Sacubitril/valsartan in real-life European patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis

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Background: Real-world data are needed to gauge how a therapy is implemented in clinical practice.

Methods: We systematically reviewed the abstracts presented at international congresses and the peer-reviewed original research articles, which described the use of sacubitril/valsartan in European patients with HFrEF from Sep 2014 until Nov 30, 2019. Meta-analysis estimates were combined using a random effects model with inverse variance weights.

Results: 15 abstracts and 11 articles, including 14,179 patients, were selected. Except for a study that evaluated 12,082 (85,2%) subjects, the sample size was 28 (0.2%) to 1,120 (7.9%) patients.

Taking as reference PARADIGM-HF, few baseline characteristic were reported for >80% of the pooled population (Table), while all other ones were available for 12% of subjects or less (Figure). Underreporting was less common for articles than for abstracts (OR 0.42, 95% CI: 0.20–0.91). Compared with the patients enrolled in PARADIGM-HF, those in real-life were older and more likely to being previously treated with ARB, MRA and diuretics (Table). NYHA class III-IV (OR 2.39, 95% CI: 1.58–3.59; I2=92%), ICD (OR 4.21, 95% CI: 2.31–7.69; I2=93%) and CRT (OR 4.53, 95% CI: 3.89–5.27; I2=0%) were also more likely, while a history of hypertension was less frequent (OR 0.61, 95% CI: 0.42–0.87; I2=82%).

The monthly achievement rate of the full dose of sacubitril/valsartan was 6%. When follow-up was ≥6 months, the percentage of subjects reaching the full dose was about 40% and very homogenous. Age and full dose attainment were inversely related (β –2.71, 95% CI: –5.3 to –0.1).

All cause-mortality and hospitalization rates were 6/100 person-year (9 studies, 1046 patients) and 25/100 person-year (5 studies, 775 patients), respectively.

Conclusions: With the limitation of being heterogeneous and of overall low quality, the literature suggests that, in Europe, sacubitril/valsartan is prescribed to patients with somehow more severe HFrEF than in the pivotal trial, who most often do not reach the full dose.

Variables reported for >80% of patients

Baseline characteristic	Reporting studies N (% of tot.)	Pooled patients N (% of tot.)	Pooled mean (SD) or N (%)	vs. PARADIGM-HF
Age, years	23 (88)	13886 (98)	70.5 (12.2)	MD +3.07 (95% CI 0.81–5.33), P=0.008 I^2 = 97%, P<0.0001
Female sex	23 (88)	13843 (98)	5969 (43.1)	OR 1.10 (95% CI 0.88–1.39), P=0.40 I^2 = 81%, P<0.0001
Diabetes	14 (54)	13191 (93)	4625 (35.1)	OR 1.07 (95% CI 0.84–1.37), P=0.58 I^2 = 81%, P<0.0001
Prior ACEi	8 (31)	12831 (90)	7295 (56.9)	OR 0.59 (95% CI 0.43–0.81), P=0.013 I^2 = 79%, P<0.0001
Beta-blocker	14 (54)	13288 (94)	12011 (90)	OR 1.14 (95% CI 0.80–1.63), P=0.46 I^2 = 57%, P=0.017
MRA	14 (54)	13288 (94)	8648 (65)	OR 3.56 (95% CI 2.24–5.65), P<0.0001 I^2 = 94%, P<0.0001
Diuretic	7 (27)	12489 (88)	10790 (86)	OR 1.50 (95% CI 1.23–1.82), P<0.0001 I^2 = 17%, P=0.16

Map of the inspected variables across the studies, which are ordered from the least to the most detailed; those in italic were presented as abstracts.