

Effect of sacubitril/valsartan vs. enalapril on changes in heart failure therapies over time: the PARADIGM-HF trial

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Aims

Sacubitril/valsartan improves morbidity and mortality in patients with heart failure and reduced ejection fraction (HFrEF). Whether initiation of sacubitril/valsartan limits the use and dosing of other elements of guideline-directed medical therapy for HFrEF is unknown. We examined the effects of sacubitril/valsartan, compared with enalapril, on β -blocker and mineralocorticoid receptor antagonist (MRA) use and dosing in a large randomized clinical trial.

Methods and results

Patients with full data on medication use were included. We examined β -blocker and MRA use in patients randomized to sacubitril/valsartan vs. enalapril through 12-month follow-up. New initiations and discontinuations of β -blocker and MRA were compared between treatment groups. Overall, 8398 (99.9%) had full medication and dose data at baseline. Baseline use of β -blocker and MRA at any dose was 87% and 56%, respectively. Mean doses of β -blocker and MRA were similar between treatment groups at baseline and at 6-month and 12-month follow-up. New initiations through 12-month follow-up were infrequent and similar in the sacubitril/valsartan and enalapril groups for β -blockers [37 (9.0%) vs. 42 (10.2%), $P = 0.56$] and MRA [127 (7.6%) vs. 143 (9.2%), $P = 0.10$]. Among patients on MRA therapy at baseline, there were fewer MRA discontinuations in patients on sacubitril/valsartan as compared with enalapril at 12 months [125 (6.2%) vs. 187 (9.0%), $P = 0.001$]. Discontinuations of β -blockers were not significantly different between groups in follow-up (2.2% vs. 2.6%, $P = 0.26$).

Conclusions

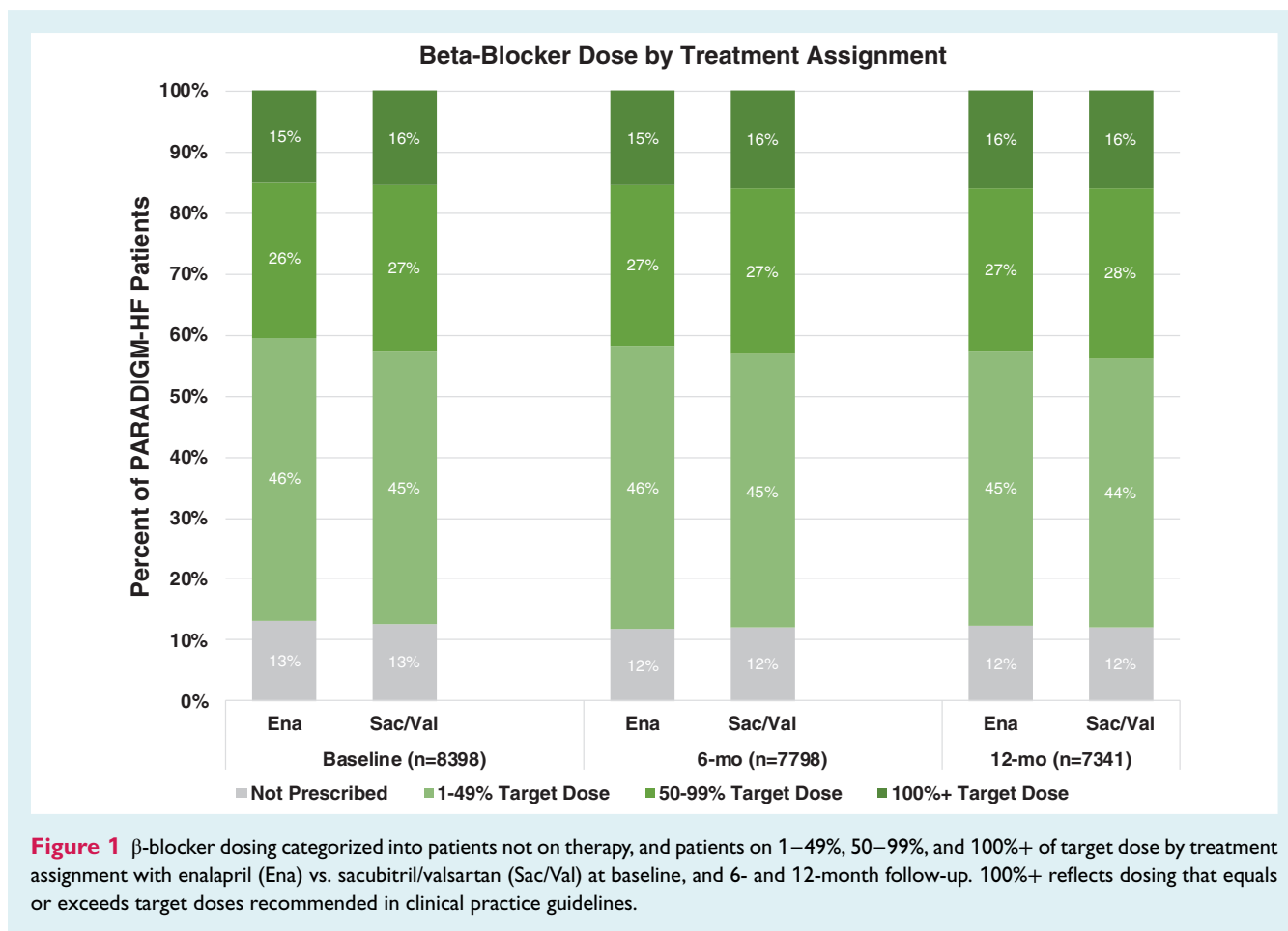
Initiation of sacubitril/valsartan, even when titrated to target dose, did not appear to lead to greater discontinuation or dose down-titration of other key guideline-directed medical therapies, and was associated with fewer discontinuations of MRA. Use of sacubitril/valsartan (when compared with enalapril) may promote sustained MRA use in follow-up.

