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EDITORIAL COMMENT

# Target Dose Versus Maximum Tolerated Dose in Heart Failure

## Time to Calibrate and Define Actionable Goals*

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Despite compelling scientific evidence and guidelines on benefits of maximum targeted doses with angiotensin-converting enzyme inhibitors (ACEIs) and beta-blockers (BBs) in heart failure (HF) clinical trials (1), target doses are usually not achieved in clinical practice (**Figure 1A**) (2). There are a variety of reasons for this gap including patient intolerance and side effects; provider aversion and inertia (3); and systems, data, and cost limitations. Target doses defined in clinical trials are important for goal-setting, and are achievable in the majority, but not in all patients, as reported in most clinical trials (**Figures 1A and 1B**). Even when achieved, doses may need to be reduced or discontinued in a small percentage of patients (**Figure 1A**). Nevertheless, guideline-directed medical therapy (GDMT) should be targeted in all patients without contraindications.

Although the evidence for benefit for HF medications such as ACEIs or BBs strengthened over time, success rates for achieving maximum doses have not increased in clinical trials or registries (**Figures 1A and 1B**). Still, interventions can result in significant improvements, as noted by the higher proportion of patients treated with GDMT post-intervention compared to baseline in the IMPROVE-HF (Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting) registry for outpatients (Online Appendix), or at discharge compared to baseline in the ADHERE (Acute Decompensated Heart Failure National Registry) registry for inpatients (Online Appendix) (**Figure 1B**). These highlight potential closable gaps in practice. On the other hand, there are also considerable gaps in data collection. Clinical documentation and coding for contraindications or intolerance to treatment; specific etiologies requiring different and individualized treatment strategies are inadequate.

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The study by Peri-Okonny et al. (4) published in this issue of *JACC: Heart Failure* adds to published reports showing that HF medications are commonly administered when indicated, but dosing is significantly lower than what is recommended by trials. They report that in outpatients with chronic HF with reduced ejection fraction with indications for GDMT, after exclusions of patients who had side effects or contraindications, and those with poor life expectancy: 61% of the patients were receiving an ACEI or angiotensin receptor blocker (ARB), 12.9% an ARB with neprilysin inhibitor (ARNi), and 82.7% a BB. Compared to the parent CHAMP-HF (Contemporary Change the Management of Patients With Heart Failure) registry (2), it appears that by exclusion of patients specified above, a proportion of patients on BBs improved from 67% to 82.7% (**Figure 1B**) (4), but a proportion of patients on ACEI/ARB or ARNi did not change. This suggests that in the parent registry, sicker or end-of-life patients were not treated with BBs. Furthermore, a proportion of patients receiving maximum target doses were low at 10.8% for ACEI/ARB, 18.7% for BB, and 2.0% for ARNi (4). These rates were only slightly higher for those patients with systolic blood pressure (SBP) ≥ 110 mm Hg compared to

