



Systematic Review/Meta-analysis

Real-World Safety of Sacubitril/Valsartan in Women and Men With Heart Failure and Reduced Ejection Fraction: A Meta-analysis

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ABSTRACT

Background: Sacubitril/valsartan (SV) is a novel and effective therapy for heart failure with reduced ejection fraction (HFrEF). Despite several sex-specific particularities that may influence drug effects, there has been no prior study evaluating the safety of SV in women with HFrEF in the “real-world.”

Methods: We performed a literature search to identify observational studies evaluating SV. We contacted all authors to obtain sex-specific data on major adverse outcomes. We compared all-cause and cardiovascular (CV) deaths, heart failure hospitalizations, hyperkalemia, and hypotension in men and women.

Sacubitril/valsartan (SV) is the first commercially available angiotensin receptor–neprilysin inhibitor¹ approved by the US Food and Drug Administration in 2015.² SV is superior to renin-angiotensin-aldosterone inhibition alone in reduction of all-cause and cardiovascular (CV) mortality in patients who have heart failure with reduced ejection fraction (HFrEF).^{3,4} In patients with heart failure and preserved left ventricle ejection fraction, SV tended to be more effective in women compared with men.^{5,6} It remains unclear whether SV has

RÉSUMÉ

Contexte : Le sacubitril/valsartan (SV) est un médicament novateur et efficace contre l'insuffisance cardiaque à fraction d'éjection réduite (ICFER). Malgré le fait que plusieurs particularités sexospécifiques peuvent influencer les effets du médicament, aucune étude préalable n'a été menée pour évaluer l'innocuité du SV chez les femmes atteintes d'ICFER dans la “vraie vie”.

Méthodologie : Nous avons effectué une recherche de la littérature pour recenser les études observationnelles évaluant le SV. Nous avons communiqué avec tous les auteurs pour obtenir des données sexospécifiques sur les principaux issues défavorables. Nous avons

different efficacy and effectiveness in women and men with HFrEF.

Moreover, the applicability of findings from randomized control trials (RCT) to the real-world setting may be limited, as women were generally underrepresented in most HFrEF trials.³⁻⁸ Furthermore, women with HFrEF are generally older and with more comorbidities than men with HFrEF.⁹ Outside the clinical trial context, SV may be less well tolerated in women than in men. Nordberg Backelin et al.¹⁰ reported that women were at increased risk of SV discontinuation compared with men. Consequently, we aim to compare the safety of SV in women to men with HFrEF in a meta-analysis of observational studies.

Methods

We performed a meta-analysis of observational studies, according to the standards detailed by the Preferred

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Ethics Statement: Our research has adhered to all relevant ethical guidelines.

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See page S207 for disclosure information.

Results: We identified five cohort studies enrolling 8,981 patients; 6,092 men (67.8%) and 2,889 women (32.2%). The mean age was 67 years in both sexes. The rates for all-cause mortality, CV mortality, heart failure hospitalizations, hypotension, and hyperkalemia were similar between women and men. Although the unadjusted aggregate rates of all-cause and CV mortalities were numerically higher in men than in women, these differences did not reach statistical differences. **Conclusion:** Our meta-analysis showed similar rates of major adverse events in men and women with HFrEF treated with SV. Larger observational studies with longer duration and a higher number of women are needed to confirm the long-term safety of SV in women in the clinical practice.

Reporting Items for Systemic Review and Meta-Analyses statement.¹¹ The conceptual basis of our search was *sacubitril/valsartan* or *Entresto* and *heart failure*. We searched the following electronic databases: Pubmed, Google Scholar, and Embase from July 2015 (date of US Food and Drug Administration Act's approval of Entresto [the commercial name of SV]) to 31 August 2020. We conducted searches using subject terms and keywords searching. We used the following MESH terms and title/abstract search terms:

((("heart failure"[MeSH Terms] AND ("sacubitril valsartan"[Title/Abstract] OR "Entresto"[Title/Abstract]) AND ("registries"[MeSH Terms] OR "cohort studies"[MeSH Terms] OR "observational"[Title/Abstract])) OR ("female"[MeSH Terms] OR "women"[Title/Abstract])) AND "reduced ejection fraction"[Title/Abstract]) AND (2015:2020[pdat]) We did not apply any language restriction.

