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Short communication

Long-term clinical outcomes of valsartan in patients with a systemic right ventricle: Follow-up of a multicenter randomized controlled trial☆

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ABSTRACT

Objectives: In the VAL-SERVE (Valsartan in Systemic Right Ventricle) trial, three-year valsartan treatment improved systemic ventricular function only in symptomatic patients with congenitally or with an atrial switch corrected transposition of the great arteries. The aim of the current study was to investigate the longer-term clinical outcomes after valsartan treatment.
Methods: From 2006 to 2009, 88 adults were randomly allocated 1:1 to either valsartan or placebo for three consecutive years. Endpoints were defined as overall survival and freedom from clinical events (arrhythmia, heart failure, tricuspid valve surgery, death).
Results: Cardiac drug use and median follow-up after trial close-out (8.3 years) was similar between the randomization groups. Six patients (valsartan $n = 3$, placebo $n = 3$) died in 364 and 365 person-years ($P = 0.999$). No difference in the composite or separate clinical endpoints was found between the randomization groups, with corresponding long-term event-free survival rates of 50% and 34%. Nevertheless, in symptomatic patients valsartan significantly reduced the risk for events compared to placebo (HR 0.37, 95% CI 0.17–0.92). Analysis for repeated events and on-treatment analysis with any renin-angiotensin-aldosterone-system-inhibitor did not alter these results.
Conclusions: Valsartan treatment in systemic RV patients did not result in improved survival at longer-term follow-up, but was associated with decreased risk of events in symptomatic patients.

1. Introduction

In patients after atrial-switch correction for complete transposition of the great arteries (TGA) or with congenitally corrected transposition of the great arteries (ccTGA), gradual failure of the systemic right ventricle (RV) seems inevitable—being the main contributor to morbidity and mortality [1,2].

To date, the few available data on heart failure treatment with renin-angiotensin-aldosterone system (RAAS)-inhibitors in this patient population are not conclusive and mostly derived from small patient numbers [3–9]. In the Valsartan in the Systemic Right Ventricle (VAL-SERVE) trial, we failed to establish an overall effect with valsartan on RV function at 3 years, but observed positive ventricular remodeling in symptomatic patients [9].

However, in the studies of systolic left ventricular (LV) dysfunction, enalapril treatment for 3–4 years reduced mortality in symptomatic but not asymptomatic patients during the trial [10,11]. In fact, surprisingly a reduction in mortality of asymptomatic patients was only seen during the 12-year follow-up [12]. Considering that most patients with systemic RVs also remain asymptomatic despite having ventricular dysfunction, we hypothesized that they bear more resemblance to the asymptomatic LV dysfunction patient population. We therefore sought to assess the longer-term effects of valsartan on clinical outcomes in patients enrolled in the VAL-SERVE trial.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. Study background

The design and conduct of the VAL-SERVE trial have been described in detail elsewhere [9,13]. In brief, between 2006 and 2009, 88 adults with TGA or ccTGA identified from the Dutch CONgenital CORvitia registry were enrolled at 6 university medical centers. Patients were randomly 1:1 assigned, in a double-blind fashion, to valsartan or placebo for three consecutive years. The ethics committee approved the study protocol. All patients provided written informed consent.

2.2. Follow-up

Definitions of events have been reported previously [9]: (supra)ventricular arrhythmias; worsening heart failure; tricuspid valve surgery; and death. To prevent selection bias, all events and data on drug use from randomization were site determined and verified by source documentation. The national mortality registry was queried to obtain the survival status. Being symptomatic was defined as New York Heart Association (NYHA) class ≥2 and asymptomatic as NYHA class 1. Review of clinical records by an independent investigator resulted in reclassification of 3 patients (2 were reclassified as asymptomatic and 1 as symptomatic).

2.3. Statistical analysis

Primary analyses were performed by intention-to-treat, according to randomization groups. Patient time was accrued from time of randomization until outcome of interest or censored at last available follow-up. Time-to-event curves were estimated by means of the Kaplan-Meier method, with inference based on the log-rank test. Treatment effects were expressed as hazard ratios (HR) with 95% confidence intervals (CI) using Cox regression. As potential effects with respect to the original allocation may dilute over time and patient-crossover may occur, additional on-treatment analyses were performed through time-dependent analysis with RAAS-inhibitors (i.e., angiotensin II receptor blocker [ARB] or angiotensin-converting-enzyme inhibitor [ACE-I]). Repeated events were analyzed by the Andersen–Gill approach, which considers each type of event as a separate term in the partial likelihood. For standard errors, a robust variance estimator that allowed for heterogeneity in event rates between patients was used.

