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Real-world effectiveness and safety of sacubitril/valsartan in heart failure: A systematic review

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ABSTRACT

Background: PARADIGM-HF demonstrated superiority of sacubitril/valsartan (sac/val) over enalapril in patients with heart failure with reduced ejection fraction (HFrEF). However, patients in clinical practice may differ in their characteristics and overall risk compared with patients in clinical trials, and additional outcomes can be observed in real world (RW). Hence, a systematic review was conducted to identify and describe RW data on sac/val.
Methods: RW studies evaluating the effects of sac/val in adult patients with HFrEF with a sample size ≥100 were identified via MEDLINE® and Embase® from 2015 to January 2020. Citations were screened, critically appraised and relevant data were extracted.
Results: A total of 68 unique studies were identified. Nearly half of the studies were conducted in Europe ($n = 34$), followed by the US ($n = 15$) and Asia ($n = 11$). Median follow-up period varied from 1 to 19 months. Mean age ranged between 48.7 and 79.0 years; patients were mostly male and in New York Heart Association (NYHA) functional class II/III, and mean left ventricular ejection fraction varied between 23%and 38%. Of studies performing comparisons, most reported superior efficacy of sac/val in reducing the risk of HF hospitalisations, all-cause hospitalisations, and all-cause mortality as compared to standard-of-care. Many studies reported significant improvements in NYHA functional class and reduction in biomarker levels post sac/val. Hypotension and hyperkalaemia were the most frequently reported adverse events.
Conclusions: This comprehensive overview of currently available RW evidence on sac/val complements the evidence from randomised controlled trials, substantiating its effectiveness in heterogeneous real-world HF populations.

1. Introduction

Sacubitril/valsartan (sac/val) is a first-in-class angiotensin receptor-neprilysin inhibitor, which demonstrated superior efficacy over enalapril in reducing the risk of the composite primary endpoint of death from cardiovascular (CV) causes or HF hospitalisation by 20% and reducing all-cause mortality by 16% in the PARADIGM-HF trial [1]. Sac/val was recommended as a new treatment option for patients with heart failure with reduced ejection fraction (HFrEF) in the 2016 European Society for Cardiology guidelines (ESC) [2] and the 2016 American College of Cardiology/American Heart Association (ACC/AHA) guidelines [3] and more recent consensus statements reflect additional evidence from studies in patients with acute decompensated heart failure [4,5].

Randomised controlled trials (RCTs) are crucial in establishing the efficacy and safety of any novel treatment, but patients in clinical trial settings may differ in their demographics, clinical characteristics and overall risk compared with patients in clinical practice. In addition, real-world evidence (RWE) allows longer follow-up and provides insights on effectiveness in a less controlled environment, including complexities of less close management of patients compared with a trial and potentially lower adherence rates. Hence, it is also important to understand the real-world outcomes with new therapies. RWE may therefore provide estimates of the effect of treatment on outcomes in a broader range of patients and is playing an increasing role in comprehensive evidence-based decision-making by clinicians, payers and health technology assessment agencies.

Since regulatory approval in 2015, a number of observational studies have been published describing patient characteristics and clinical outcomes with sac/val when used in real-world clinical practice. However, no study to date has reviewed this literature systematically to provide synthesised insights. For instance, Joly et al. [6] have reviewed sac/val clinical trials that led to the key updates to guidelines and also reviewed utilisation in clinical practice but did not report on effectiveness in a

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real-world setting. Moliner-Abos et al. [7] conducted a retrospective study to analyse the efficacy and safety of sac/val in an advanced heart failure (HF) cohort and have also reviewed systematically previous real-world studies. However, only an overview of the studies and patient characteristics were reported. We therefore performed a systematic review to identify and describe real-world observational studies of sac/val in patients with HFrEF.

2. Methods

2.1. Identification of studies and search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. Medical Literature Analysis and Retrieval System Online® (MEDLINE®; including MEDLINE® In-Process) and Excerpta Medica® (Embase®) databases were searched for original research articles and conference abstracts (from 2015 to 14 January 2020). The search strategy included both free-text words and medical subject headings. The main search terms included disease keywords ('heart failure', 'congestive cardiomyopathy', 'cardiac failure', 'cardiac insufficiency'), treatment ('sacubitril/valsartan', 'lcz696') and keywords for real-word studies (full search strategy is shown in Supplementary Table 8). References cited in key publications and/or systematic reviews identified during screening were also manually searched to identify any additional published literature not identified during the database searches.

2.2. Eligibility criteria and study selection

Publications eligible for inclusion were English-language, observational, original research studies of adult patients with HFrEF (sample size ≥100) that reported clinical outcomes with sac/val in real-life practice. The study selection process was carried out according to predefined eligibility criteria and was performed by two independent reviewers, with any discrepancies between the reviewers reconciled by a third independent reviewer.

