

Supplement

Efficacy and safety of sacubitril/valsartan in heart failure compared to renin-angiotensin-aldosterone system inhibitors: a systematic review and meta-analysis of randomised controlled trials

Hernandez AV *et al.*

1. Search strategies

CENTRAL

- #1 MeSH descriptor: [Neprilysin] this term only
- #2 (Neprilysin NEAR/2 inhibitor*)
- #3 (sacubitril NEAR/2 valsartan)
- #4 ARNI*
- #5 (LCZ696 or LCZ 696)
- #6 #1 or #2 or #3 or #4 or #5
- #7 MeSH descriptor: [Heart Failure] explode all trees
- #8 ((heart* or cardiac* or myocard*) NEAR/2 (fail* or insuff*))
- #9 (heart* NEAR/2 decomp*)
- #10 (chf or hf)
- #11 #7 or #8 or #9 or #10
- #12 #6 and #11

MEDLINE Ovid

- 1 Neprilysin/ and inhibitor*.tw. (1596)
- 2 (Neprilysin adj2 inhibitor*).tw. (473)
- 3 (sacubitril adj2 valsartan).tw. (593)
- 4 ARNI*.tw. (725)
- 5 (LCZ696 or LCZ 696).tw. (231)
- 6 1 or 2 or 3 or 4 or 5 (2807)

7 exp Heart Failure/ (118504)

8 ((heart* or cardiac* or myocard*) adj2 (fail* or insuff*)).tw. (179700)

9 (heart* adj2 decomp*).tw. (4049)

10 (chf or hf).tw. (56345)

11 7 or 8 or 9 or 10 (236709)

12 6 and 11 (896)

13 randomized controlled trial.pt. (500725)

14 controlled clinical trial.pt. (93588)

15 randomized.ab. (470103)

16 placebo.ab. (205240)

17 drug therapy.fs. (2181883)

18 randomly.ab. (327297)

19 trial.ab. (494722)

20 groups.ab. (2009490)

21 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (4635894)

22 exp animals/ not humans.sh. (4674278)

23 21 not 22 (4016804)

24 12 and 23 (551)

Embase Ovid

1 membrane metalloendopeptidase/ and inhibitor*.tw. (1584)

2 (Neprilysin adj2 inhibitor*).tw. (825)

3 (sacubitril adj2 valsartan).tw. (1168)

4 ARNI*.tw. (1221)

5 (LCZ696 or LCZ 696).tw. (714)

6 1 or 2 or 3 or 4 or 5 (4123)

7 exp heart failure/ (474515)

8 ((heart* or cardiac* or myocard*) adj2 (fail* or insuff*)).tw. (285593)

9 (heart* adj2 decomp*).tw. (8302)
 10 (chf or hf).tw. (99479)
 11 7 or 8 or 9 or 10 (557726)
 12 6 and 11 (1944)
 13 random\$.tw. (1487437)
 14 factorial\$.tw. (36457)
 15 crossover\$.tw. (72743)
 16 cross over\$.tw. (30722)
 17 cross-over\$.tw. (30722)
 18 placebo\$.tw. (296792)
 19 (doubl\$ adj blind\$).tw. (199004)
 20 (singl\$ adj blind\$).tw. (24054)
 21 assign\$.tw. (380818)
 22 allocat\$.tw. (146728)
 23 volunteer\$.tw. (246062)
 24 crossover procedure/ (61996)
 25 double blind procedure/ (166433)
 26 randomized controlled trial/ (586195)
 27 single blind procedure/ (37896)
 28 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
 (2241780)
 29 (animal/ or nonhuman/) not human/ (5495622)
 30 28 not 29 (1984145)
 31 12 and 30 (360)

Web of Science Core Collection

12 #11 AND #10

11 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)

10 #9 AND #5

9 #8 OR #7 OR #6

8 TS=(chf or hf)

7 TS=(heart* NEAR/2 decomp*)

6 TS=((heart* or cardiac* or myocard*) NEAR/2 (fail* or insuff*))

5 #4 OR #3 OR #2 OR #1

4 TS=(LCZ696 or LCZ 696)

3 TS=ARNI*

2 TS=(sacubitril NEAR/2 valsartan)

1 TS=(Neprilysin NEAR/2 inhibitor*)

SCOPUS

TITLE-ABS-KEY (neprilysin OR sacubitril OR valsartan OR lcz696 OR lcz 696 OR arni*
AND “heart failure” OR chf OR hf) AND NOT INDEX (medline)

Clinical trials registries

(Neprilysin OR sacubitril/valsartan OR LCZ696 OR ARNI) AND (heart failure OR acute
heart failure OR chronic heart failure)

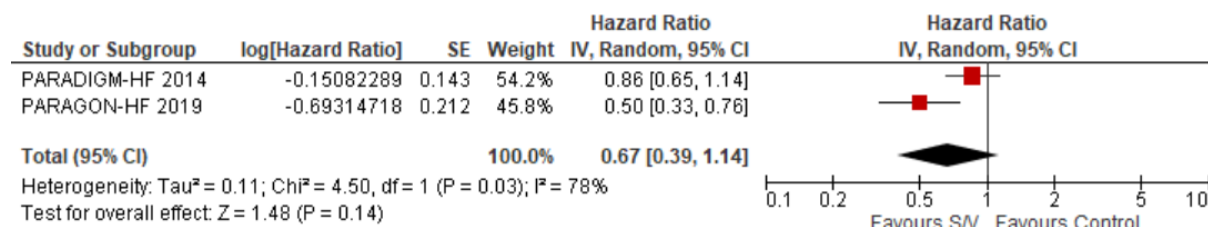
2. Risk of bias assessments of included studies