We anticipated finding a clinically relevant difference between symptomatic and asymptomatic patients because of positive ventricular remodeling during the trial in the former. Thus, Cox models were also stratified by this subgroup, and tested for interaction.

Statistical analyses were performed using SPSS 23 (IBM Corporation, Armonk, USA) and Rstudio (Vienna, Austria). A 2-tailed P value of <0.05 was considered statistically significant.

3. Results

Of the 88 patients, 44 were randomly assigned to valsartan and 44 to placebo treatment. The randomization groups were well-balanced with respect to baseline characteristics. At inclusion, average age was 33 ± 10 years, one-third was symptomatic (27% vs. 34%), and the majority was male (66% vs. 64%) and had TGA (64% vs. 80%). During the trial, 16 patients (n = 10 valsartan [23%], n = 6 placebo [14%]) discontinued their study medication, resulting in mean treatment duration of 338 vs. 452 days, respectively (P = 0.52). Follow-up data after trial close-out were available for 87 patients (99%). Follow-up duration was similar for the randomization groups; median of 8.3 (interquartile range 7.2–9.0) years since randomization.

3.1. Drug use after trial close-out

After trial close-out, 17 patients (n = 10 valsartan [23%], n = 7 placebo [16%]) continued valsartan treatment whereas 11 patients in both groups (26%) switched to other ARBs or ACE-Is (Fig. 1). No difference was observed in the proportion of patients taking RAAS-inhibitors (49% vs. 42%, P = 0.668), nor in duration of treatment (4.0 ± 1.9 vs. 3.3 ± 1.7 years, P = 0.262). Similarly, use of other cardiac drugs was comparable (β-blockers 44 vs. 53%, P = 0.394, diuretics 21 vs. 23%, P = 0.800, antiarrhythmic drugs 23 vs. 37%, P = 0.165).

3.2. Mortality

Mortality was similar for the randomization groups with 3 deaths in 363.5 person-years in the valsartan and 3 deaths in 365.0 person-years in the placebo group (P = 0.999). Time-dependent analysis with total RAAS-inhibitor use rendered similar results. Three deaths were attributable to heart failure; two patients died suddenly, and one patient died from complications of bronchiectasis.

3.3. Clinical events

During follow-up, 23 patients in the valsartan group (52%) and 30 patients in the placebo group (60%) experienced a primary clinical event. In the primary analysis, valsartan treatment resulted in a non-significant reduction in the composite end point of all-cause mortality or events (HR 0.65, 95% CI 0.38–1.12). The separate clinical endpoints were observed equally after valsartan or placebo treatment; supraventricular arrhythmias (41 [n = 18] vs. 50% [n = 22]), ventricular arrhythmias (27 [n = 12] vs. 27% [n = 12]), worsening heart failure (23 [n = 10] vs. 23% [n = 10]), and tricuspid valve surgery (6 [n = 3] vs. 6% [n = 3]). The absolute number of event rate also did not differ significantly (event rates 36.3 vs. 44.4 per 100 person-years in the valsartan vs. placebo groups). Results from time-dependent analysis with RAAS-inhibitors were similar to those of the main analysis. One-third of patients experienced more than one type of event. In repeated event analysis, valsartan did not prolong time of onset between consecutive events. Seven (8%) patients received a pacemaker and nine (10%) an implantable cardioverter-defibrillator. No patient underwent cardiac transplantation.

3.4. Symptomatic versus asymptomatic patients

In symptomatic patients, survival was lower (81%) compared to asymptomatic patients (98%; P = 0.010) and risk of events was higher (HR 2.04, 95% CI 1.17–3.56). Valsartan did not improve survival, but significantly reduced the risk for events in symptomatic patients (HR 0.37, 95% CI 0.14–0.93; Fig. 2A) and not in asymptomatic patients (HR 0.84, 95% CI 0.42–1.69; Fig. 2B). Yet, we were unable to demonstrate a significantly greater treatment benefit among symptomatic compared to asymptomatic patients (P = 0.146 for interaction).