2.3. Data assessment and interpretation

Outcomes of interest were: study characteristics; patient characteristics; clinical effectiveness outcomes (HF hospitalisations, all-cause hospitalisations, CV mortality, all-cause mortality, New York Heart Association [NYHA] functional class, change in the biomarker N-terminal pro-brain natriuretic peptide [NT-proBNP], health-related quality of life); information on dosing and titration; and safety outcomes (adverse events, intolerance, treatment discontinuation). Data were extracted into a specifically designed data extraction grid in MS Excel. Data from multiple publications of the same study were merged. Data extraction was performed by one reviewer and verified independently by another reviewer. When studies reported duplicate data, the most recent report from the same cohort was included to reflect contemporary practice. The methodological quality of each study was evaluated using the Newcastle-Ottawa scale (NOS). This scale is widely used to assess the risk of bias in observational studies [9]. Briefly, this scale has eight questions, and allocates up to nine points in four domains: selection of study groups (four points), comparability of groups (two points) and ascertainment of exposure and outcomes (three points). Higher numbers indicate higher methodologic quality/lower risk of bias.

2.3.1. Quantitative assessment

A number of studies compared clinical outcomes in patients treated with sac/val versus angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEi/ARBs). The feasibility of undertaking meta-analysis for these outcomes was examined. Both fixed effect and random effect models were adopted and chi-square tests used to examine heterogeneity between studies. The I^2 statistic was used to estimate the percentage of total variation across studies, with an I^2 value of greater than 50% considered indicative of substantial heterogeneity. A two-sided P value <0.05 was considered statistically significant. All statistical analyses were conducted with R software version 3.5.3 (R project for statistical computing) [10].

3. Results

3.1. Study selection and included studies

The literature search yielded 988 citations from which 114 publications (sample size ≥100) were included after screening; an additional 10 publications were identified from bibliographic searches. Following linking of multiple publications, 68 unique studies (from 124 publications) were included. The PRISMA diagram and details of the study characteristics are described in Supplementary Fig. 1 and Table 1. Among the included evidence were 26 manuscripts and 42 conference abstracts. Nearly half of the studies were conducted in Europe ($n = 34$), followed by the US ($n = 15$), Asia ($n = 11$), Canada ($n = 5$) and Australia ($n = 1$); two studies did not report the country. Most studies ($n = 49$) were retrospective in design; 19 were prospective observational studies. The number of study participants ranged from 100 to 91,609; 26% ($n = 18$) included ≥500 patients. The median follow-up period varied from 1 to 19 months; most of the studies ($n = 55$) had a median

Table 1
Comparison of baseline characteristics of real world studies and PARADIGM-HF trial.

Baseline characteristics	PARADIGM-HF Sacubitril/valsartan ($N = 4187$)	Real world data Sacubitril/valsartan ($N = 100–8291$) Median[a] (range)
Age, years, mean (SD)	63.8 (11.5)	67.4 (48.8–79.0)
Female sex, (%)	21.0	25.4 (1.5–41.2)
White, (%)	66.0	72.8 (45.6–99.0)
NYHA functional class, (%)		
I	4.3	2.0 (0–16.2)
II	71.6	63.3 (25.0–87.4)
III	23.1	30.0 (10.3–95.3)
IV	0.8	2.8 (0–15.0)
Lab parameters, mean (SD)		
Systolic blood pressure, mm Hg	122.0 (15.0)	121.0 (109.0–130.0)
Heart rate, beats/min	72.0 (12.0)	69.8 (67.0–85.0)
Body mass index, kg/m^2	28.1 (5.5)	28.9 (24.2–32.8)
Serum creatinine, mg/dL	1.1 (0.3)	1.2 (1.0–1.5)
Clinical features of heart failure		
Ischemic cardiomyopathy, (%)	59.9	53.8 (25.0–82.0)
Left ventricular ejection fraction, % (SD)	29.6 (6.1)	28.9 (23.0–38.0)
Median NT-proBNP (IQR), pg/ml, median (IQR)	1631.0 (885.0–3154.0)	2201.4 (992.0–4044.0)
Medical History, (%)		
Hypertension	70.9	71.7 (16.7–98.0)
Diabetes	34.7	39.8 (10.0–61.0)
Atrial fibrillation	36.2	39.5 (19.6–60.0)
Myocardial infarction	43.4	19.7 (4.0–54.0)
Treatments at randomization, (%)		
Diuretic	80.3	67.2 (43.7–88.0)
β-Blocker	93.1	92.4 (64.6–100.0)
Mineralocorticoid antagonist	54.2	72.1 (18.4–98.0)
Implantable cardioverter–defibrillator	14.9	47.2 (17.0–65.2)
Cardiac resynchronization therapy	7.0	25.9 (6.0–60.9)

N=No. of patients; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; IQR: Interquartile range; SD: Standard deviation.
[a] Median values for RW studies represent the median from the range of values reported from individual included studies (no adjustment was made for sample size).

follow-up period of ≤12 months. Quality assessment scores were higher for manuscripts (ranged from 5 to 7 of 9) and lower for conference abstracts (ranged from 2 to 5 of 9), mainly owing to the limited information available around patient selection and outcome description in the latter (Supplementary Table 7).

