 70% of patients were receiving a conventional inhibitor of the renin-angiotensin system; $< 5\%$ were receiving a neprilysin inhibitor; and it is not known if patients were treated with the target doses of class I agents that have been shown to reduce mortality.⁶ Furthermore, the medical review process in COAPT was applied only at the start of the trial; following randomization, uptitration of medications was discouraged, an approach that is inconsistent with best clinical practice. Interestingly, in the MITRA-FR trial (which studied the same intervention as in COAPT), patients received more intensive medical therapy for heart failure than in the COAPT trial, even though there was no external oversight process.⁷

Given the current state of affairs, most practitioners who claim that patients are receiving 'guideline-directed medical therapy' are making a judgment that is not based on objective criteria.⁸ No set of standards has been developed to define 'optimal medical therapy'. Anyone who asserts that their patients are being managed appropriately is providing a well-intentioned (but personal) opinion, since no one has defined what combination of treatments should be considered 'optimal', 'acceptable', 'adequate', 'reasonable' or 'guideline-directed'.

How should we identify treatments that are essential in the management of chronic heart failure and a reduced ejection fraction?

Guideline documents include hundreds of recommendations; however, the class I recommendations that are considered essential for

most patients with heart failure and a reduced ejection fraction are the treatments that prolong survival.

Prolongation of survival versus improvement in symptoms

Why do class I recommendations focus on interventions that reduce the risk of death? This emphasis does not imply that an improvement in symptoms and signs is unimportant. However, all clinical trials that form the basis of current recommendations focused on major outcomes, and thus, we have little data about the effect of treatments on quality of life. Furthermore, strategies that are directed primarily towards the relief of symptoms and signs must be tailored to the needs of individual patients and vary considerably among patients and over time in the same patients.⁹ The doses of drugs that are needed to ameliorate symptoms are unpredictable, and it is nearly impossible to determine whether the degree of achieved symptom relief is appropriate or adequate on an individual basis. Importantly, efforts to treat symptoms are not exquisitely time-sensitive, i.e. there is no ethical mandate to achieve a specific level of symptom improvement in a defined period of time.

The highly unpredictable and non-standardized approach to achieving symptom relief contrasts markedly with the principles that govern the prescribing of drugs that prolong life. The efficacy of mortality-reducing treatments has been established on a population basis in clinical trials where patients were treated using a standardized approach; thus, the strategies that prolong survival do not vary among patients or over time in the same patients. Furthermore, the use of drugs that reduce mortality cannot be ethically delayed; any meaningful delay means that deaths will occur that could have been prevented by early intervention.^{10,11} Because of this high level of standardization, it is much easier to ascertain whether patients are receiving appropriate treatment with life-prolonging drugs than to determine if they are receiving adequate therapy for the relief of symptoms.

Challenging in assessing the adequacy of treatment with devices and with drugs that act primarily to reduce hospitalizations for heart failure

Both drugs and devices have been shown to reduce the risk of death in patients with chronic heart failure and a reduced ejection fraction. However, it is often difficult to determine the appropriateness of use of device therapy for two important reasons. First, whereas drugs with survival benefits are intended to be prescribed to a broad spectrum of patients, devices are typically recommended for use in select populations. Cardiac resynchronization is recommended only in patients with a meaningfully prolonged QRS duration,¹ and implantable cardioverter-defibrillators are most effective in those with an ischaemic cardiomyopathy and mild symptoms and only after they have received class I drugs for a meaningful length of time.¹² Second, devices are more expensive than drugs; thus, access to devices is often severely limited by the

resources of healthcare systems and individual patients. A lack of access to devices is particularly important for patients with heart failure who are treated outside of the United States or Western Europe.

Certain treatments for heart failure (e.g. digoxin, ivabradine and vericiguat) act primarily to reduce the risk of hospitalizations for heart failure.^{13–15} Although hospitalizations have prognostic significance, their occurrence is largely related to worsening symptoms, and thus, an effect to prevent hospitalizations is a benefit akin to the mitigation of symptoms. Furthermore, the decision to admit patients to a hospital is dependent on physician preferences and healthcare access. Although both digoxin and ivabradine might prolong survival in certain patients, the possibility of this benefit is based on post hoc subgroup analyses.^{16,17} In the broad range of patients with a reduced ejection fraction, the survival benefit with these drugs is modest or negligible. Accordingly, drugs that act only to reduce hospitalizations are typically given a class II recommendation in current guidelines.^{1,2}

What drug treatments should be considered essential to the management of patients with chronic heart failure and a reduced ejection fraction?