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
AWAKE-HF 2021	+	?	+	?	?	+	+
EVALUATE-HF 2019	+	?	+	+	-	+	+
Fan 2020	?	?	?	?	?	?	?
OUTSTEP-HF 2021	+	?	+	+	+	+	+
PARADIGM-HF 2014	+	+	+	+	+	+	+
PARAGON-HF 2019	+	?	+	+	+	+	+
PARALLAX 2021	?	?	+	+	+	+	?
PARAMOUNT 2012	+	?	+	?	-	+	+
PIONEER-HF 2019	+	?	+	+	-	+	+
PRIME 2019	+	+	+	?	+	+	+
Tumasyan 2019	?	?	?	?	?	?	?

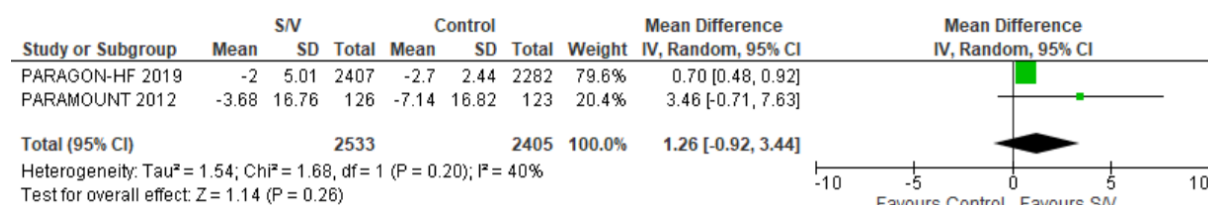
3. Supplementary Figures

3.1. S/V vs. ACEI or ARB

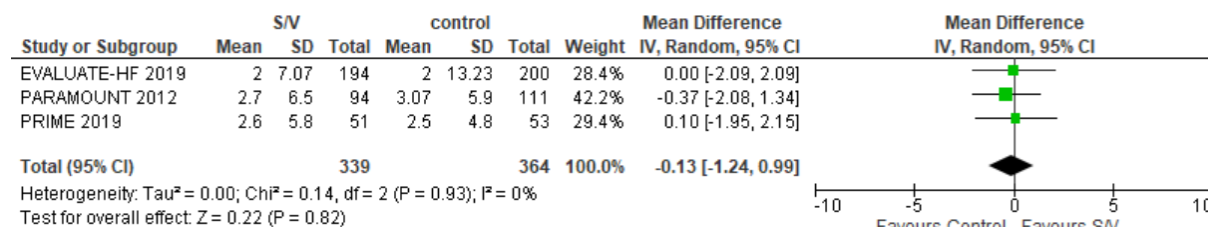
Supplementary Figure S1. Effect of sacubitril/valsartan vs. ACEI or ARB on decline in renal function



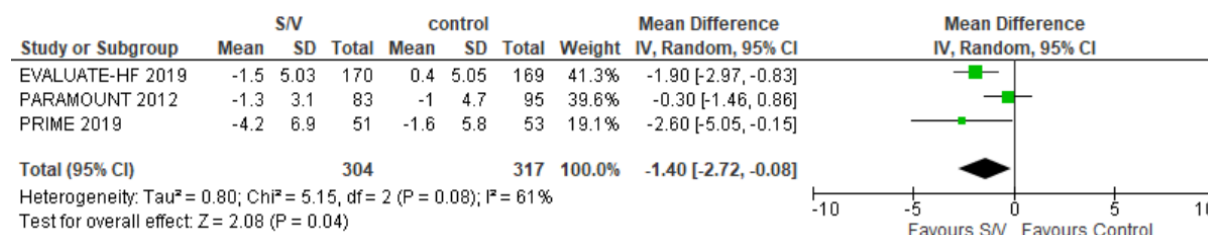
Supplementary Figure S2. Effect of sacubitril/valsartan vs. ACEI or ARB on change in eGFR



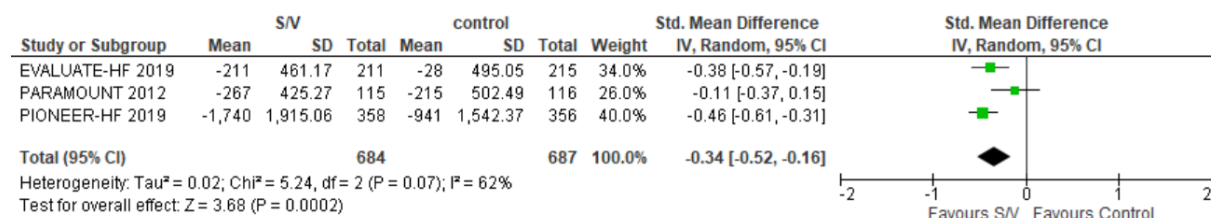
Supplementary Figure S3. Effect of sacubitril/valsartan vs. ACEI or ARB on LVEF (%)