3.2. Patient characteristics

Mean age of patients ranged from 48.7 to 79.0 years, >50% were male (58.8%-98.5%) and most belonged to the NYHA class II/III. Ischaemic aetiology was reported in a wide-ranging proportion of patients (25%–82%), and the mean left ventricular ejection fraction (LVEF) was between 23% and 38%. Hypertension (16.7%–98%) and diabetes (10%–61%) were the most commonly reported comorbidities across studies. Table 1 provides a comparison of baseline characteristics extracted from real-world studies with those of PARADIGM-HF. Although baseline characteristics varied considerably, median values from across the studies were quite similar to PARADIGM-HF, with some notable exceptions – for example more patients in NYHA class III and less in NYHA class II, fewer patients with a history of myocardial infarction, and higher use of MRA and cardiac devices in real-world patients.

3.3. Clinical effectiveness outcomes

Overall, 25 studies analysed hospitalisations due to HF after initiation of sac/val, wherein the proportion of patients hospitalised with HF ranged from 2% to 22.2% over a follow-up period of 1-–18.6 months. Nearly half of the studies ($n = 11$) presented a comparative assessment either with standard of care ($n = 6$) or before versus after sac/val use ($n = 5$). Of the six studies (five in US, one in Taiwan) comparing the effects of sac/val with standard of care (ACEi/ARBs), three studies reported a significantly lower risk of HF hospitalisation with sac/val [11–13] Fig. 1A. Most performed propensity scoring to provide matched control patients receiving ACEi/ARBs. In one study the comparator group comprised patients who did not receive sac/val, with 70% receiving ACEi/ARBs [11]. All five studies comparing HF hospitalisation before and after initiation of sac/val showed a significant reduction in the number of hospitalised patients, varying from 5.4% to 15% over a period of 3–7.4 months [7,14–17] (Supplementary Fig. 2). The rest of the studies, which did not provide a comparative evaluation, reported hospitalisations or mortality only as a safety event during the follow-up. These studies assessed tolerability of sac/val, effects of the treatment on NT-proBNP or changes in the NYHA functional class as their primary objectives.

Hospitalisations due to any cause after initiation of sac/val were analysed in 16 studies. The proportion of patients hospitalised ranged from 3.4% to 59% over a follow-up period of 1–15.8 months. Of these 16 studies, most ($n = 10$) compared either with standard of care ($n = 6$) or before versus after sac/val use ($n = 4$). All six studies comparing the effects of sac/val with ACEi/ARBs were conducted in the US and reported a significantly lower risk of all-cause hospitalisation with sac/val [12,13,16,18–20] (Fig. 1A). All studies performed adjusted comparisons, typically using propensity score matching. Three of four studies reporting all-cause hospitalisation before and after initiation of sac/val showed a significant reduction in the proportion of patients hospitalised, varying from 14.5% to 18% ($p < 0.05$) [16,21,22]. The fourth one, Albert et al. reported marginally significant results ($p = 0.050$) [15] (Supplementary Fig. 2).

After initiation of sac/val, the proportion of patients who died due to CV causes varied from 0% to 15% over a follow-up period of 3-–18.6 months, as reported in 13 studies. Of these 13 studies, only one study by Chang et al., conducted in Taiwan, performed a comparative assessment with standard HF treatment and found that sac/val was associated with a significantly lower risk of CV death during a period of 15 months in 466 patients in each group (HR: 0.50 [95% CI: 0.33–0.78], $p = 0.002$) [11] (Fig. 1A).

Across the 24 studies reporting all-cause mortality, the proportion of patients who died due to any cause varied from 0% to 28.9% over a follow-up period of 3–17 months. Of these 24 studies, three studies (two in US, one in Taiwan) compared the survival of patients taking sac/val against standard of care. One study was a matched comparison of sac/val with ACEi/ARBs using claims data [18], a second compared sac/val with ACEi/ARBs specifically in patients following hospitalisation [20] and a third was conducted in patients from a tertiary referral centre, with a comparator group of patients not receiving sac/val (70% received ACEi/ARBs) [11]. Follow-up duration varied considerably, from a median of 4.8 to 15 months. All three studies found that sac/val was associated with a significantly lower risk of all-cause mortality compared with ACEi/ARBs [11,18,20] (Fig. 1A). Meta-analysis showed significantly lower risk of all-cause mortality with sac/val as compared to ACEi/ARBs, in both fixed effect (HR: 0.78 [95% CI: 0.68–0.88]), and random effect (HR: 0.75 [95% CI: 0.61–0.92]) models. Moderate to high heterogeneity was observed ($I^2 = 57\%$), as presented in Fig. 1B.