Accordingly, for purposes of the present review, the treatments that are considered to be essential and broadly applicable to patients with chronic heart failure and a reduced ejection fraction are (i) inhibitors of the renin–angiotensin system; (ii) neprilysin inhibitors (i.e. sacubitril/valsartan); (iii) beta-adrenergic blockers that have been shown to prolong life (carvedilol, metoprolol succinate, and bisoprolol); and (iv) mineralocorticoid receptor antagonists.^{1,2,11} The evidence base for each of these drug classes is clinically persuasive and statistically robust. The magnitude of the incremental benefit of each drug class is meaningful (at least 20% reduction in the risk of death) for neprilysin inhibitors, beta-blockers and mineralocorticoid receptor antagonists.¹¹ Furthermore, these three classes of drugs have each been shown to reduce the risk of sudden death¹⁸; consequently, the utilization of these drugs cannot be reasonably delayed even if patients are clinically stable.^{10,11} In contrast, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers have only a modest benefit on the risk of death (5–16% risk reduction)¹⁹; the survival benefit cannot be enhanced by intensification of treatment^{20,21}; and they do not reduce the risk of sudden death.²²

Hydralazine and isosorbide dinitrate can prolong survival, but the combination may be inferior to ACE inhibitors with respect to mortality.²³ Use of this drug combination in the modern era is based on an analysis of a relatively small number of events in a select population.¹¹ Furthermore, sodium–glucose co-transporter 2 inhibitors are not considered in the current framework, since the evidence base supporting their ability to reduce mortality in patients with established heart failure is still evolving.²⁴ If the survival benefits are confirmed by additional trials, these drugs can be included in our proposed system.

Which strategies are effective for the use of life-prolonging drugs in patients with heart failure and a reduced ejection fraction?

In the landmark trials with neurohormonal antagonists, investigators were required to follow a forced-titration strategy to achieve and maintain treatment with specified target doses for long periods of time. Therapy was initiated at a low dose, and the doses were progressively increased in planned increments at specific time intervals, until the target dose was achieved or unless patients experienced clinically meaningful or serious adverse events, which persisted or recurred despite adjustment of other medications. In general, asymptomatic changes in vital signs and laboratory tests were not considered to represent events that would prevent uptitration to target doses. If the study medication was discontinued or the dose was decreased, these were considered to be temporary events, and investigators were strongly encouraged to reinstitute treatment and achieve target doses. Importantly, in most trials, the target dose was the same for every patient in the study, and a large majority achieved and were continued on target doses for the duration of the trial. Patients were maintained on subtarget doses only if the use of higher doses had been shown to threaten clinical stability. This ‘forced-titration’ strategy ensured that few patients were maintained for long periods on the doses that had been used for initiation of treatment.

However, in clinical practice, these forced-titration strategies are followed very infrequently. As a result, most patients are not receiving all mandated classes of drugs, and when treated, they commonly receive doses that were prescribed at the time of initiation of treatment.^{3–5} Although these subtarget dosing regimens may have benefits, their ability to prolong life has not been established.

Why are patients receiving subtarget doses of critical treatments?

In clinical practice, physicians initiate treatment at a low ‘starting dose’, but most patients continue to receive the starting dose for long periods of time, often indefinitely, with no or minimal uptitration. When new treatments are initiated at low doses during a hospitalization for heart failure, these doses are typically maintained following discharge.²⁵ This pattern of practice is prevalent whether patients are treated by primary care physicians or by heart failure specialists.