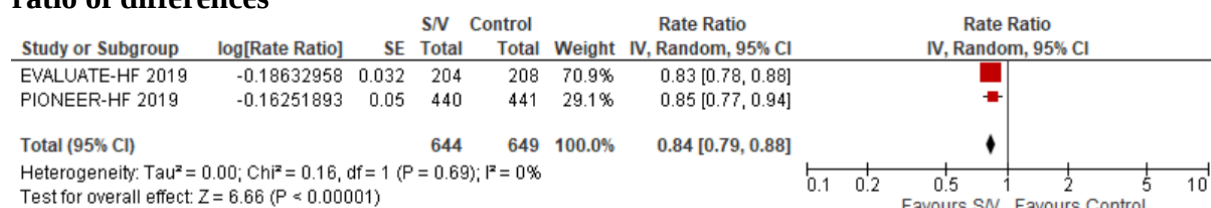
Supplementary Figure S4. Effect of sacubitril/valsartan vs. ACEI or ARB on E/E' ratio



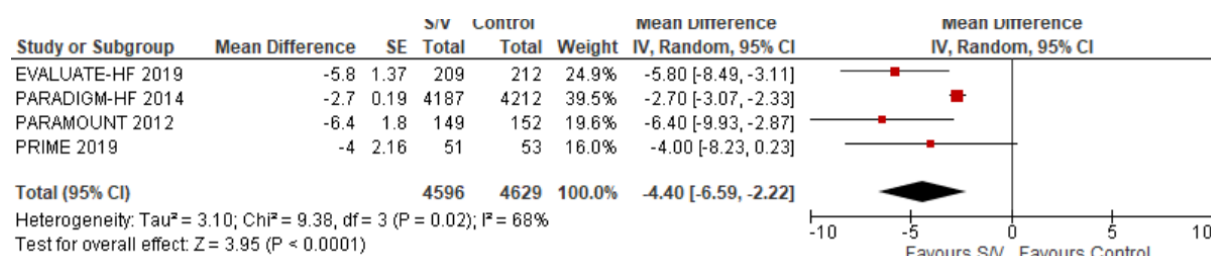
Supplementary Figure S5. Effect of sacubitril/valsartan vs. ACEI or ARB on NT-proBNP level (pg/ml)



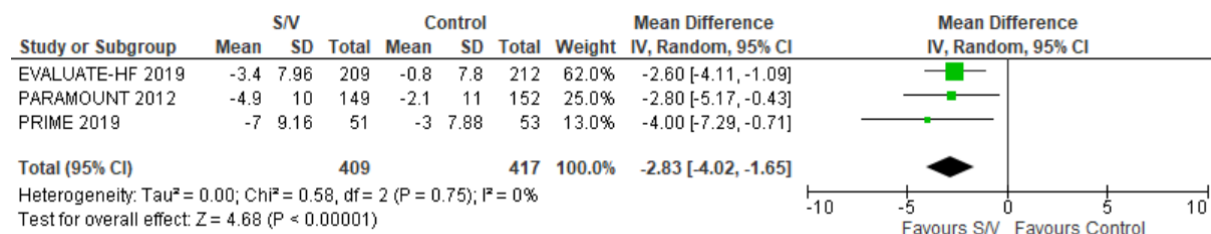
Supplementary Figure S6. Effect of sacubitril/valsartan vs. ACEI or ARB on hsTnT ratio of differences



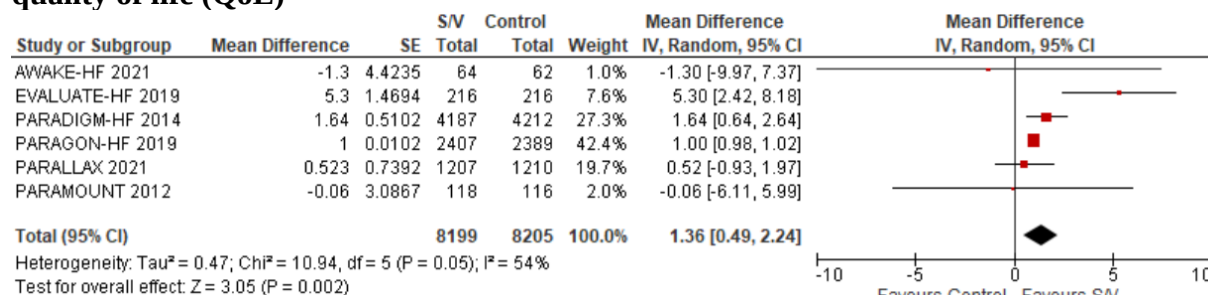
Supplementary Figure S7. Effect of sacubitril/valsartan vs. ACEI or ARB on systolic blood pressure (mm Hg)



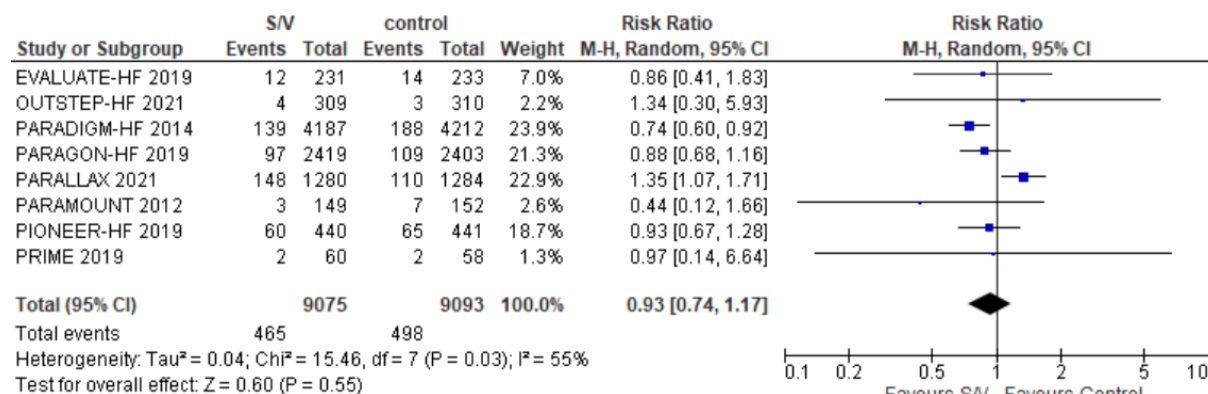
Supplementary Figure S8. Effect of sacubitril/valsartan vs. ACEI or ARB on diastolic blood pressure (mm Hg)