Keywords

β -blockers • Guideline-directed medical therapy • Heart failure with reduced ejection fraction • Mineralocorticoid receptor antagonists • Sacubitril/valsartan

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doses were based on the 2016 European Society of Cardiology (ESC) HF guidelines.² Target doses for β -blockers were bisoprolol 10 mg daily, carvedilol 25 mg twice daily, and extended-release metoprolol 200 mg once daily. Given variable definitions of target dosing for MRA and lack of consistent demonstrated dose response on clinical outcomes, dosing was summarized for β -blocker only.

Among patients not receiving β -blocker and MRA at baseline, new initiations were compared by treatment arm in follow-up. Similarly, among patients receiving β -blocker and MRA at baseline, discontinuations were compared during follow-up by treatment arm. New initiations and discontinuations were assessed among patients alive and with available data at each follow-up time point. A P -value <0.05 was considered statistically significant.

Results

Baseline characteristics

Overall, of 8399 patients validly randomized in PARADIGM-HF, 8398 (99.9%) had full medication/dose data for β -blocker and MRA at baseline. Full medication/dose data were available in 7341 (87.4%) and 7340 (87.4%) patients for β -blocker and MRA, respectively at 12 months. Baseline characteristics by randomization assignment according to baseline β -blocker and MRA use have been previously reported.^{6,7} Of note, age, systolic blood pressure, heart

rate, and kidney function were well balanced between treatment arms.

β -blocker use during 12-month follow-up

β -blocker use was similar between groups at baseline (sacubitril/valsartan: 87.4% vs. enalapril: 86.8%, $P = 0.40$), and at 6-month (88.0% vs. 88.2%, $P = 0.88$), and 12-month follow-up (87.9% vs. 87.6%, $P = 0.63$). As previously reported, of all patients on β -blockers at baseline, 47.7% were on $\geq 50\%$ target dose and 17.4% were on $\geq 100\%$ target dose.⁶ Mean β -blocker doses were not significantly different between those on sacubitril/valsartan and enalapril at any time point (Table 1). Patients receiving sacubitril/valsartan had higher rates of $\geq 50\%$ target β -blocker dose at baseline (42.7% vs. 40.4%, $P = 0.036$), though there were no significant differences at 6 months (43.2% vs. 41.9%, $P = 0.24$) and 12 months (43.8% vs. 42.6%, $P = 0.24$) post-randomization (Figure 1).

Among patients not on β -blocker, new initiations were infrequent and similar based on treatment with sacubitril/valsartan vs. enalapril at 6-month [31 (7.0%) vs. 36 (8.0%), $P = 0.57$] and 12-month follow-up [37 (9.0%) vs. 42 (10.2%), $P = 0.56$] (Figure 2A). Among patients on β -blocker, discontinuations occurred at similar