We included all cohorts with available cardiovascular outcomes in HFrEF patients treated with SV for women and men separately. We excluded review articles, case reports, meeting abstracts, and duplicates. We also examined all references of fully reviewed manuscripts to ensure retrieval of all potentially relevant articles. Two readers independently reviewed the selected studies and completed data extraction (K.N. and T.H.). We evaluated individual studies for biases (Newcastle-Ottawa scale)¹² (Supplemental Table S1). We resolved conflicts by consensus. For studies that did not report sex-specific outcomes, we contacted the individual investigators to obtain sex-specific data.

For data analysis, we used the longest follow-up period provided in the included studies. We computed the weighted mean age, proportions of diabetes mellitus (DM), hypertension, heart failure hospitalization (HFH), all-cause mortality, CV mortality, hyperkalemia (serum potassium > 5.5 mEq/L), and hypotension (systolic blood pressure < 90 mm Hg). We compared the odds ratios of all major

comparé les données sur les décès toutes causes confondues et les décès d'origine cardiovasculaire (CV), les hospitalisations pour cause d'insuffisance cardiaque, l'hyperkaliémie et l'hypotension tant chez les hommes que chez les femmes.

Résultats : Nous avons recensé cinq études de cohortes auxquelles ont participé 8 981 patients, soit 6 092 hommes (67,8 %) et 2 889 femmes (32,2 %). L'âge moyen était de 67 ans chez les patients des deux sexes. Les taux de décès toutes causes confondues, de décès d'origine CV, d'hospitalisation pour cause d'insuffisance cardiaque, d'hypotension et d'hyperkaliémie chez les femmes étaient similaires à ceux notés chez les hommes. Les taux globaux non ajustés de décès toutes causes confondues et de décès d'origine CV étaient numériquement plus élevés chez les hommes que chez les femmes, mais il n'y avait pas de différence sur le plan statistique.

Conclusion : Notre méta-analyse a mis en évidence des taux similaires d'événements indésirables majeurs chez les hommes et chez les femmes atteints d'ICFER traités par le SV. Des études observationnelles à plus grande échelle avec de plus longue durée et un nombre plus élevé de femmes devront être menées pour confirmer l'innocuité à long terme du SV en pratique clinique chez les femmes.

adverse events in women to men by random-effects model SAS version 9.4.

Results

We retrieved a total of 577 citations, evaluated 95 abstracts, and thoroughly reviewed 24 pertinent manuscripts. Of the reviewed manuscripts, 10 studies were relevant for inclusion. We contacted the 10 authors for sex-specific data. The final analysis included 5 observational studies for which sex-specific

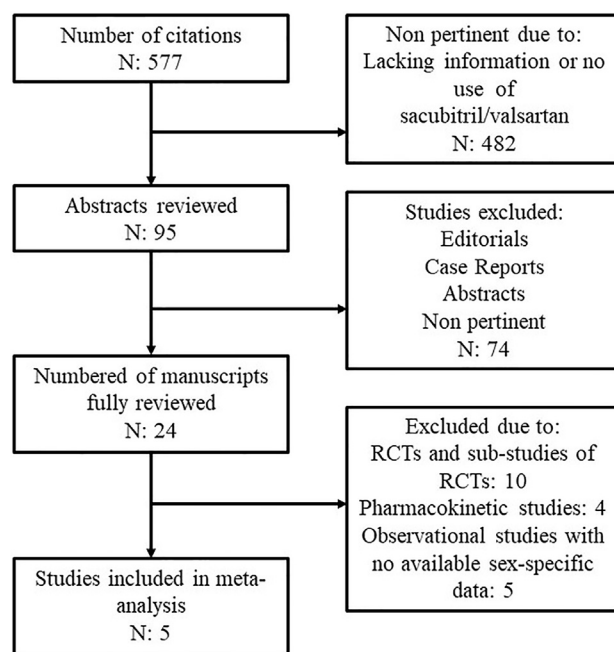


Figure 1. Selection of studies. RCT, randomized controlled trials.