Among three studies [11,23,24] reporting the composite outcome of CV death or HF hospitalisation, only one study by Chang et al. performed a comparative assessment with standard of care and reported significantly lower rates of the composite outcome associated with sac/val (HR: 0.65 [95% CI: 0.51–0.83], $p = 0.001$) over a period of 18.9 months [11] (Fig. 1A). Full details of hospitalisation and mortality outcomes are provided in Supplementary Table 6.

Apart from hospitalisations and mortality outcomes, many studies assessed changes in NYHA functional class ($n = 25$) and NT-proBNP levels ($n = 21$) before and after initiation of sac/val. A significant improvement in NYHA functional class was observed in 12 studies [14,17,21,22,25–32]. Fig. 2A shows functional class at baseline and follow-up. Percentage decrease in NT-proBNP levels varied considerably - from 4.14% to 70.19% across 20 studies, and a statistically significant decrease ($p < 0.05$) was observed in nine studies [7,22,27,29,30,32–35] as presented in Fig. 2B. A study by De Vecchis et al. [36] reported a significantly higher reduction in NT-proBNP levels compared with that seen with conventional therapy over a period of 3 months (65.6% vs 24.8%; $p < 0.0001$). The rest of the studies comparing the before and after NYHA class or NT-proBNP levels did not report the level of statistical significance (NYHA, $n = 10$; NT-proBNP, $n = 8$), were non-significant (NYHA, $n = 2$; NT-proBNP, $n = 3$) or did not provide data for the overall population (NYHA, n = 1; NT-proBNP, n = 1) (Supplementary Table 2 and Table 3).

One study by Khariton et al. described health-related quality of life. This study reported that patients on sac/val experienced a clinically meaningful average 5.3-point improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score compared with 2.5--points for the non- sac/val comparator group over a period of 2 months. In addition, 20% of patients on sac/val experienced a very large benefit (patient-level changes of ≥20-points) compared with 12% of patients who were not on sac/val therapy [37].

3.4. Safety and tolerability

In most studies, patients were initiated at a low dose of sac/val (24/26 mg) and may then have been up-titrated. Seven out of 29 studies reported that > 50% of total patients achieved the target dose over the follow-up period [26,33,36,38–41] (Supplementary Fig. 3 and Table 4). The rate of discontinuation reported for sac/val varied from 2% to 35.7% across studies during the follow-up period of 1–17.3 months (Fig. 3A). The main adverse event and deterrent to up-titration observed across studies assessing safety (n = 48) was symptomatic hypotension, followed by rising serum potassium levels and worsening renal function (Fig. 3B and Supplementary Table 5). Three studies compared the tolerability of sac/val with standard of care. Mohanty et al. [19] and Elasfar et al. [42] reported similar or fewer patients with discontinuation and intolerance with sac/val compared with standard of care, respectively (6.8% vs 11% and 6.4% vs 7.8%). In contrast, Tan et al. [18] reported