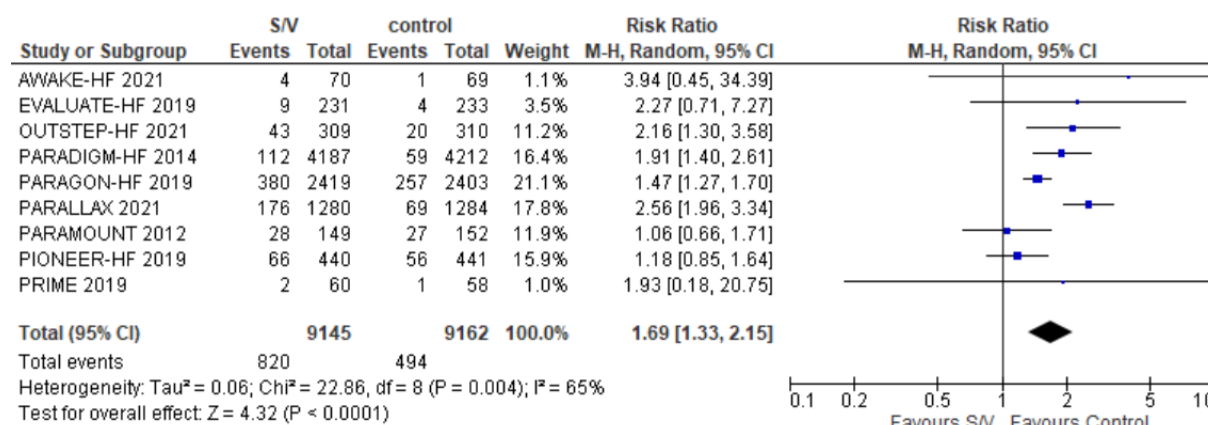
Supplementary Figure S9. Effect of sacubitril/valsartan vs. ACEI or ARB on KCCQ-quality of life (QoL)



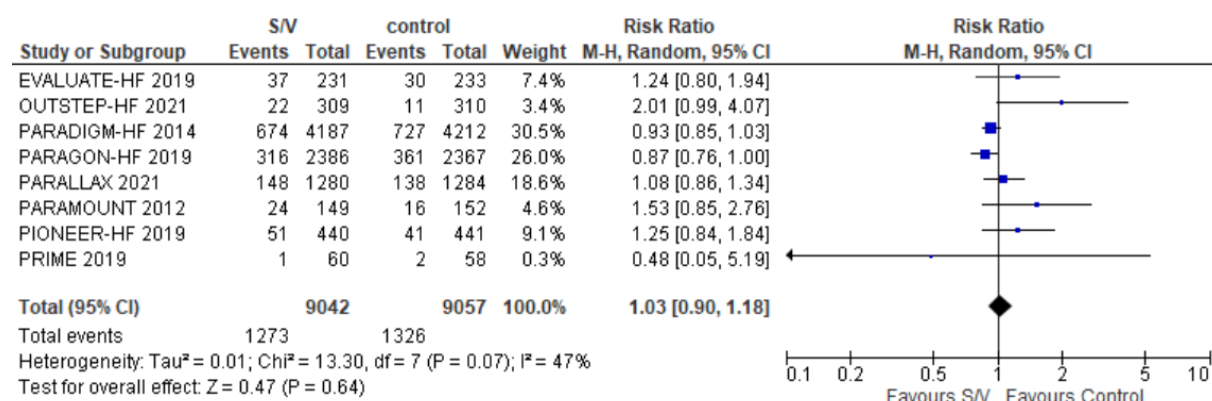
Supplementary Figure S10. Effect of sacubitril/valsartan vs. ACEI or ARB on worsening SCr and/or eGFR



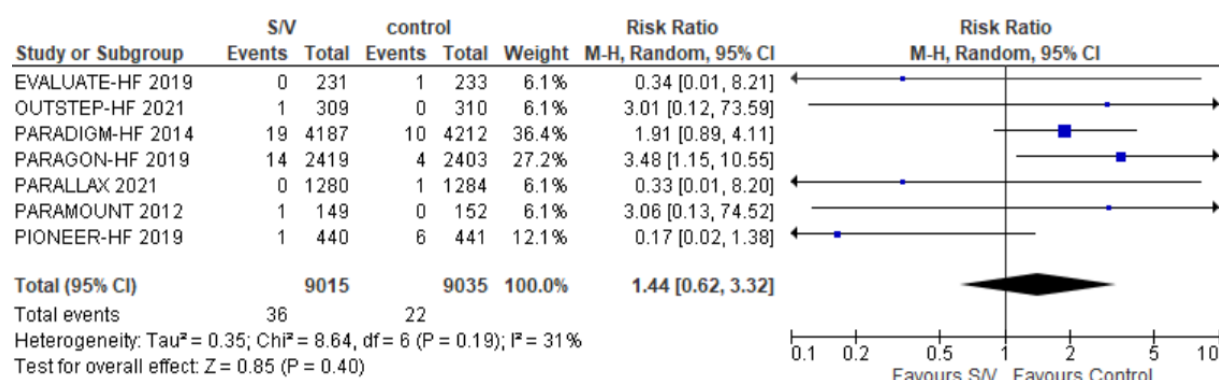
Supplementary Figure S11. Effect of sacubitril/valsartan vs. ACEI or ARB on symptomatic hypotension