Table 1. Baseline characteristics and heart failure pharmacotherapies

Year of publication	Martens et al. ¹⁴		Vicent et al. ¹⁶		Nordberg Backelin et al. ¹⁰		Russo et al. ¹³		Tan et al. ¹⁵		Total	
	2019	F	M	F	M	2020	F	M	2020	F		M
Sex	M	N = 309	N = 92	N = 301	N = 126	N = 75	N = 141	N = 26	N = 5,268	N = 2,625	N = 6,094	F
Mean age (SD)	68 (11.0)	69 (12.0)	68.8 (13.2)	67.8 (12.1)	65.3 (12.1)	65.3 (12.1)	69.0 (13.0)	66.0 (9.0)	67.8 (11.8)	69.2 (12.3)	67.6 (5.3)	N = 2,889
Diabetes mellitus, %	28.0	28.0	35.7	41.5	28.0	28.0	29.8	26.0	54.0	54.0	36.1 (23.8, 50.5)*	67.5 (5.1)
Hypertension, %	55.0	54.0	77.7	65.9	34.7	34.7	52.5	40.0	93.0	92.3	66.8 (33.1, 89.1)*	55.4 (10.7, 92.8)*
β-blockers, %	NA	NA	88.0	85.0	89.4	87.0	97.9	100	87.3 combined for both sexes	92.3	NA [†]	64.5 (18.9, 93.4)*
Mineralocorticoid antagonists, %	NA	NA	61.5	65.0	46.3	35.5	89.4	92.3	36.2 combined for both sexes	92.3	NA [†]	NA [†]
Maximal doses of sacubitril/valsartan, %	NA	NA	10.9	9.5	64.8	55.6	56.0	57.7	NA	NA	NA [†]	NA [†]

NA, Not available; SD, standard deviation.

*% (95% confidence intervals).

[†] Not available due to limited studies with small numbers of patients.

data could be provided.¹⁰⁻¹⁵ Of these studies, 2 were prospective^{10,11} and 3 were retrospective cohorts.¹²⁻¹⁵ We presented the selection of studies in Figure 1, their designs in Supplemental Table S1 and their qualities in Supplemental Table S2. All studies were of high quality and did not have any major bias that could affect substantively the results.

There were 8,981 patients enrolled in these registries; 6,092 men (67.8%) and 2,889 women (32.2%). The definition of HF rEF varied across the included studies: The cohorts of Vicent et al.¹⁶ and Tan et al.¹⁵ included patients with left ventricular ejection fraction (LVEF) < 45%, Nordberg Backelin et al.¹⁰ and Russo et al.¹³ enrolled patients with LVEF < 40%, and the study of Martens et al.¹⁴ included patients with LVEF < 35%.

We summarized the patients' baseline clinical features in Table 1. The weighted mean age was 67.6 ± 5.3 years and 67.5 ± 5.1 years in women and men, respectively. The baseline characteristics and concomitant HF pharmacotherapies were comparable in both sexes. Most of the patients were on β-blockers. The uses of mineralocorticosteroid antagonists were variable among the cohorts with rates as low as 36%¹³ to as high as 93%.¹⁵ We presented other important comorbidities (pooled for women and men) in Supplemental Table S3.

The follow-up ranged from 2 to 12 months, with approximately half of the patients (48.7%) followed up for 5 months. We presented the pooled incidence rates of major adverse outcomes in Table 2. The pooled all-cause mortality rates were 3.6% and 2.1% for men and women, respectively. The pooled mean rates of hyperkalemia and hypotension were low at 2.1% and 3.6% for men, respectively, and 2.3% and 5.0% for women, respectively.

We presented the forest plots comparing all-cause and CV mortalities, hypotension, worsening renal function and hyperkalemia in men and women in Figures 2-4. There was no significant heterogeneity in all outcomes evaluated. The odds for all-cause mortality, CV mortality, HFH, hypotension, and hyperkalemia were similar between women and men (Figs. 2-4). Both hyperkalemia and symptomatic hypotension were infrequent and occurred at similar frequencies in both sexes. Although the unadjusted rates of all-cause and CV mortalities were numerically higher in men, these differences did not reach statistical differences. For partial adjustment of the variable duration of follow-up between studies, we compared projected incidence rates of adverse outcomes per 100 person-years between men and women (Supplemental Table S4).