4. Discussion

The results of this long-term follow-up study demonstrate that there was no overall clinical benefit associated with valsartan treatment after >8 years in patients with systemic RVs. Yet, our data suggest that valsartan reduces morbidity in symptomatic patients, extending the favorable outcomes from the previous trial.

We did not observe the clinical benefits from RAAS-inhibition as expected from the major LV dysfunction studies [12,14]. This may be partially explained by study limitations, such as low patient number, low mortality numbers and insufficient power to evaluate clinical endpoints. On the other hand, intrinsic reasons should also be considered. First, as the angiotensin II receptor density is equal in right and left ventricles [15], one might expect similar effects of valsartan in LV and RV dysfunction. Yet, systemic RV dysfunction is heterogeneous in pathophysiology and clinical course, rather than being a single disease. Second, despite having ventricular dysfunction many patients remain clinically stable for a long period. Third, half of our patients had just mild dysfunction at baseline, in contrast to patients with clearly reduced ejection fraction (EF) (≤35%) included in most LV studies. Indeed, in heart failure with preserved LVEF, the effects of RAAS-inhibitors have also been disappointing [16].

It is noteworthy that valsartan reduced morbidity in symptomatic patients, albeit in absence of an interaction effect (notably because of lack of power). Possibly, symptomatic patients may derive greater gain from treatment because of more neurohormonal activation. Bolger et al. [17] reported that the degree of neurohormonal activation strongly relates to NYHA class in patients with congenital heart disease. Indeed, we found a trend towards higher baseline N-terminal pro-brain natriuretic peptide and aldosterone levels in symptomatic patients