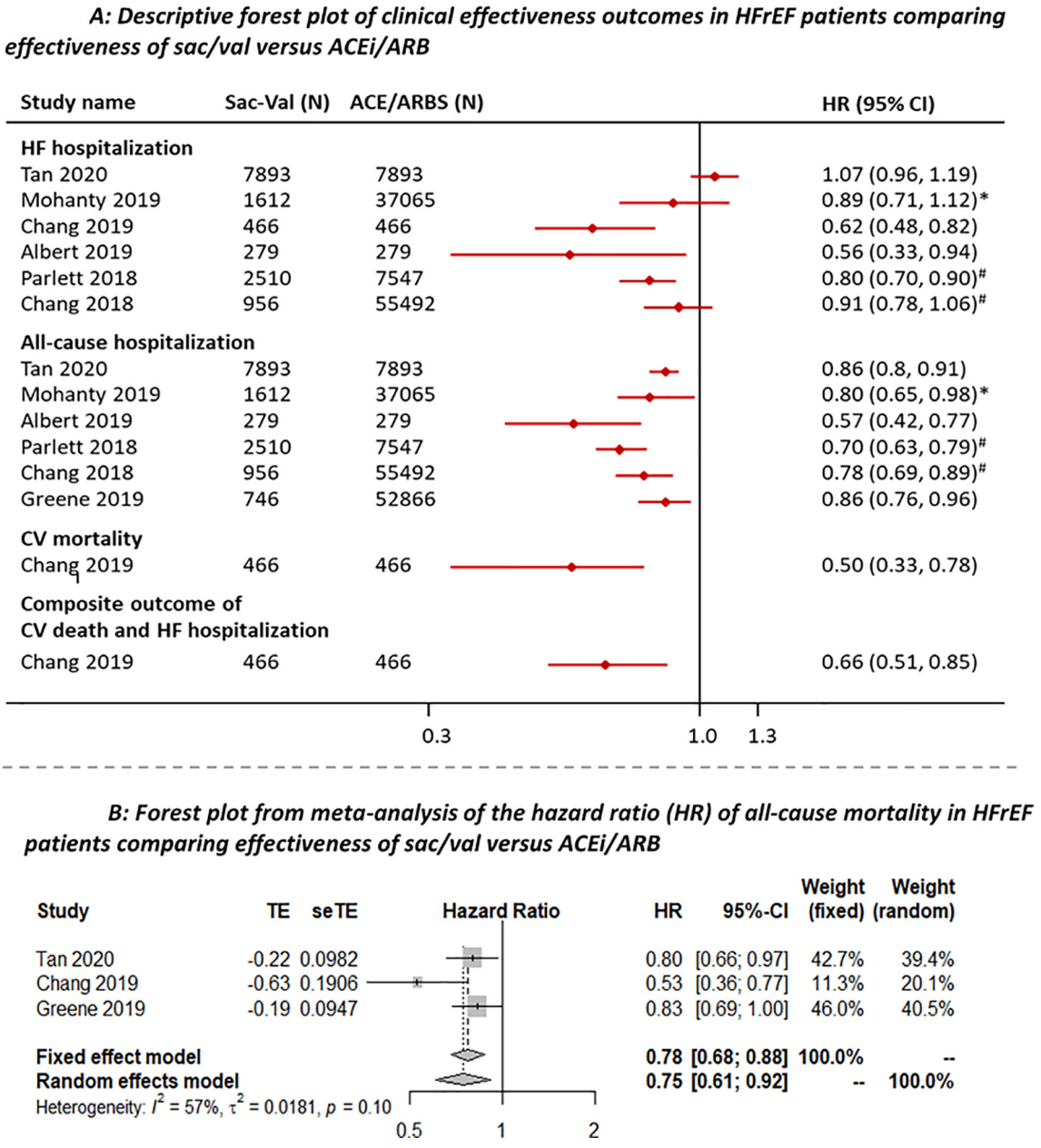

Fig. 1. Studies reporting comparative effectiveness of Sacubitril/Valsartan versus SoC (ACEi/ARBs). *Risk ratio; #Rate ratio. ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blocker; CI: Confidence intervals; CV: Cardiovascular; HF: Heart Failure; HR: Hazards ratio; N: Number of patients; Sac-Val: Sacubitril/valsartan; SoC: Standard of Care; seTE: standard error of total effect; TE: Total effect.

that the proportion of patients experiencing hypotension and hyperkalaemia were higher with sac/val treatment compared with ACEi/ARBs treatment (HR: 1.35 [95% CI: 1.05–1.75]; $p = 0.022$ and HR: 1.05 [95% CI: 0.66, 1.67]; $p = 0.84$, respectively).

4. Discussion

Understanding real-world efficacy and safety outcomes of new therapies, in broader patient populations and less controlled settings, can complement the evidence from gold standard RCTs, and support decision-making in clinical practice. To our knowledge, this is the first systematic review of a rich and growing RW evidence base for sac/val including 68 observational studies. Patient baseline characteristics varied considerably across the studies, reflecting the variation in real-world populations receiving sac/val across the globe. Although some studies were limited by small sample size, there were some notably large studies available, for instance, the study by Tan et al. included 8291 patients on sac/val, with 2244 in the study by Sangaralingham et al. [43].

In the PARADIGM-HF trial, sac/val reduced the risk of all-cause mortality by 16%, risk of CV death by 20% and risk of hospitalisation for HF by 21% ($p < 0.001$) compared with enalapril [1]. As seen in Fig. 1, most comparative observational studies assessing clinical outcomes showed significantly lower rates of HF hospitalisations and all-cause hospitalisations in patients receiving sac/val in routine practice compared with standard of care, consistent with the PARADIGM-HF results. Three of six studies reported that sac/val was associated with a significantly lower risk of HF hospitalisation [11–13]; Mohanty et al. and Chang et al. reported non-significant risk reductions [19], while Tan et al. [18] reported that the risk of HF hospitalisation was similar in