A striking example is the prescribing of sacubitril/valsartan. The drug is commonly initiated at 24/26 mg twice daily, but is uptitrated only in a small fraction of patients.²⁶ In contrast, few patients received long-term treatment with 24/26 mg twice daily in the large-scale clinical trial that established the survival benefit of neprilysin inhibition (PARADIGM-HF).^{27,28} All patients in that trial received target doses of the drug at randomization, and >70% were maintained on this dose for the duration of the study²⁷; yet, in

clinical practice, <25% of patients are ever titrated to the target dose of 97/103 mg twice daily. Interestingly, 40% of the patients who required temporary dose reduction in PARADIGM-HF were subsequently restored to target doses. In contrast, in clinical practice, the vast majority of dose reductions are permanent, leading to indefinite treatment with subtarget doses.

The approach to treating life-threatening heart failure in clinical practice differs markedly from that used by oncologists to treat life-threatening cancers. Cancer specialists initiate simultaneous therapy with multiple-drug regimens at target doses and down-titrate only if serious adverse reactions occur that cannot be mitigated with additional treatments. Efforts to prolong life are valued far more highly than efforts to minimize drug toxicity. In striking contrast, the treatment of heart failure is routinely initiated with low doses of a single drug; additional therapies are added at a later time; and avoidance of adverse effects represents the clinical priority. The difference in the two approaches is medically inexplicable, since heart failure is more lethal than most forms of cancer.²⁹ Furthermore, the median improvement in survival produced by most treatments for heart failure exceeds that for most therapies for metastatic cancer.

Critical factors that contribute to the widespread failure to achieve and maintain target doses of neurohormonal antagonists

Why are most patients with chronic heart failure treated for long periods of time with only one or two drugs or with doses that are much lower than the doses that have been shown to prolong life? There are several contributory factors.

First, many physicians may be unfamiliar with the doses of neurohormonal antagonists that have been shown to prolong survival in chronic heart failure. The target doses of most neurohormonal antagonists used to treat heart failure are typically higher than the doses of the drugs when they are used to treat other cardiovascular disorders. For example, the usual doses of candesartan and valsartan used for the treatment of hypertension (4–8 mg daily and 40–80 mg daily, respectively) are far lower than the target doses in the large-scale trials in heart failure (32 and 320 mg daily, respectively).^{30,31} Similarly, the optimal dose for losartan for heart failure (150 mg daily) is higher than that approved in the US for any cardiovascular indication¹⁹; the commonly prescribed dose of 50 mg daily appears to be inferior to ACE inhibitors with respect to mortality reduction.^{32,33} The dose of metoprolol succinate used for hypertension or angina is 25–100 mg daily, but the target dose used in the landmark heart failure trial was 200 mg daily.³⁴

Second, physicians may recognize the inadequacy of low starting doses but may nonetheless believe that medium-range doses provide most of the benefits of target doses. Theoretically, this premise would be true if medium-range and high target doses were on the upper flat portion of the dose–response curve. Yet, in a clinical trials, higher doses have provided greater benefits than lower doses,^{19,20,35,36} and there is little evidence that medium-range subtarget doses reduce the risk of death. Interestingly, the final step in the dose-titration process to target doses

may provide unexpectedly large survival benefits. In the COMET trial,³⁷ carvedilol (25 mg twice daily) was compared with metoprolol tartrate (50 mg twice daily) in a large double-blind trial of >3000 patients who were followed for nearly 5 years. At these doses, the heart rate reduction in the metoprolol group was within 1–2 bpm of that achieved in the carvedilol group, suggesting that metoprolol tartrate provided >75% of the beta-1 receptor blockade produced by carvedilol.³⁸ Yet, when compared with metoprolol, carvedilol was accompanied by a 20% lower risk of cardiovascular death. Since beta-blockers reduce mortality by ≈30–35% when compared with placebo,³⁹ these observations suggest that more than half of the mortality reduction produced by target doses of beta-blockers may be provided by the final step in the dose titration protocol.⁴⁰