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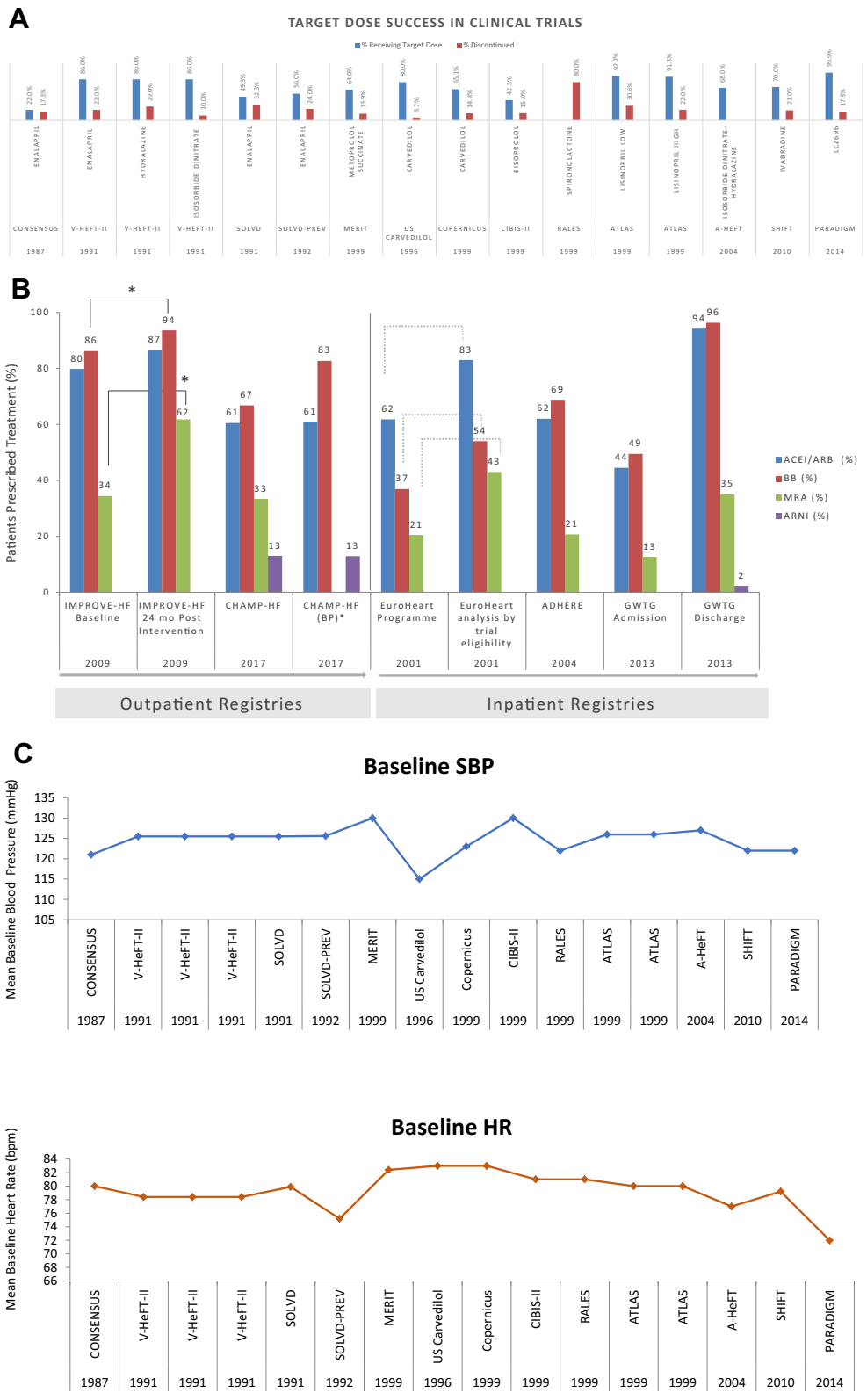
**FIGURE 1** **Proportion of Patient Doses**

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patients with SBP <110 mm Hg. Approximately 10% of the patients with SBP ≥110 mm Hg and 6% of those with SBP <110 mm Hg were receiving target doses of ACEI/ARB or ARNI and a BB. This improved only slightly when SBP cutoff levels were increased from 100 to 130 mm Hg. Contrary to former concerns, SBP did not appear to be a major reason for failure to up-titrate HF medications to target doses; but among patients who could be titrated to optimal doses, BP may have played a role for success. Additionally, after excluding patients with heart rate (HR) <60 beats/min, similar results were noted, suggesting bradycardia was not a major limitation either.

BP can imply different things in HF. It can be a target for HF treatment and BP control, a diagnostic and prognostic sign of pump failure, and a limitation to tolerability. Further, SBP has a complex nonlinear association with mortality in patients with HF. Whereas, it has a U-shaped association in patients with HF with mild left ventricular dysfunction; it has a linear association with mortality in patients with HF with low ejection fraction (5), with lower SBP reflecting advanced pump failure and association with mortality. Thus, the impact of BP cannot be inferred solely from the BP value itself, but differentially in the context of the phenotype and trajectory of the patient. It would have been interesting to see how SBP played a role in different patient phenotypes, such as those with advanced symptoms and low SBP versus those with mild symptoms. The interquartile range of 110 to 130 mm Hg in this study suggests a rather stable SBP profile (4). This can partially be explained by exclusion of hypotensive patients, which may have masked a larger difference in proportion of patients on target doses according to low BP (4). Nevertheless, even if we accept that low BP may have played a role in inability to up-titrate GDMT in patients with SBP <110 mm Hg, there is no obvious explanation for under-treatment of patients with SBP ≥110 mm Hg.

Major limitations of the study by Peri-Okonny et al. (4) include lack of data on subsequent measurements of BP, changes in treatment or clinical status over time, reasons for suboptimal doses, and adjustment for risk or comorbidities. Furthermore, the CHAMP-HF registry included stable ambulatory patients with HF from diverse practices with a high representation of white male patients (2,4); therefore, results may not be generalizable to other populations or practices. Although higher rates of prescription rates were reported from cardiology practices compared to family medicine or internal medicine practices (4), it would not be realistic to expect specialty intervention as the main solution to close the treatment gap.