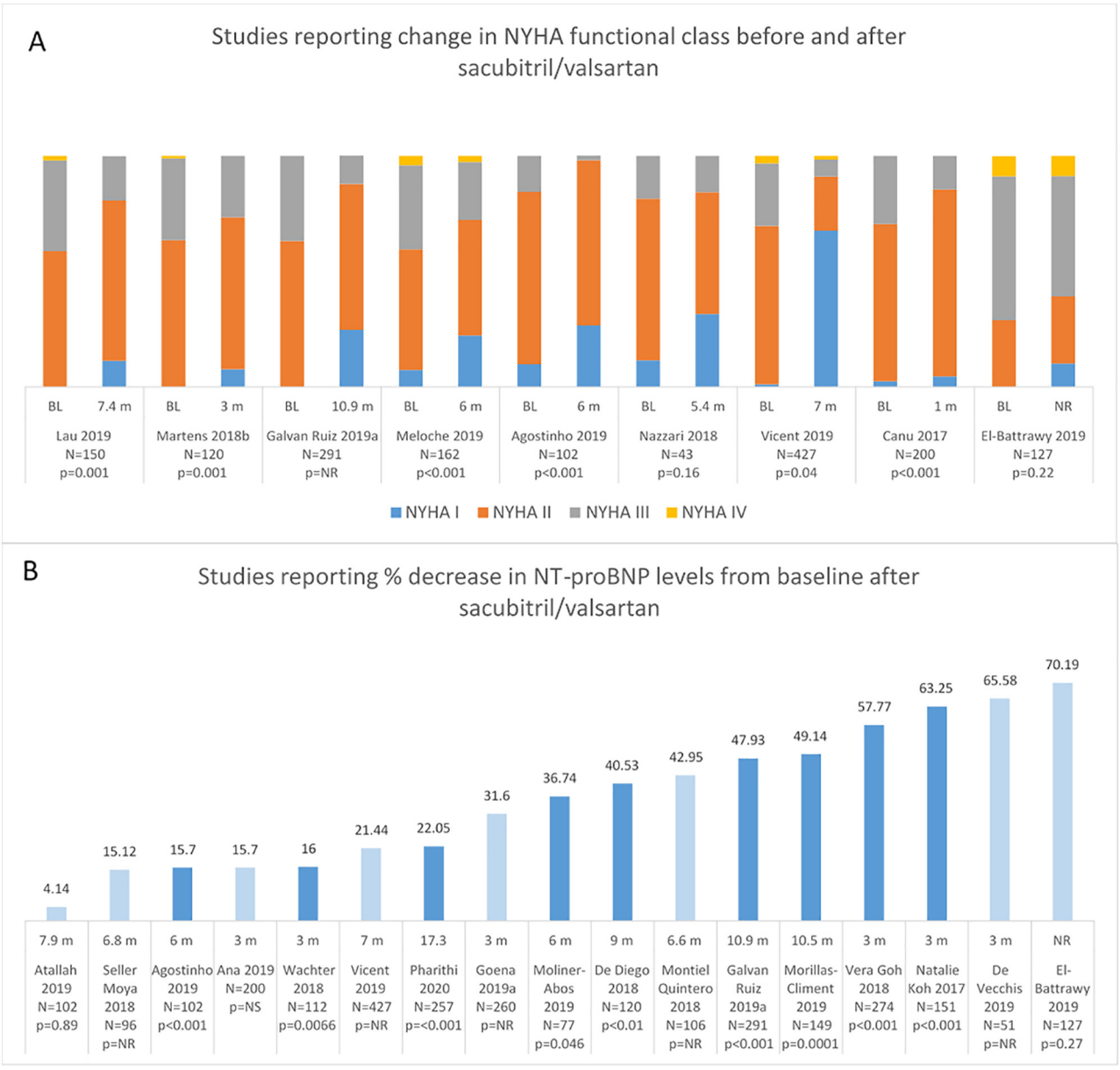

Fig. 2. Change in NYHA functional class and in NT-proBNP levels from studies comparing before and after sacubitril/valsartan initiation. Note: Fig. 1A is a simple forest plot developed by using data given in respective studies, no further statistical analysis was conducted. (A) Studies reporting NYHA functional class data for all patients at both baseline and follow-up have been presented here. For details of additional studies please refer to the Supplementary Table 2. (B) Studies providing overall data for all patients at both baseline and follow-up have been presented here. For details of additional studies please refer to the Supplementary Table 3.

both treatment groups (HR: 1.07; $p = 0.26$), despite finding a lower risk of all-cause hospitalisation with sac/val. The authors considered this discrepancy could have been due to differences in coding practices. Accurate identification of cause of death is more problematic in real-world data and CV mortality data from RWE does not have the accuracy of carefully adjudicated RCTs, although one study reported significantly lower CV mortality with sac/val than with ACEi/ARBs treatment. Due to variability in reporting of effect size measures (hazard ratio, risk ratio, rate ratio) and high heterogeneity for other outcomes, meta-analysis was conducted only for all-cause mortality. This analysis showed a significant reduction of 25% (random effect model, $p = 0.0053$) with sac/val compared with ACEi/ARBs based on all three comparative RW studies reporting this endpoint. Despite the limitations to meta-analysis of RW studies and observed between-study heterogeneity, it is reassuring to see data from RW studies in line with that from the pivotal RCT.