Third, physicians may be unaware of the directions that were provided to investigators in clinical trials regarding the uptitration of neurohormonal antagonists. In these trials, physicians were required to increase the dose of the study medication to the specified target dose in a standardized manner, and to make an ongoing and concerted effort to achieve and maintain the target dose, even if patients experienced unwanted changes in blood pressure, renal function, or electrolytes. Reaching values for systolic blood pressure or heart rate in the ‘normal range’ was not considered a valid reason for interruption of the forced-titration strategy. For example, many physicians mistakenly believe that systolic blood pressures of 100–120 mmHg are sufficiently low to prevent further dose uptitration.⁴¹ However, in the landmark clinical trials, physicians were typically advised to continue uptitration as long as the systolic blood pressure was >85–90 mmHg, if patients were not experiencing recurrent symptoms related to hypotension. Similarly, in trials of beta-blockers, investigators were required to uptitrate to target doses even if the heart rate on a subtarget dose declined to 65 bpm. These strategies are contrary to commonly-held beliefs that patients with chronic heart failure require certain levels of perfusion pressure or that they need a heart rate of 70–80 bpm to maintain cardiac output.

Fourth, many physicians are unfamiliar with the strategies that were used in large-scale trials to manage and mitigate adverse effects of drug treatments, thereby, allowing uptitration to target doses. If clinically important hypotension occurs, it often does not recur with rechallenge at the same dose, and recurrences can be further minimized by downtitration of diuretics or the elimination of other drugs that can decrease blood pressure. Similarly, most increases in blood urea nitrogen should not prevent uptitration of neurohormonal antagonists, and azotaemia can be minimized by decreases in the dose of diuretics or discontinuation of other drugs that can worsen renal function. Increases in serum potassium were not considered actionable until the value exceeded 5.5 mmol/L, and the risk of hyperkalaemia can be mitigated by potassium-binding agents.⁴² Decreases in heart rate produced by beta-blockers were not regarded as worrisome unless the heart rate declined to <60 bpm. These strategies were essential to the treatment plan used to achieve target doses in the landmark clinical trials with neurohormonal antagonists. When these strategies are deployed, the highest tolerated subtarget dose yields survival benefits that approximate those produced by target doses.²⁸ Unfortunately, in clinical practice, asymptomatic hypotension and worsening renal

function are important causes of underutilization of evidence-based treatment.⁴³

Fifth, many physicians are reluctant to uptitrate drug treatments because they harbour personal fears that patients will not be able to tolerate the next increment in dose. Many physicians believe that medium and target doses are particularly likely to produce intolerable decreases in systolic blood pressure, worsening of renal function, or electrolyte disturbances. However, the most dramatic decreases in blood pressure with inhibitors of the renin–angiotensin system and carvedilol are seen with the low starting dose, and subsequent changes in blood pressure with each dosing increment are comparatively modest. Furthermore, most occurrences of worsening of renal function are reflective of changes in intrarenal haemodynamics and not renal injury; and can be mitigated without a change in dosing.⁴⁴ Nevertheless, if drugs are not uptitrated because of physician fears, it is not possible to know whether the higher dose would have been well-tolerated if the patient was not given the opportunity to receive it.

Sixth, an important contributor to the lack of dose uptitration is the absence of a reliable biomarker that can serve as a motivation for dose adjustment. Physicians often rely on a physiological or biochemical measurement to drive increases in dose dosages. These biomarkers are routinely used in the management of hypertension, hypercholesterolaemia and diabetes; however, no biomarkers exist to guide the treatment of chronic heart failure. Although some physicians titrate therapy based on circulating levels of N-terminal pro B-type natriuretic peptide, the assay is quite variable, and the approach has not been validated. Most importantly, many drugs that are essential to the treatment of chronic heart failure do not have meaningful effects to lower natriuretic peptides. In the GUIDE-IT trial,⁴⁵ patients whose treatment was adjusted based on the level of natriuretic peptides did not fare better than those who were managed using trial-based uptitration strategies.

Seventh, a common reason for the failure of uptitration of life-prolonging therapy is clinical inertia, i.e. patients are maintained on low doses because – at each encounter with a practitioner – it is easier to simply continue existing treatment than to optimize it. Maintenance of the *status quo* is particularly appealing if patients are considered to be clinically stable. Many physicians incorrectly believe that stability of symptoms equates to stability of the underlying disease process. However, even if symptoms are alleviated, the underlying disease continues to progress and leads to death. A good quality of life does not obviate the need to receive medical therapy at doses that have been shown to reduce mortality. In clinically stable patients with only mild limitation of activity, neurohormonal antagonists have striking effects to reduce sudden death.^{46,47}

Proposal for a new framework for describing the degree of adherence to evidence-based treatment

Given the broad range of possible reasons why physicians do not prescribe and uptitrate drugs that prolong survival in chronic heart

failure, how can we objectively describe the adequacy of treatment in individual patients? Although it is possible to simply record the doses of drugs, such an approach provides no information about whether the practitioner actually utilized the forced-titration strategies that were shown to be effective in prolonging life in large-scale clinical trials.