We also completed sensitivity analyses with fixed-effect models, which may be more sensitive to small differences (Supplemental Table S5). The results of these models were similar to those with random-effect models except for higher I-squared suggesting heterogeneity for CV mortality and HFH (Supplemental Table S5). Additionally, Breslow-Day, Cochran's Q did not detect any significant heterogeneity (Supplemental Table S5).

Discussion

Our meta-analysis showed that women with HF rEF treated with SV had similar all-cause mortality, CV mortality,

Table 2. Incidences of major adverse outcomes by individual study

Sex	Martens et al. ¹⁴		Vicent et al. ¹⁶		Nordberg Backelin et al. ¹⁰		Russo et al. ¹³		Tan et al. ¹⁵		Total	
	M	F	M	F	M	F	M	F	M	F	M	F
Duration of follow-up, mo	N = 309	N = 92	N = 301	N = 126	N = 75	N = 20	N = 141	N = 26	N = 5,268	N = 2,625	N = 6,092	N = 2,889
Heart failure hospitalization, %	12	7.0	NA	NA	12	26.7	1.4	7.7	Mean, 6.3	9.0	9.2 (1.7, 36.6)*	9.2 (7.6, 11.1)*
All-cause mortality, %	5.0	1.0	3.0	2.3	10.7	15.0	2.1	3.8	2.2	2.0	3.6 (1.8, 7.4)*	2.1 (1.5, 3.0)*
Cardiovascular mortality, %	4.0	1.0	2.7	0.8	NA	NA	1.4	3.8	NA	NA	2.9 (1.2, 7.1)*	1.2 (0.1, 13.2)*
Hyperkalemia, %	4.0	2.2	7.3	10.3	16.0	15.0	0.7	3.8	0.4	0.5	2.1 (0.3, 11.7)*	2.3 (0.5, 10.2)*
Hypotension, %	0.6	1.1	16.3	16.7	8.0	10.0	3.5	3.8	1.7	1.7	3.6 (0.8, 14.1)*	5.0 (1.2, 18.9)*

NA, not available.
 *% (95% confidence intervals).

hyperkalemia, and hypotension as men with HFrEF treated with sacubitril-valsartan. The adverse events were infrequent in both men and women in the real world and comparable to the findings of the pivotal trials.³⁻⁸ Overall, our results suggested that the safety with SV can be replicated outside the clinical trial context.

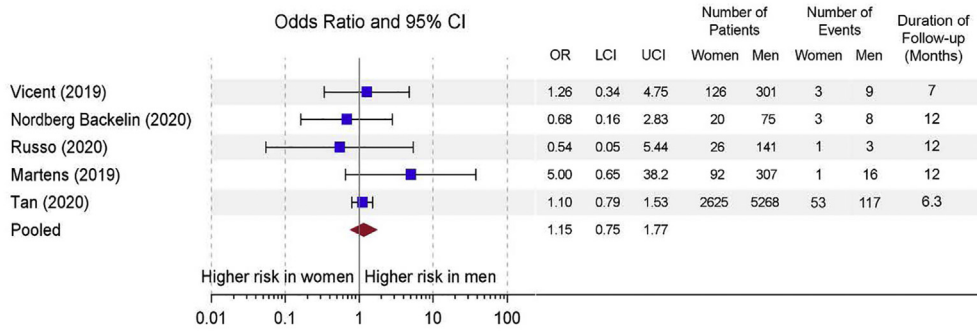
Current heart failure guidelines^{17,18} recommended sex-neutral target dose recommendations for SV. The Food and Drug Act² did not provide any sex-specific recommendations for SV (apart from a warning of potential fetal toxicity in pregnant women and advised discontinuation of SV in breastfeeding women). However, women have several biological characteristics that may influence the pharmacodynamic and pharmacokinetic of SV.^{19,20} Women have reduced body weight, hepatic flow, glomerular filtration rate, plasma volume, and a higher proportion of body fat compared with men.^{19,20} In particular, women can have high peak plasma concentrations with hydrophilic medication such as SV.^{21,22} The above differences in drug metabolism between women and men emphasize the need for a detailed evaluation of SV in women with HFrEF.²²