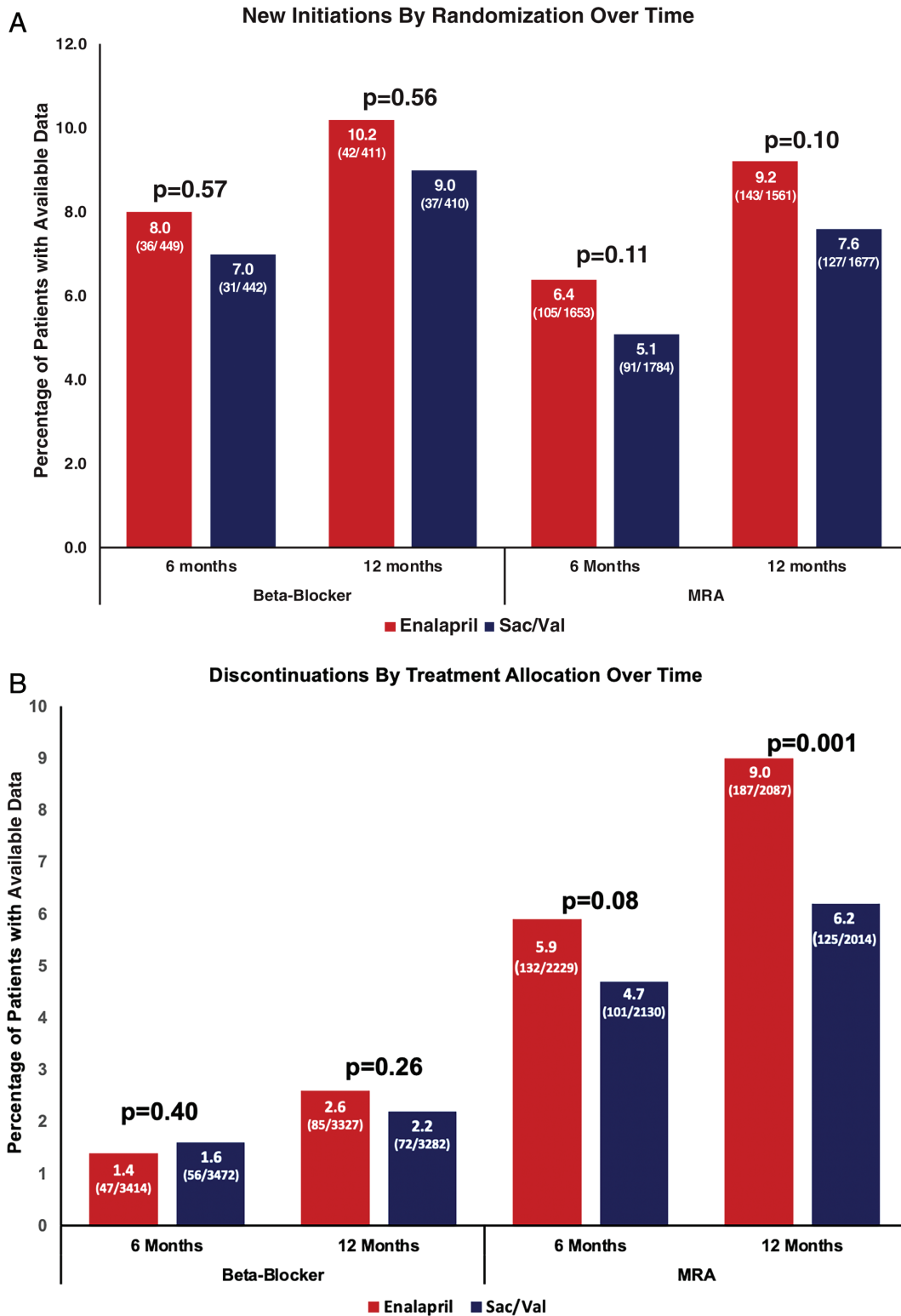


Figure 2 New initiations (A) and discontinuations (B) of β -blocker and mineralocorticoid receptor antagonist (MRA) at 6 and 12 months post-randomization. Sac/Val, sacubitril/valsartan. Note: Percentage for new initiations are calculated as the proportion of patients newly initiating therapy among all patients not previously on this particular therapy. Percentages for discontinuations are calculated as the proportion of patients discontinuing therapy among all patients previously on this particular therapy.

rates at 6 months [56 (1.6%) vs. 47 (1.4%), $P = 0.40$] and 12 months [72 (2.2%) vs. 85 (2.6%), $P = 0.26$] (Figure 2B).

Mineralocorticoid receptor antagonist use during 12-month follow-up

Patients receiving sacubitril/valsartan had lower MRA use as compared with those receiving enalapril at baseline (53.9% vs. 56.4%, $P = 0.02$) and at 6 months post-randomization (53.4% vs. 56.9%, $P = 0.05$). At 12 months post-randomization, there were no significant differences in MRA use by treatment arm (54.6% vs. 56.0%, $P = 0.23$). Mean doses of spironolactone and eplerenone were similar between groups at all time points (Table 1).