Supplementary Figure S12. Effect of sacubitril/valsartan vs. ACEI or ARB on hyperkalaemia

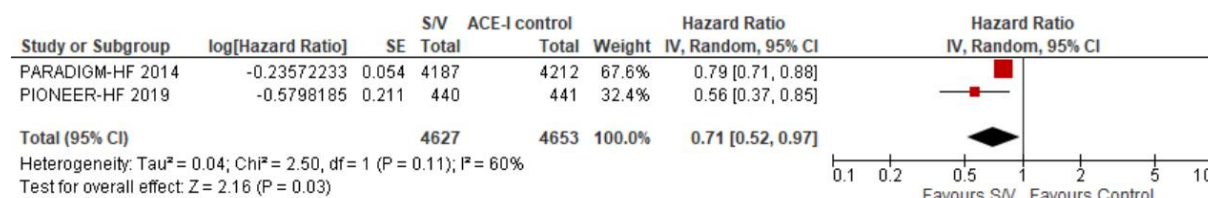


Supplementary Figure S13. Effect of sacubitril/valsartan vs. ACEI or ARB on angioedema

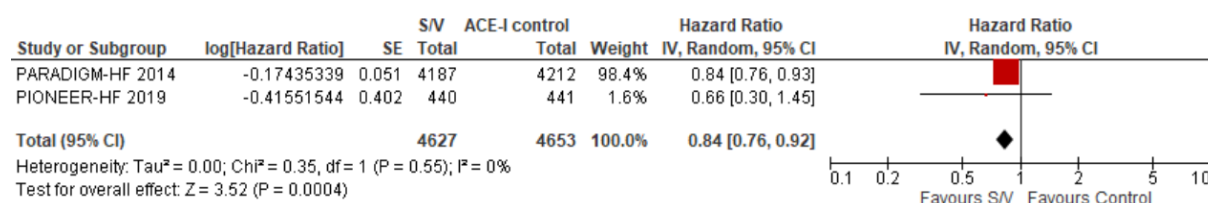


3.2. S/V vs. ACEI

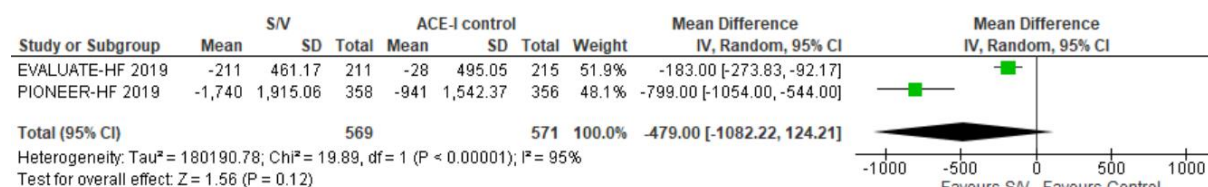
Supplementary Figure S14. Effect of sacubitril/valsartan vs. ACEI on HF hospitalisation



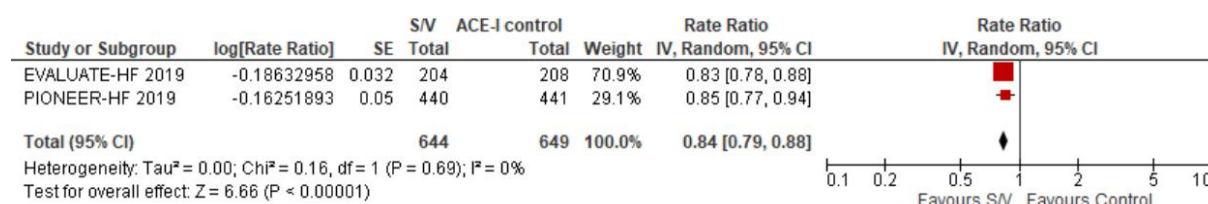
Supplementary Figure S15. Effect of sacubitril/valsartan vs. ACEI on all-cause mortality



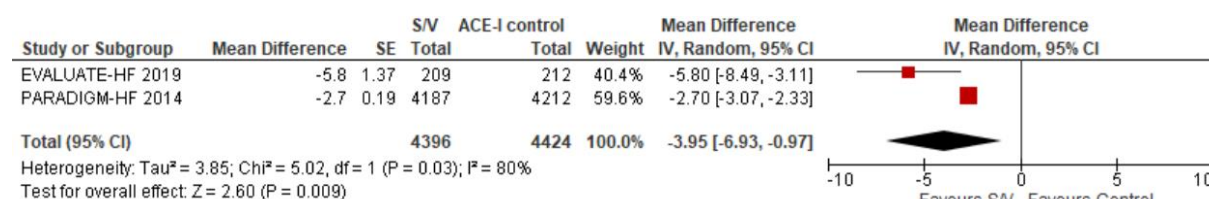
Supplementary Figure S16. Effect of sacubitril/valsartan vs. ACEI on NT-proBNP level (pg/ml)



