Does treatment with Sacubitril-Valsartan compared to ACE-inhibitors or ARBs vary by sex among patients with Heart Failure?

Z. Sohani, H. Behlouli, C. Soares de Moura, M. Abrahamowicz, & L. Pilote
Department of Medicine, McGill University

McGill UNIVERSITY

Introduction

Congestive heart failure (CHF) is a global pandemic affecting approximately 26 million people worldwide[1]

Current CHF guidelines are based on trials largely conducted among men. Most trials included less than 20% women[2]

Subgroup analyses of CHF trials have suggested a difference in efficacy of medical management by sex

- TOPCAT trial[3] showed that women with preserved ejection fraction appeared to benefit across the ejection fraction spectrum, but men only at a lower ejection fractions
- PARAGON-HF[4] reported benefit of treatment with Sacubitril-Valsartan among women

Objective

Does effectiveness of treatment with Sacubitril-Valsartan compared to ACE inhibitors or ARBs vary by sex for a cardiac-specific composite outcome?

Summary of findings

Table 1 Characteristics of Patients with Congestive Heart Failure at the Time of Index Prescription by Drug Use

	ACE-inhibitors (n=61,585)	ARBs (n = 42,746)	Sacubitril–Valsartan (n=8,338)
Demographic Characteristic			
Age (mean, SD)	70.4 (14.4)	72.35 (13.37)	61.79 (13.74)
Women (%)	45.78	53.99	32.78
Drug use (%)			
Calcium channel blockers	10.25	13.23	4.74
Beta blockers	39.10	44.80	38.93
Diuretics	55.86	59.92	62.69
Nitrates	5.77	6.36	2.35
Digoxin	12.60	12.18	11.75
Clopidogrel	3.87	4.49	4.02
Statins	26.80	32.28	22.40
Warfarin	5.85	7.02	5.22
Amiodarone	6.02	6.77	6.13
Procedures at baseline (%)			
PCI	5.02	4.03	7.35
CABG	3.04	2.04	3.75
Comorbidities (%)			
Previous MI	16.30	12.99	14.07
Diabetes	32.65	33.67	20.94
Liver disease	0.59	0.36	0.24
COPD	29.55	29.69	18.41
Malignancy	10.04	10.93	6.68
Atrial fibrillation	30.16	31.63	21.11
PVD	13.61	12.76	20.36
Hypertension	64.22	61.67	41.65
CKD	17.29	19.74	13.38
Cerebrovascular disease	20.54	21.19	11.89

Overall findings:

- Treatment with Sacubitril–Valsartan compared to ACE-inhibitor or ARB was associated with a reduction in primary composite outcome for both sexes
- Sacubitril–Valsartan was associated with lower rate of adverse events: HR 0.64 (95% CI 0.58-0.72)

Figure 1 Kaplan-Meier Curve for Survival Probabilities by Sex and Treatment Group

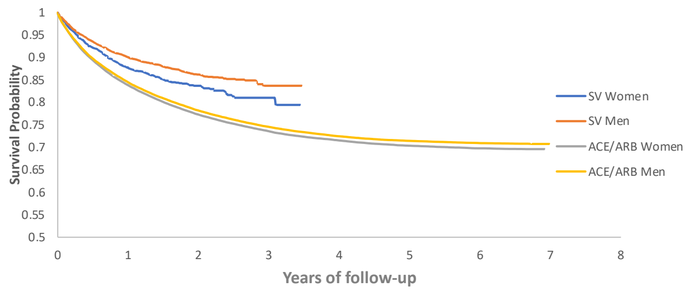
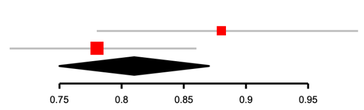


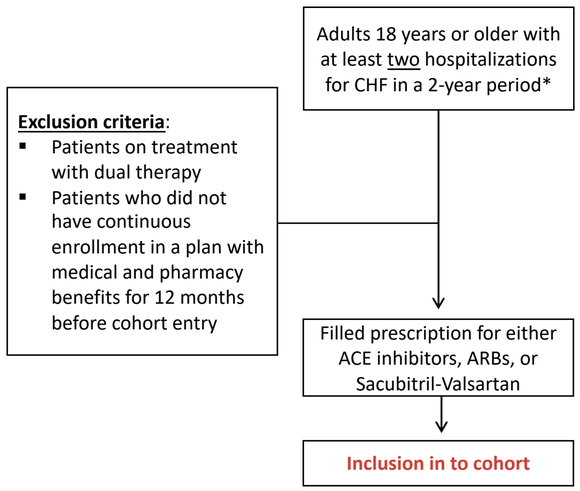
Figure 2 Effect of Sacubitril–Valsartan compared to ACE-inhibitor or ARB by Sex

	Events SV*	Events AA$^{\Psi}$	HR	95% CI
Women	348	14441	0.88	0.78–0.99
Men	605	14414	0.78	0.71–0.86
Overall	**953**	**28855**	**0.81**	**0.75–0.87**



SV = Sacubitril–Valsartan

Methodology



Data was derived from the Truven Health MarketScan Database for the period January 1, 2011 to December 31, 2018

Outcomes:
The primary outcome was a composite of CHF hospitalizations, mortality, stroke, MI, and cardiac arrest
Safety outcome was a composite of hypotension, renal dysfunction, hyperkalemia, and angioedema

Statistical Methods: Cox proportional hazards regression was used to compare users of ACE-inhibitors and ARBs with sacubitril-valsartan for the composite outcome. Similarly, a time-to-event model was created for safety outcomes. All models were adjusted for baseline traits.

*Diagnosis of CHF was based on International Classification of Diseases (ICD) codes 428 and I50. Hospitalizations for CHF in a 2-year period were based on primary diagnosis (DX1) in the MarketScan Database

Conclusions

We observe reduced hospitalizations, death, MI, stroke, and cardiac arrests from treatment with sacubitril-valsartan for both women and men with CHF regardless of ejection fraction. This is the first report of overall efficacy of sacubitril-valsartan evident for both sexes.

Key next steps include delineating efficacy by ejection fraction among these patients.

References

1. Jessup, M. & Brozena, S. Heart Failure. *N. Engl. J. Med.* **348**, 2007–2018 (2003).
2. Lawson, C. A. *et al.* 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. *Lancet. Public Heal.* **4**, e406–e420 (2019).
3. Dewan, P. *et al.* Sex-Related Differences in Heart Failure With Preserved Ejection Fraction. *Circ. Heart Fail.* **12**, e006539 (2019).
4. Solomon, S. D. *et al.* Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. *N. Engl. J. Med.* **381**, 1609–1620 (2019).