It is appealing to simply ask physicians to describe why target doses of drugs were not prescribed, but such an approach would be impossible to implement. Imagine asking each practitioner to document at each visit the ability of patients to tolerate each drug class, the nature of the adverse event that prevented uptitration, the steps that were taken to enhance tolerability, and whether failure to achieve target doses was related to misconceptions held by the prescribing clinician. The reasons for failing to achieve target doses varies from patient to patient and may change over time in the same patient. Additionally, there may be many simultaneous reasons for a decision to maintain subtarget doses.

To complicate matters further, it is not possible to state with confidence that differences in dosing within the subtarget range lead to different benefits. Can we claim that 10 mg of enalapril daily is superior to 5 mg daily? Do we know that metoprolol succinate 100 mg daily is superior to 50 mg daily? Because physicians cannot answer these questions, it is not possible to make evidence-based comparative judgments. One can only ask if the patient was treated using the forced-titration strategies that were deployed in the landmark clinical trials. We cannot assume that subtarget strategies are ineffective or inferior, but we do know that they are untested and unproven.

Therefore, we can ask physicians to describe (i) whether patients are receiving each of the recommended neurohormonal antagonists; (ii) whether patients are being treated with target doses of each of these drugs; and (iii) if they are receiving the drug at subtarget doses, whether the patient had been tried on higher doses that could not be tolerated, despite reasonable efforts at rechallenge or adjustment of concomitant medications. Accordingly, three strata are proposed. *Stratum I* represents the deployment of the specific trial-based strategies that have been shown to prolong survival, i.e. the use of target doses or the use of the highest tolerated doses using the forced-titration regimens shown to be effective in reducing mortality. *Stratum II* represents the use of the drug at a subtarget dose for reasons that are unrelated to demonstrable and clinically important intolerance (e.g. patient or physician preferences, overemphasis of clinical stability, fears of the possibility of adverse effects, lack of knowledge of target doses); all of these reasons are grouped together in a non-hierarchical manner. This stratum is intended to encompass the prescribing of drugs in all ways that do not specifically replicate the strategies that were utilized in the landmark clinical trials. *Stratum III* indicates that the patient is not receiving the critical drug at any dose.

The proposed approach is non-judgmental, i.e. it does not designate any stratum as being 'optimal', 'acceptable' or 'adequate'. It does not make reference to a guideline, since there are numerous different guidelines throughout the world. The proposed approach also does not ask physicians to distinguish among all possible reasons for the prescribing of non-target doses, since it is failure

Table 1 Proposed framework for characterizing the adherence of individual patients to trial-based strategies for the prescribing of neurohormonal antagonists for heart failure and a reduced ejection fraction