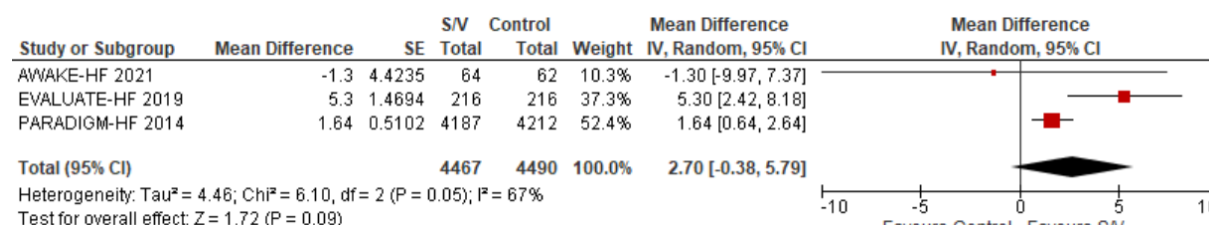
Supplementary Figure S17. Effect of sacubitril/valsartan vs. ACEI on hsTnT ratio of differences



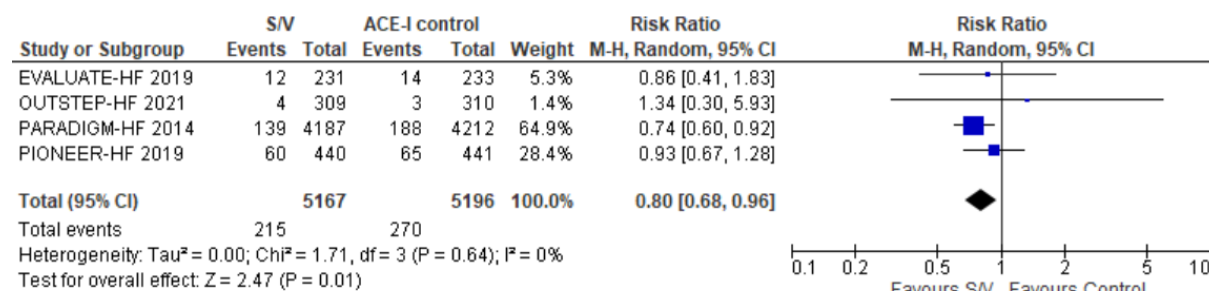
Supplementary Figure S18. Effect of sacubitril/valsartan vs. ACEI on systolic blood pressure (mm Hg)



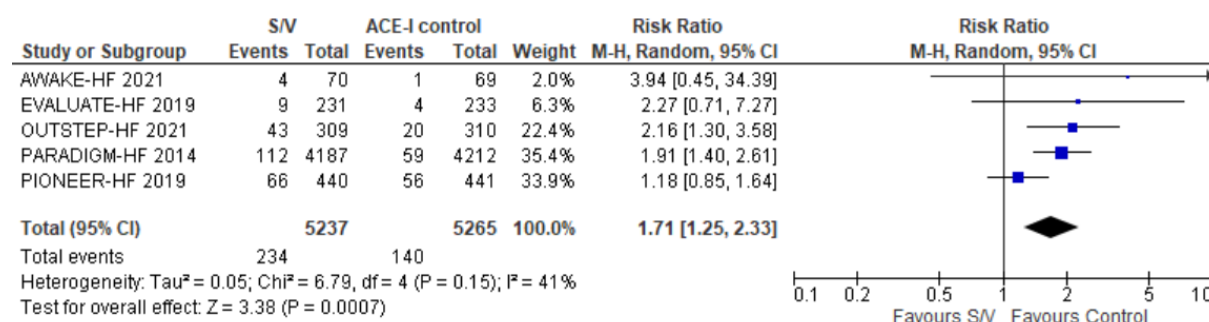
Supplementary Figure S19. Effect of sacubitril/valsartan vs. ACEI on KCCQ-quality of life (QoL)



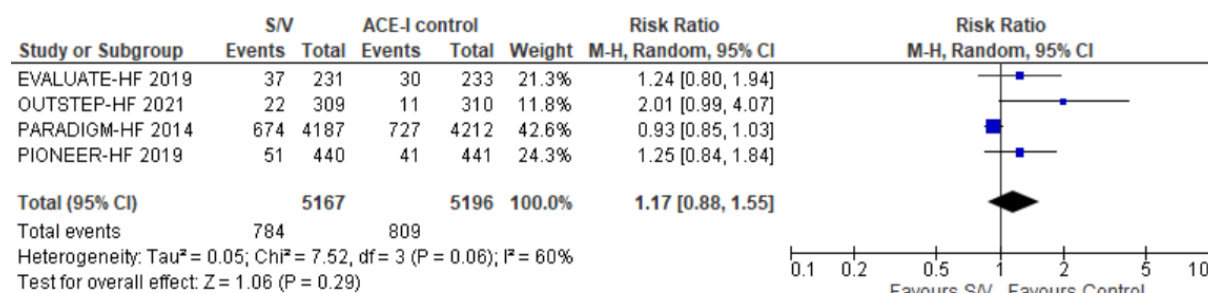
Supplementary Figure S20. Effect of sacubitril/valsartan vs. ACEI on worsening SCr and/or eGFR