The proportion of women and the mean age of patients in our observational studies were analogous to those of the landmark studies of SV in HFrEF.³⁻⁸ The prevalences of hypertension and DM were comparable between the cohorts of the observational studies^{9,13-16} and those enrolled in the Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF) trial.³ The overall similarities in the mean age, DM, and hypertension in the cohort studies and RCTs were reassuring and suggested that the benefits of SV shown in the RCTs may be extrapolated to the real world. All-cause mortality was infrequent and comparable to the mortality rates reported in the RCTs evaluating SV with short follow-up durations (Comparison of Pre-discharge and Post-Discharge Treatment Initiation of LCZ696 in Heart Failure Patients With Reduced Ejection-Fraction After an Acute Decompensation Event [TRANSITION] and Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure [PIONEER-HF]).^{7,8}

The potential superiority in mortality reduction of SV in women compared with men with HF and preserved ejection fraction in the PARAGON-HF trial suggested that this drug may have a differential sex-specific impact.^{5,6} There was no sex-interaction noted with SV mortality reduction in the PARADIGM trial.³ It is of note that our sample size of 2,889 women exceeded the 879 women enrolled in the PARADIGM-HF trial.³ Notwithstanding the lack of significance, all-cause and CV mortalities were numerically lower in women compared with men in our meta-analysis. The short follow-up of the included studies may have limited our statistical power to detect significant differences in mortalities between the men and women.

Hypotension was infrequent and slightly higher in women in the observational studies. Its incidence was comparable to the rate observed in the PARADIGM-HF trial when limited to hypotension defined as systolic blood pressure of less than 90 mm Hg. In the observational studies, hyperkalemia was rare and similar between men and women. The markedly reduced incidence of

A All-cause mortality



B Cardiovascular mortality

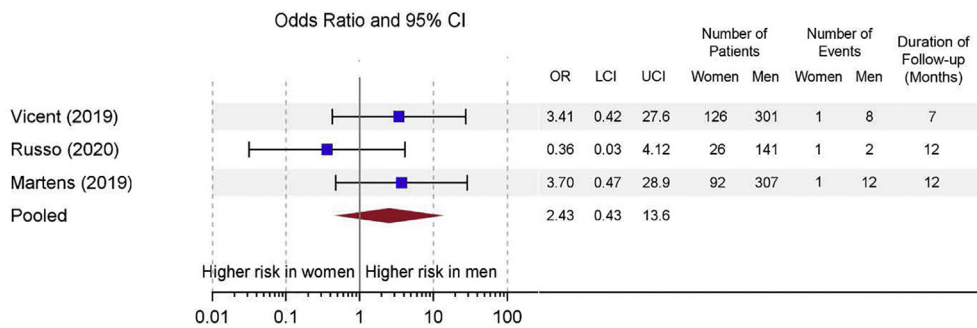


Figure 2. Forest plot comparing all-cause mortality and cardiovascular mortality in women and men treated with sacubitril/valsartan. I^2 is 0% for all-cause mortality and 2.23% for cardiovascular mortality. CI, confidence interval; LCI, lower bound of the confidence interval; OR, odds ratio, UCI, upper bound of the confidence interval.

hyperkalemia in our meta-analysis of observational studies compared to hyperkalemia observed in the RCTs (2% vs 12%),^{3,5} may reflect less frequent serum potassium monitoring outside the RCT context. The low incidence of clinically significant hyperkalemia in the observational studies was reassuring, considering the appropriate use of

concomitant mineralo-corticosteroid antagonists in these cohorts, with rates as high as 93% in one cohort.¹³

Approximately 9% of patients in the pooled cohort studies had at least 1 HFH. This incidence was similar between the 2 sexes and comparable with the incidence reported in the PIONEER-HF trial.⁸ Finally, we could not ascertain accurately