	Beta-blocker	Mineralocorticoid receptor blocker	Nephrilysin inhibitor	Inhibitor of renin-angiotensin system
Status I Receiving treatment consistent with strategy described in the landmark trial demonstrating a survival benefit	In sinus rhythm and receiving a trial-proven beta-blocker at target doses (carvedilol 25 mg twice daily, metoprolol succinate 200 mg once daily, or bisoprolol 10 mg daily)	Receiving spironolactone or eplerenone at target doses, (spironolactone ≥ 25 mg daily or eplerenone 50 mg daily)	Receiving target doses of sacubitril/valsartan (97/103 mg twice daily)	Receiving sacubitril/valsartan
	In sinus rhythm and receiving subtarget doses of a trial-proven beta-blocker; was prescribed higher doses, but these could not be maintained because of documented clinically relevant bradycardia or intolerable drug-related symptoms, which persisted despite adjustment of other medications or In atrial fibrillation or atrial flutter and is receiving carvedilol, metoprolol succinate, or bisoprolol	Receiving spironolactone or eplerenone at subtarget doses; was prescribed higher doses, but these could not be maintained because of documented serum $K^+ \geq 5.5$ mmol/L or intolerable drug-related adverse effects, which persisted despite adjustment of other medications	Receiving subtarget doses of sacubitril/valsartan; was prescribed higher doses, but these could not be maintained because of documented symptomatic hypotension, doubling of serum creatinine, serum $K^+ \geq 5.5$ mmol/L, or intolerable drug-related adverse effects, which persisted despite adjustment of other medications	Receiving enalapril ≥ 10 mg twice daily or equivalent or Receiving candesartan 32 mg daily or valsartan 160 mg twice daily or Receiving subtarget doses of ACE inhibitor; candesartan or valsartan; was prescribed higher doses, but these could not be maintained because of documented symptomatic hypotension, doubling of serum creatinine, serum $K^+ \geq 5.5$ mmol/L, or intolerable drug-related symptoms, which persisted despite adjustment of other medications
Status II Receiving treatment according to a strategy that differs from that described in the landmark trial demonstrating a survival benefit	The patient is in sinus rhythm and receiving a trial-proven beta-blocker or In sinus rhythm and receiving subtarget doses of trial-proven beta-blocker and has not been prescribed higher doses or In sinus rhythm and receiving subtarget doses of trial-proven beta-blocker; was prescribed higher doses that were not maintained because of asymptomatic changes in heart rate or blood pressure or due to physician or patient preferences	Receiving spironolactone or eplerenone at subtarget doses and was not prescribed higher doses or Receiving spironolactone or eplerenone at subtarget doses; was prescribed higher doses that were not maintained but there has been no documentation of serum $K^+ \geq 5.5$ mmol/L or intolerable drug-related adverse effects, which persisted despite adjustment of other medications or Receiving spironolactone or eplerenone; was prescribed higher doses that were not maintained due to physician or patient preferences	Receiving subtarget doses of sacubitril/valsartan and has not been prescribed higher doses or Receiving subtarget doses of sacubitril/valsartan and was prescribed higher doses that were not maintained due to asymptomatic changes in blood pressure or laboratory tests or Receiving subtarget doses of sacubitril/valsartan and was prescribed higher doses that were not maintained due to physician or patient preferences	Receiving subtarget doses of an ACE inhibitor or ARB and has not been prescribed higher doses or Receiving subtarget doses of an ACE inhibitor or ARB; was prescribed higher doses that were not maintained due to asymptomatic changes in blood pressure or laboratory tests or Receiving subtarget doses of an ACE inhibitor or ARB; was prescribed higher doses that were not maintained due to physician or patient preferences
Status III Not receiving the specified treatment	Not receiving beta-blocker	Not receiving spironolactone or eplerenone	Not receiving sacubitril/valsartan	Not receiving an ACE inhibitor or ARB

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

to follow a forced-titration strategy that matters rather than the reasons for not following it.

Table 1 displays one possible approach to the definition of the three strata. Thresholds are proposed for the identification of patients who would reside in stratum I, stratum II, or stratum III. The table is presented only for purposes of illustration. The clinical community needs to debate and revise the proposed criteria and

reach consensus as to the definitions of specific strata. However, the debate must start somewhere, and Table 1 represents a starting point.

An advantage of the approach presented in the table is that it allows physicians to readily describe the degree to which an individual patient's treatment adheres to a trial-proven strategy. Simple abbreviations could be used to refer to each drug class,

i.e. RAS for ACE inhibitors and angiotensin receptor blockers; BB for beta-blockers; MRA for spironolactone or eplerenone; and ARNI for neprilysin inhibition. Accordingly, a patient receiving target doses of carvedilol, sacubitril/valsartan and spironolactone might be described as BB1/ARNI1/MRA1. Conversely, a patient who is taking enalapril 5 mg twice daily and metoprolol tartrate 50 mg twice daily but no mineralocorticoid receptor antagonist or neprilysin inhibitor would be designated as RAS2/BB2/MRA3/ARNI3. Finally, a patient who is receiving sacubitril/valsartan, carvedilol and spironolactone at subtarget doses and was prescribed higher doses but shown to be intolerant despite a concerted effort would be designated as BB1/ARNI1/MRA1, since the patient received treatment in accordance with forced strategies used in the landmark trials.