Among patients not on MRA, new initiations did not significantly differ by treatment with sacubitril/valsartan vs. enalapril at 6 months [91 (5.1%) vs. 105 (6.4%), $P = 0.11$] and 12 months [127 (7.6%) vs. 143 (9.2%), $P = 0.10$] (Figure 2A). However, in patients on MRA, there were fewer discontinuations of MRA in patients assigned to sacubitril/valsartan as compared to enalapril at 6 months post-randomization [101 (4.7%) vs. 132 (5.9%), $P = 0.08$], reaching significance at 12 months post-randomization [125 (6.2%) vs. 187 (9.0%), $P = 0.001$] (Figure 2B).

Discussion

Given multiple disease-modifying benefits in patients with HFrEF,¹⁰ achieving comprehensive combination regimens is a high treatment priority. However, many of these therapies influence haemodynamics, electrolytes, and kidney function; upfront initiation of certain GDMT components may influence the subsequent tolerability of other core elements. Integration of new GDMT without compromising other foundational therapies is a major therapeutic goal in HFrEF management, and these data from PARADIGM-HF provide some reassurance that this can be practically achieved when initiating sacubitril/valsartan. This tolerability should be interpreted within the context of the PARADIGM-HF study design, in which enrolled subjects were optimized on these classes of therapies and tolerated sequential open-label run-in phases (including with full-dose sacubitril/valsartan) prior to enrolment.

Patients on sacubitril/valsartan had lower discontinuation rates of MRA in follow-up. This finding suggests that transitioning to sacubitril/valsartan may facilitate sustained MRA use. Favourable effects on kidney function¹¹ may promote sustained MRA therapy. Previous reports have also found lower rates of incident hyperkalaemia with sacubitril/valsartan compared with enalapril, which may also contribute to lower MRA discontinuation rates.⁷ Similar findings of lower treatment-attendant hyperkalaemia have been observed with the sodium–glucose co-transporter 2 inhibitors, dapagliflozin and empagliflozin.^{12,13} As sacubitril/valsartan is well-recognized to promote clinical stability,¹⁴ it is plausible that lower frequency of MRA discontinuation was related to lower rates of HF hospitalization and therapeutic destabilization in the sacubitril/valsartan-treated patients.¹⁵ As therapeutic changes to GDMT may be more likely to occur during hospitalization,

this may also in part account for the reduction in MRA discontinuations in those on sacubitril/valsartan. We observed a non-significant trend towards fewer MRA new initiations among sacubitril/valsartan-treated participants by 12 months compared with enalapril-treated participants. Similar patterns of MRA use in follow-up have been observed in contemporary evaluations with the sodium–glucose co-transporter 2 inhibitor empagliflozin.¹³ These consistent patterns reinforce that clinicians may be less likely to modify GDMT among patients who are considered clinically stable. Contemporary consensus statements now recommend early ARNI initiation among eligible patients, in addition to other core GDMT elements.¹⁶ These data support that sacubitril/valsartan does not appear to lead to discontinuation of other foundational GDMT.

Limitations of post-hoc investigation should be acknowledged. We did not have information regarding prior medication trials, including previous attempts at initiation of β -blockers and MRA. While patients were well-balanced with respect to most baseline characteristics, differences that emerged over time may have influenced initiations or discontinuations that were not fully captured within this analysis. Baseline medication use differs slightly from those reported in the original PARADIGM-HF trial⁴ as this analysis focused only on evidence-based β -blocker and MRA recommended in current HFrEF guidelines as opposed to any drug within the respective class.^{1,2} Target doses included in this study (derived from ESC clinical practice guidelines) may differ from those included in other international guidelines or those tested in pivotal randomized clinical trials. Sequential run-in phases may have selected for patients who had demonstrated ability to tolerate sacubitril/valsartan in addition to background therapy. Unmeasured confounding leading to differential tolerability to MRA in each arm may also in part explain these findings. Finally, reasons for treatment changes in background therapies were not prospectively collected from site investigators.

Conclusion

Multi-drug regimens in HFrEF require simultaneous balancing of multiple factors (haemodynamics, kidney function, electrolytes, affordability, and adherence). In PARADIGM-HF, initiation of sacubitril/valsartan did not influence use and dosing of β -blocker and was associated with less discontinuations of background MRA therapy, compared with enalapril. These data are reassuring that in a well-monitored clinical trial cohort, initiation of sacubitril/valsartan leads to minimal disruption of other background HFrEF therapy and may promote sustained MRA use. Further data are needed from usual care settings to understand the practicalities of various combinations and sequencing of contemporary GDMT in HFrEF.

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