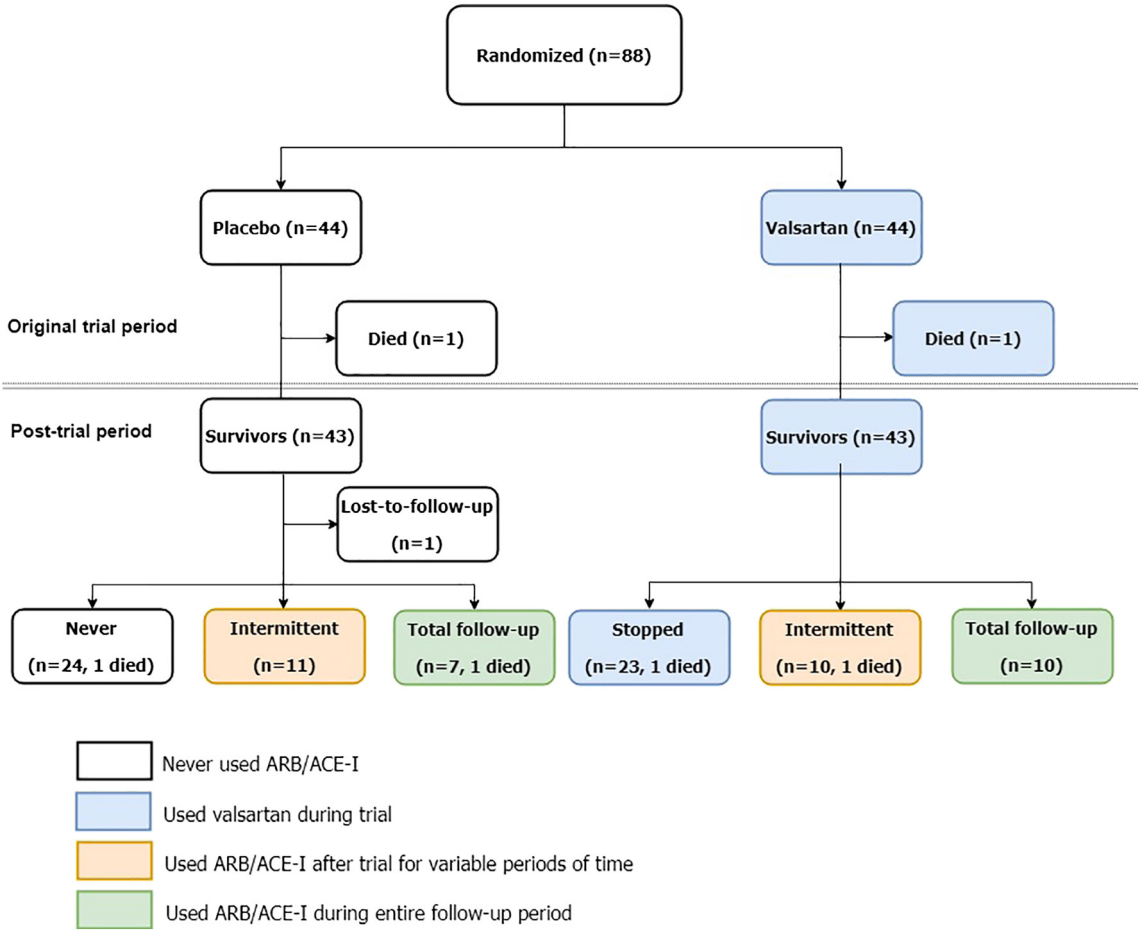

Fig. 1. Post-trial use of angiotensin II receptor blockers and ACE-inhibitors. ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor agonist.

($P = 0.07$ and $P = 0.06$). Another possible mechanism is that positive ventricular remodeling in symptomatic patients during the trial [9] translated into the favorable clinical outcomes later observed.

5. Limitations

The limitations of the study include its retrospective design and the fact that the trial was originally not designed nor explicitly powered for clinical endpoints. No a-priori hypothesis for long-term follow-up was defined. Also, we used the NYHA criteria for the classification of symptomatic patients because of its long-established role in heart failure. Nonetheless, this classification is a rough estimate of functional status and inherent to subjective judgment. Subgroup analysis must be interpreted cautiously since the hypothesis was derived from the entire study cohort.

6. Conclusions

Treatment with valsartan is not associated with an overall improved clinical outcome in systemic RV patients after >8 years. Our results

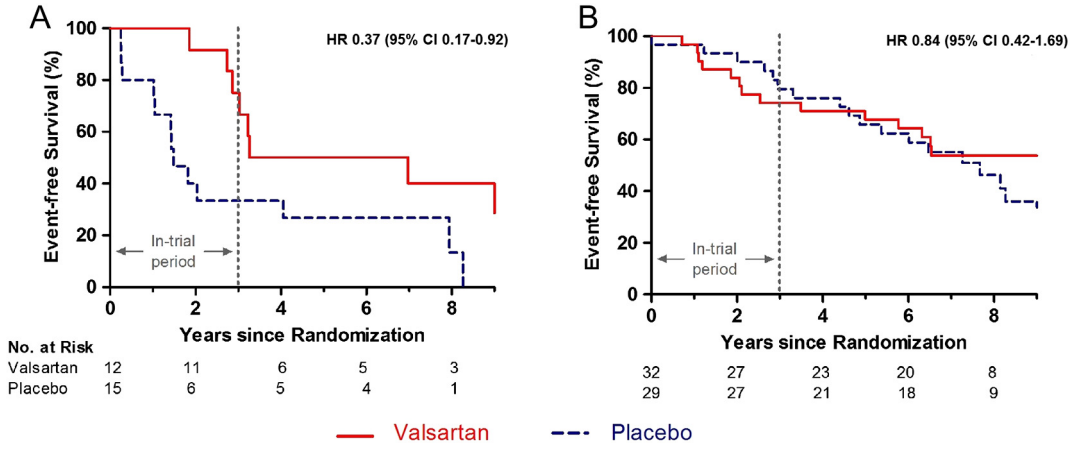

Fig. 2. Event-free survival curves for (A) the symptomatic subgroup, and (B) the asymptomatic subgroup - Time = 0 refers to the date of randomization. The dotted line indicates the end of the 3-year in-trial period. HR, hazard ratio; CI, confidence interval.

suggest, however, that symptomatic patients could benefit from treatment with favorable long-term clinical outcomes. Until more prospective long-term data become available, such heart failure therapy should be considered for symptomatic patients.

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Conflict of interest

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