Each of the criteria proposed in the table deserves thought and deliberation, particularly with respect to the use of beta-blockers. Since not all beta-blockers reduce mortality, the only members of the drug class that warrant inclusion in stratum I are those that have been specifically shown to reduce mortality in large-scale trials. Furthermore, analyses of these trials have raised important questions about the ability of beta-blockers to prolong survival in patients with atrial fibrillation,⁴⁸ potentially because the target doses used in the pivotal trials may have caused excessive slowing of the ventricular response, which predisposed to fatal bradyarrhythmic events.⁴⁹ Consequently, patients with atrial fibrillation who are treated with a beta-blocker are assigned to stratum I with no designated target heart rate, since heart rates of 80–90 bpm may be appropriate targets for the use of beta-blockers if patients have atrial fibrillation.⁵⁰

Concluding remarks and future directions

Despite compelling evidence that several neurohormonal antagonists used in combination have a striking effect to prolong survival in patients with chronic heart failure and a reduced ejection fraction, most eligible patients are not receiving all recommended classes of drugs, and treated patients are usually prescribed subtarget doses. Typically, patients are receiving doses that are used for initiation of treatment; these doses are maintained for long periods of time, and no or little attempt is made to achieve target doses or show that patients are intolerant of higher doses. As a result, the vast majority of patients with heart failure and a reduced ejection fraction in clinical practice are receiving treatments that have been demonstrated to exert meaningful effect on the natural history of the disease.

The failure of physicians to treat patients with trial-proven regimens has numerous complex causes. However, an important contributor to the current state of affairs is the fact that physicians can readily claim that the use of subtarget doses is fully compatible with recommendations of current guidelines. Practice guidelines do not describe what regimens are acceptable, adequate or reasonable; thus, most treatments can be labelled as consistent with 'guideline-directed medical therapy'.

Perhaps, adherence to the trial-proven regimens might be markedly improved if physicians were asked to document the degree to which a patient's treatment adheres to or deviates from

the strategies that were used to demonstrate the benefits of the neurohormonal antagonists that have demonstrated survival benefits. All of the landmark trials were 'strategy trials', i.e. the studies mandated a standardized forced-titration treatment plan to a target dose. Investigators were required to increase the dose at specified increments and intervals to achieve a target dose, even if the patient experienced asymptomatic but unwanted changes in vital signs or laboratory tests. Investigators were also required to make repeated efforts to achieve and maintain target doses, often adjusting concomitant medications to improve the likelihood of tolerance. 'Forced-titration strategies' were an essential element of every trial that demonstrated a survival benefit.

The proposed framework reminds practitioners that these 'forced-titration strategies' are the basis for current class I recommendations about the use of combinations of neurohormonal antagonists. If subtarget doses are prescribed, physicians are asked if they faithfully utilized the 'forced-titration strategy' used in the landmark trials. Using the proposed framework, it is possible for a clinician to fully describe the status of heart failure therapy for each patient with a reduced ejection fraction in a single line of four words or less.

As a first step towards implementation of our framework, we suggest that authors should refrain from using the terms, 'guideline-directed medical therapy' or 'optimal medical therapy' as a description of background therapy. Whenever possible, investigators should provide a granular description of how trial-based strategies and target doses of neurohormonal antagonists were actually utilized in their study population. *Table 1* may be used as one of several possible templates.

The proposed framework should increase practitioner awareness about the use of unproven subtarget doses that are prescribed outside the structure of forced-titration strategies. Our proposal would also allow clinical investigators to precisely describe the adequacy of background medical therapy in clinical studies. The framework is a starting point for initiating the community-wide discourse that is desperately needed to enhance adherence to evidence-based treatments for patients with chronic heart failure and a reduced ejection fraction. Our proposal can be expanded to include other treatments for heart failure (e.g. devices), but this initial effort is best served by being focused, rather than inclusive. Prospective evaluation and validation of the merits of the proposed framework are warranted.⁴

Conflict of interest: M.P. has consulted for Abbvie, Actavis, Akcea, Amgen, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi-Sankyo, Johnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance. M.M. has consulted for Bayer, Novartis and Servier.

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