Current GDMT entails multiple new medications (1) raising the questions of whether lower doses of more medications are better than maximum doses of a few, and whether the increases in number of medications will reduce the room for up-titration. Although the HR appears to have declined, baseline SBP levels do not appear to have changed over time in clinical trials (**Figure 1C**). This may be due to enrollment criteria; yet mean SBP or HR do not appear to have changed in population based HF registries either (Online Appendix). For example, in the IMPROVE-HF outpatient registry (2005 to 2009), mean baseline SBP was 120 mm Hg and HR was 71 beats/min. In the contemporary CHAMP-HF registry (2015 to 2017), mean baseline SBP or HR values were similar at 120 mm Hg and 72 beats/min, respectively (Online Appendix). Among eligible patients, the GDMT use was not higher in the CHAMP-HF (2) registry compared to the IMPROVE-HF registry (Online Appendix), and the proportion of patients on maximum doses of multiple therapies was <1% to 2% (2,4). Overall, there was a lack of improvement in the GDMT rates, along with lack of changes in SBP or HR in outpatient HF registries in the last decade. Hence, we can safely conclude that there is room for up-titration of GDMT in most patients.

Although target dose can be an important goal and should be attempted in most, further

**FIGURE 1 Continued**

**(A)** Proportion of patients (%) on maximum target doses of medications in clinical trials in patients with heart failure (HF) and reduced ejection fraction **(blue bars),** and proportion (%) of patients discontinued from study medication due to intolerance or side effects **(red bars).** Names of trials, study medication, and year of publication are shown on the x-axis. Trials noted are referenced in the Online Appendix. **(B)** Proportion of patients (%) prescribed angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) **(blue),** beta blockers (BB) **(red),** mineralocorticoid receptor antagonists (MRA) **(green),** and ARB with neprilysin inhibitor (ARNI) **(purple)** in outpatient **(left)** and inpatient **(right)** registries. Registry names, and last year of follow-up completion is represented on the x-axis. **Solid lines** indicate significant improvement (*) in BB and MRA use at 24 months after intervention to optimize medical treatment, compared to baseline in the Improve HF registry (Online Appendix). **Dashed lines** represent EuroHeart analysis by trial eligibility criteria reveal that by restricting patient eligibility to trial criteria, proportion of patients on guideline-directed medical therapy appear higher. Registries noted are referenced in Online Appendix. **(C)** Mean baseline blood pressure (mm Hg) **(blue line)** and heart rate (beats/minute, [BPM]) **(orange line)** across clinical trials over time. Names of trials, study medication, and year of publication are shown on the x-axis.

individualization of therapy according to etiology, clinical profile, tolerance, and side effects is also critical. In the study by Peri-Okonny et al. (4), 27% of the patients were excluded due to potential contraindications or side effects. Still, even among subgroups of trial-eligible patients, GDMT rates and doses were significantly lower than targets, indicating that under-use of evidence-based therapies is only partially explained by dissimilarity to patients enrolled in trials. In the CHAMP registry (2), the proportion of patients on target doses of mineralocorticoid receptor antagonists (76.6 %) was higher than the proportion of patients on target doses of ACEI/ARB (17.5 %) or BBs (27.5%) (2). Despite a narrow therapeutic margin, simplicity of dosing may have played a role in achieving target doses for spironolactone or eplerenone (2).

We are reminded 1 more time that the glass is not full regarding optimization of standard therapies in patients with HF. In addition to raising awareness to optimize GDMT, there is a need for capturing the optimal dose for an individual patient when the target dose cannot be tolerated, so that the provider versus patient or system reasons can be clearly separated. Appropriate documentation of the "maximum tolerated dose," with reasons for intolerance after repeated attempts to achieve a higher dose can be an alternative as a performance indicator, as long as it is further up-titrated with an intend to reach the target dose. Similarly, it is important to specify the proportion of patients expected to be on target doses as a goal, rather than expecting all patients to be on target doses. This would allow clinicians to be able to specify patient factors, eliminate the excuse of the impossibility of maximum doses in all patients, make goals achievable on an individual basis, and help close the gaps due to provider inaction.

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**KEY WORDS** dose, guidelines, heart failure, maximum tolerated dose, target dose, treatment

**APPENDIX** For additional references, please see the online version of this paper.