One of the treatment goals in patients with HFrEF is to improve health-related quality of life [HRQoL] and functional status [44]. A significant improvement in NYHA functional class with sac/val was observed across many studies reporting this outcome. The first RWE describing the potential HRQoL benefits of sac/val in patients from the CHAMP-HF registry was described by Khariton et al., who found that patients prescribed sac/val experienced early improvements in KCCQ score compared with patients not on sac/val, with more sac/val treated patients experiencing large improvements in HRQoL [37]. These

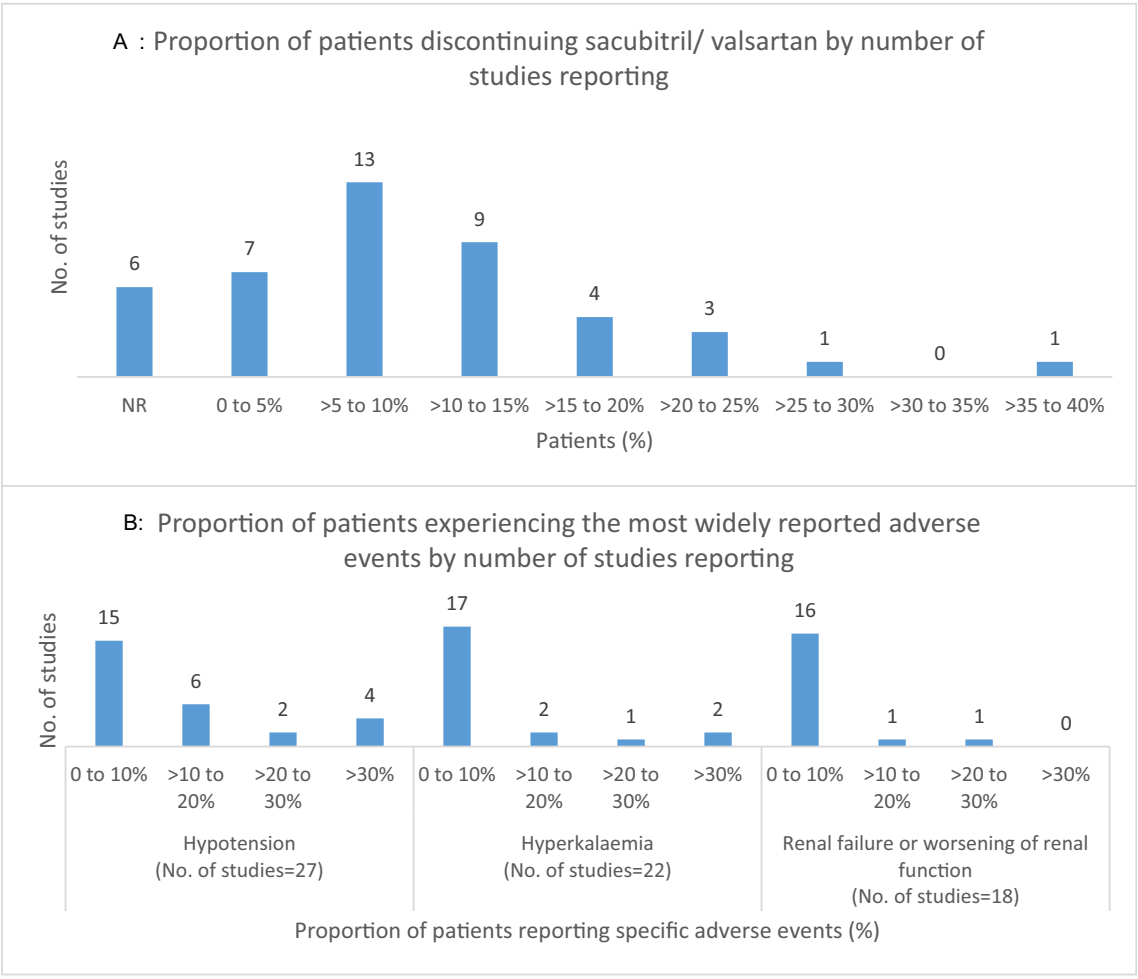

Fig. 3. Studies reporting discontinuations and adverse events following sacubitril/valsartan initiation. Additional details for A and B are available in Supplementary Table.5.

findings, from a heterogeneous RW population in USA, support the use of sac/val to improve patients' symptoms, and HRQoL.