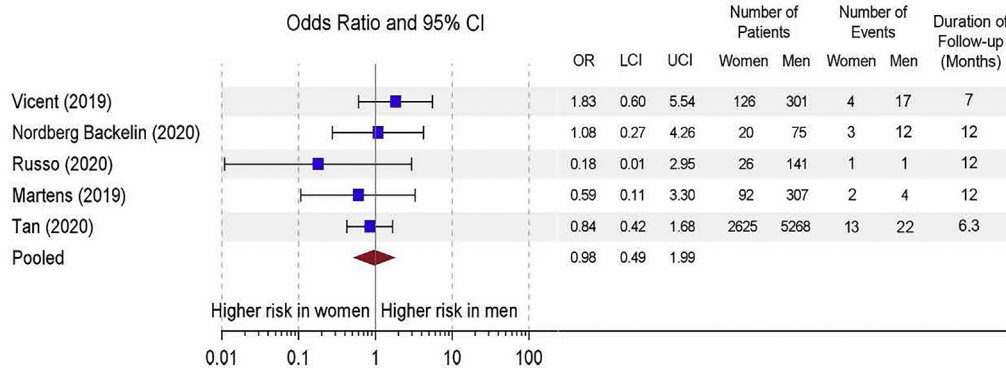


Figure 3. Forest plot comparing hyperkalemia in women and men treated with sacubitril/valsartan. I^2 is 0% for all-cause mortality and 2.23% for cardiovascular mortality. CI, confidence interval; LCI, lower bound of the confidence interval; OR, odds ratio, UCI, upper bound of the confidence interval.

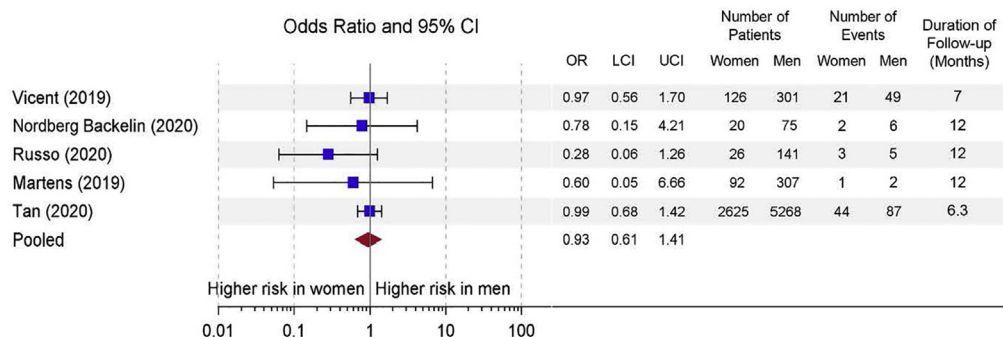


Figure 4. Forest plot comparing hypotension in women and men treated with sacubitril/valsartan. I^2 is 0% for all-cause mortality and 2.23% for cardiovascular mortality. CI, confidence interval; LCI, lower bound of the confidence interval; OR, odds ratio, UCI, upper bound of the confidence interval.

the incidence of worsening renal function, as there were only 3 studies that reported this endpoint in 661 patients.^{9,13,14}

Limitations

Our meta-analysis has some limitations worth addressing. First, all meta-analyses are subject to publication bias. It was possible that despite an extensive search, we may have missed important cohort studies evaluating the safety of SV. Furthermore, we could not obtain sex-specific data from five observational studies evaluating SV. However, these studies were small with their combined number of patients totaling only 716 and followed only for 7 months. Therefore, it would be unlikely that inclusion of these studies would substantially alter our findings. Second, because of the novelty of SV as a therapy for HFrEF, the number of studies with sufficient data to be included was modest. Accordingly, the power of our meta-analysis to detect meaningful differences in adverse outcomes between the 2 sexes was limited. Third, we did not obtain individual patient data. Therefore, we could not adjust for patient-level characteristics. Fourth, all of our studies were completed in countries with predominant white populations.^{9,13-16} Consequently, our findings could not be extrapolated to other races. Finally, although we did not explicitly evaluate the short-term safety outcomes of SV therapy, the incidences of long-term safety outcomes did include the short-term adverse outcomes.

Conclusion

The safety of SV is similar in women and men in the real world and comparable to that in the RCTs. Future observational studies with a larger number of women and of longer duration are needed to confirm the long-term safety of SV in women in the clinical practice.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at <https://www.cjcopen.ca/> and at <https://doi.org/10.1016/j.cjco.2021.09.009>.