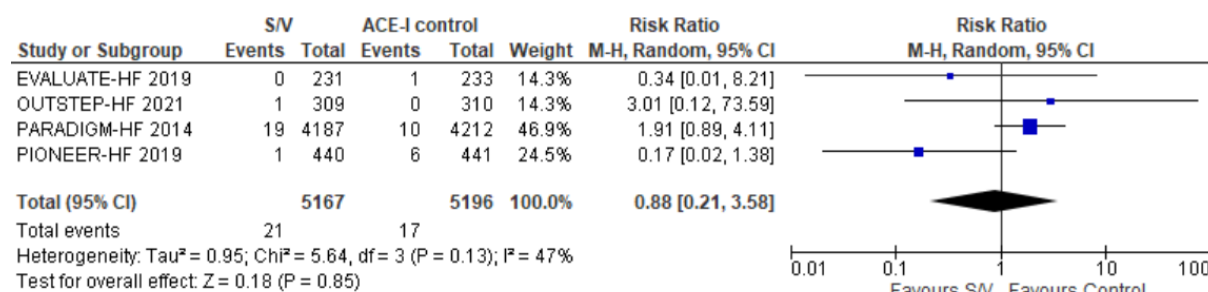
Supplementary Figure S21. Effect of sacubitril/valsartan vs. ACEI on symptomatic hypotension



Supplementary Figure S22. Effect of sacubitril/valsartan vs. ACEI on hyperkalaemia

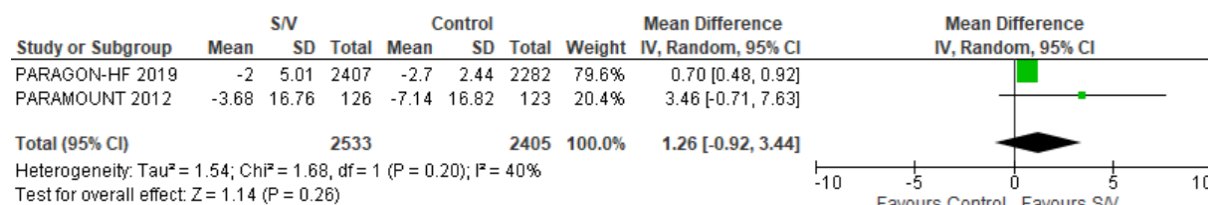


Supplementary Figure S23. Effect of sacubitril/valsartan vs. ACEI on angioedema

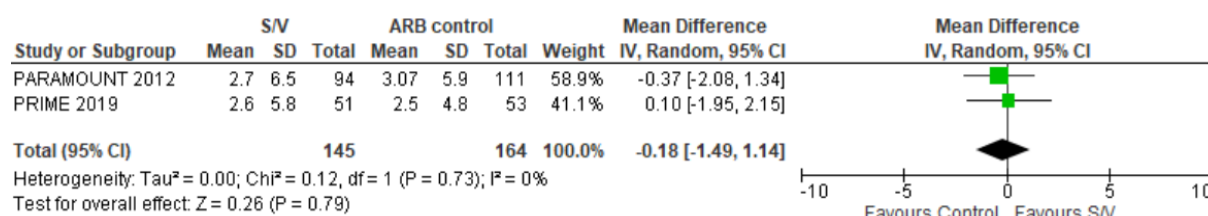


3.3. S/V vs. ARB

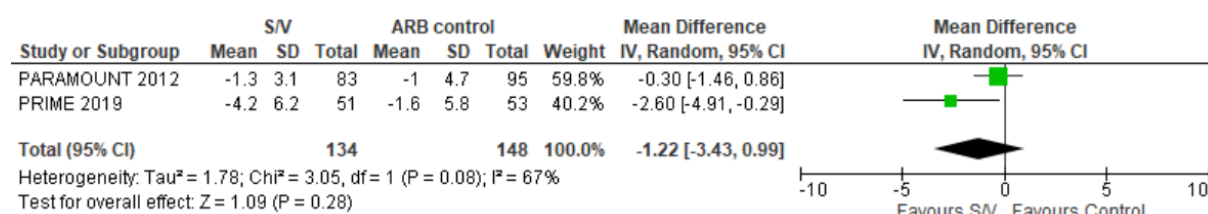
Supplementary Figure S24. Effect of sacubitril/valsartan vs. ARB on change in eGFR



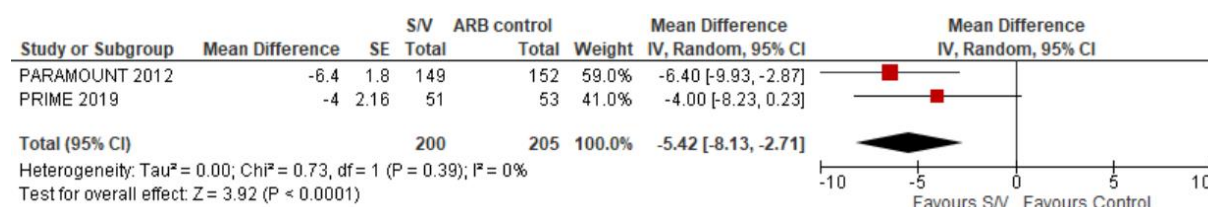
Supplementary Figure S25. Effect of sacubitril/valsartan vs. ARB on LVEF



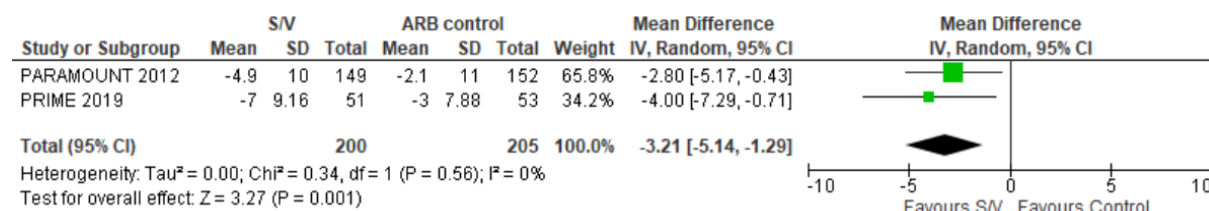
Supplementary Figure S26. Effect of sacubitril/valsartan vs. ARB on E/E' ratio