Clinically, elevated levels of natriuretic peptides are useful for assessing prognosis in HF, and hence a number of real-world studies have also examined the effect of sac/val treatment on NT-proBNP. These studies showed consistent patterns of reduction in NT-proBNP in clinical practice. The results of PROVE-HF [45], an open-label study in patients with HFrEF, showed that the reduction in NT-proBNP concentration achieved with sac/val correlated significantly with signs of reverse cardiac remodelling at 1 year, suggesting that these widely reported real-world effects on NT-proBNP may translate into longer-term improvements in cardiac structure and function.

Across these real-world studies, the safety profile of sac/val appeared to be manageable and broadly in line with that observed in PARADIGM-HF and local labels. The main deterrent to up-titration was discontinuation owing to hypotension and worsening renal function. Despite that, the median value for drop-outs or discontinuations from real-world studies was 10.3% (range: 2%–35.7%), compared with 17.8% in PARADIGM-HF. One limitation to this comparison is, of course the differences in study duration.

Discontinuations due to renal impairment were less frequent in the sac/val group than in the enalapril group in the PARADIGM-HF trial, with less of a decrease in estimated glomerular filtration rate (eGFR) during follow-up [1]. In clinical practice, concern about renal function deterioration often limits the prescription of ACEi/ARBs in HF patients. As reported by Chang et al. [11], sac/val has potential benefits on renal function even in patients with chronic kidney disease with eGFR between 30 and 60 mL/min/1.73 m^2. The relative risk reduction of the composite endpoint of CV death or HF hospitalisations with sac/val compared with standard treatment was 28% in patients with chronic kidney disease stages IV or V ($p = 0.041$) and 14% in patients with chronic kidney disease stages I to III ($p = 0.039$). Consequently, this study emphasised the benefits of sac/val in patients with various stages of kidney disease.

Chang et al. [11] also reported that among the patients with baseline systolic blood pressure (SBP) ≥100 mmHg who fulfilled the inclusion criteria of the PARADIGM-HF trial, those treated with sac/val had 24% fewer cardiovascular deaths or hospitalisations for HF than those treated with standard HF treatment ($p < 0.001$). However, among patients with severe hypotension and baseline SBP <100 mmHg, both groups had similar event rates of cardiovascular deaths or unplanned hospitalisations for HF ($p = 0.331$).The authors noted that the sample sizes were relatively small, so should be interpreted with caution, and hypothesised that the hypotensive patients in their study could have been too sick and treated too late to derive benefit from sac/val. A post hoc analysis of the PARADIGM-HF trial showed the benefit of sac/val over enalapril was consistent across all baseline SBP groups for all outcomes [46].

4.1. Limitation

Some limitations should be noted. A limited number of comparative studies versus standard of care ($n = 7$) were identified. Most comparative studies were from the US, which likely reflects the time since launch, data infrastructure, differences in uptake, and thus patient numbers across geographies. Study objectives, designs, follow-up duration, included patient population and outcome definitions varied among the studies, which limits synthesis and conclusions. Attribution of endpoints to causes – for example specifying CV mortality as compared to all-cause, and HF hospitalisations as compared to all-cause – is much less precise in RWE data sources than in carefully adjudicated RCTs. Moreover, much of the data are from conference abstracts ($n = 42$), which have limited information on patient selection and outcome description, although they provided the most recent data to be included. The small number of comparative studies and heterogeneity in observational data for certain outcomes precluded extensive quantitative synthesis, therefore, results of most outcomes are descriptive in nature, although meta-analysis was performed for the key outcome of all-cause mortality.

5. Conclusion

This review provides a comprehensive overview of currently published real-world observational data showing effectiveness and safety of sac/val. In studies comparing before/after use of sac/val or comparing sac/val with ACEi/ARBs, improvements in HF hospitalisations, all-cause hospitalisations, all-cause mortality and CV mortality were reported. Benefits were also seen on NT-proBNP and NYHA class. The safety and tolerability profile was broadly consistent with that observed in PARADIGM-HF. This comprehensive evidence from real world complements the conclusions drawn from RCTs and supports the use of sac/val to replace ACEi/ARBs in patients with HFrEF.

Statement of authorship

Clare Proudfoot, Rachel Studer, Tanvi Rajput, Ramandeep Jindal, Rumjhum Agrawal, Stefano Corda, and Michele Senni take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Declaration of competing interest

The authors report no additional relationships that could be construed as a conflict of interest

Michele Senni is the Chief of Cardiovascular Department and Cardiology 1, Unit ASST Papa Giovanni XXIII hospital, Bergamo, Italy and declares financial interest for consultancy with Novartis, Merck, Bayer, Vifor Pharma, Abbott, Boehringer Ingelheim, AstraZeneca, and Servier. Clare Proudfoot, Rachel Studer and Stefano Corda are employees and stockholders in Novartis Pharma AG. Tanvi Rajput, Ramandeep Jindal and Rumjhum Agrawal are employees of Novartis Healthcare Pvt. Ltd. This study was funded by Novartis Pharma AG.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.01.061.

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