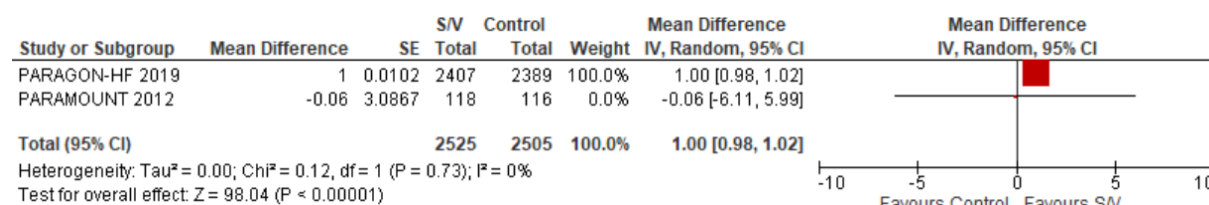
Supplementary Figure S27. Effect of sacubitril/valsartan vs. ARB on systolic blood pressure (mm Hg)



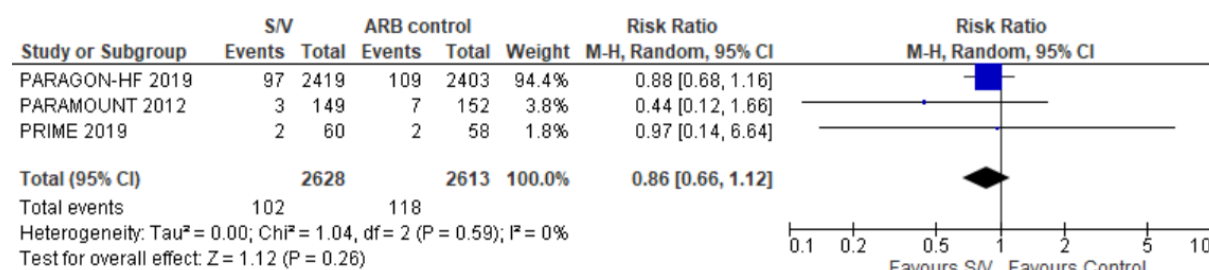
Supplementary Figure S28. Effect of sacubitril/valsartan vs. ARB on diastolic blood pressure (mm Hg)



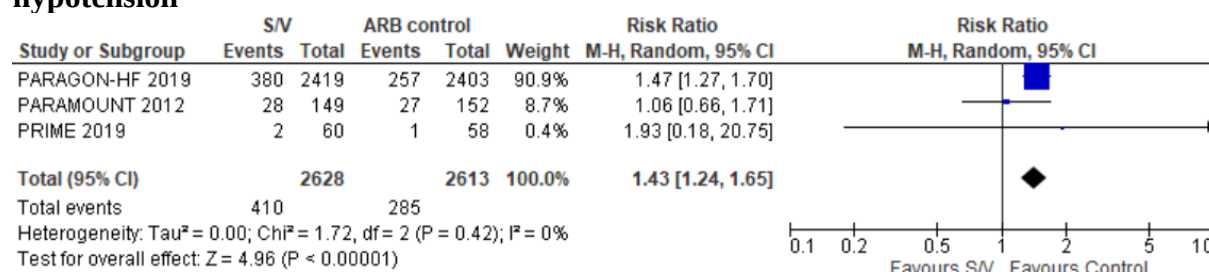
Supplementary Figure S29. Effect of sacubitril/valsartan vs. ARB on KCCQ-quality of life (QoL)



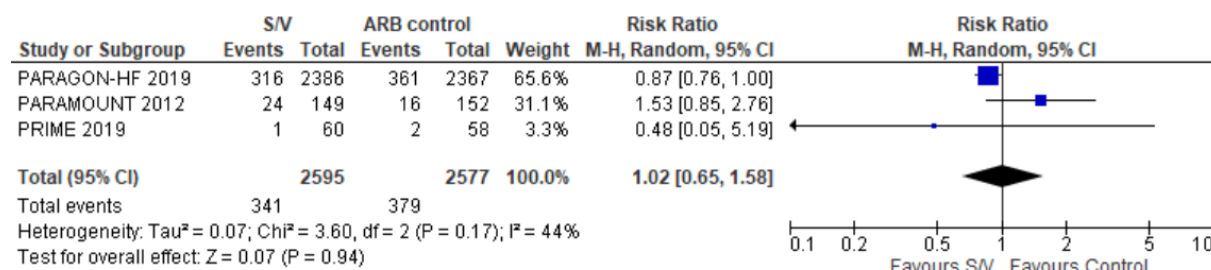
Supplementary Figure S30. Effect of sacubitril/valsartan vs. ARB on worsening SCr and/or eGFR



Supplementary Figure S31. Effect of sacubitril/valsartan vs. ARB on symptomatic hypotension



Supplementary Figure S32. Effect of sacubitril/valsartan vs. ARB on hyperkalaemia



Supplementary Figure S33. Effect of sacubitril/valsartan vs. ARB on angioedema

