

# **SUPPLEMENTAL MATERIAL**

## Supplemental Methods

### Search strategy

We search for all relevant articles published in English from 2010 up to December 2018, in PubMed, Embase, the Cochrane Library, Web of Science and the trial registry Clinicaltrials.gov.

We conduct the following searches:

#### PubMed search strategy:

#1 Search (((((((LCZ696[Title/Abstract]) OR LCZ-696[Title/Abstract]) OR sacubitril[Title/Abstract]) OR sacubitril-valsartan [Title/Abstract]) OR entresto[Title/Abstract]) OR endopeptidase[Title/Abstract]) OR neutral endopeptidase[Title/Abstract]) OR neprilysin[Title/Abstract]

#2 Search (((((((("Ventricular Dysfunction, Left"[Mesh]) OR Left Ventricular Dysfunction[Title/Abstract]) OR Dysfunction, Left Ventricular[Title/Abstract]) OR Dysfunctions, Left Ventricular[Title/Abstract]) OR Left Ventricular Dysfunctions[Title/Abstract]) OR Ventricular Dysfunctions, Left[Title/Abstract])) OR (("Heart Failure, Systolic"[Mesh]) OR (((((((Heart Failures, Systolic[Title/Abstract]) OR Systolic Heart Failures[Title/Abstract]) OR Systolic Heart Failure[Title/Abstract]) OR Heart Failure, Left-Sided[Title/Abstract]) OR Heart Failure, Left Sided[Title/Abstract]) OR Left-Sided Heart Failure[Title/Abstract]) OR Left Sided Heart Failure[Title/Abstract]) OR heart failure with reduced ejection fraction[Title/Abstract]))

#3 Search (((("Angiotensin-Converting Enzyme Inhibitors"[Mesh]) OR (((((((((((((((Angiotensin Converting Enzyme Inhibitors[Title/Abstract]) OR Inhibitors, Kininase II[Title/Abstract]) OR Kininase II Antagonists[Title/Abstract]) OR Kininase II Inhibitors[Title/Abstract]) OR Angiotensin I-Converting Enzyme Inhibitors[Title/Abstract]) OR Angiotensin I Converting Enzyme Inhibitors[Title/Abstract]) OR Antagonists, Angiotensin-Converting Enzyme[Title/Abstract]) OR Antagonists, Angiotensin Converting Enzyme[Title/Abstract]) OR Antagonists, Kininase II[Title/Abstract]) OR Inhibitors, ACE[Title/Abstract]) OR ACE Inhibitors[Title/Abstract]) OR Inhibitors, Angiotensin-Converting Enzyme[Title/Abstract]) OR Enzyme Inhibitors, Angiotensin-Converting[Title/Abstract]) OR Inhibitors, Angiotensin Converting Enzyme[Title/Abstract]) OR Angiotensin-Converting Enzyme Antagonists[Title/Abstract]) OR Angiotensin Converting Enzyme Antagonists[Title/Abstract]) OR Enzyme Antagonists, Angiotensin-Converting[Title/Abstract])))) OR (("Angiotensin Receptor Antagonists"[Mesh]) OR (((((((Antagonists, Angiotensin Receptor[Title/Abstract]) OR Receptor

Antagonists, Angiotensin[Title/Abstract]) OR Angiotensin Receptor Blockers[Title/Abstract]) OR Receptor Blockers, Angiotensin[Title/Abstract]) OR Angiotensin II Receptor Antagonists[Title/Abstract]) OR Angiotensin II Receptor Blockers[Title/Abstract]) OR angiotensin receptor antagonist[Title/Abstract]))

#4 Search (((("Clinical Trials as Topic"[Mesh]) OR clinical trial[Publication Type]) OR ((clinical[Title/Abstract]) AND trial[Title/Abstract])) OR random\*[Title/Abstract]) OR "Random Allocation"[Mesh]) OR "therapeutic use" [Subheading]

#5 Search (((#1) AND #2) AND #3) AND #4 **TOTAL 139**

**EMBASE search strategy:**

#1 'sacubitril plus valsartan'/exp OR 'lcz696':ti,ab OR 'lcz-696':ti,ab OR 'entresto':ti,ab OR 'sacubitril-valsartan':ti,ab OR 'sacubitril':ti,ab OR 'endopeptidase':ti,ab OR 'neutral endopeptidase':ti,ab OR 'neprilysin inhibitor':ti,ab

#2 'heart failure with reduced ejection fraction'/exp OR 'systolic heart failures':ti,ab OR 'systolic heart failure':ti,ab OR 'heart failure, left-sided':ti,ab OR 'heart failure, left sided':ti,ab OR 'left-sided heart failure':ti,ab OR 'left sided heart failure':ti,ab OR 'ventricular dysfunction, left':ti,ab OR 'left ventricular dysfunction':ti,ab OR 'dysfunction, left ventricular':ti,ab OR 'left ventricular dysfunctions':ti,ab

#3 'dipeptidyl carboxypeptidase inhibitor'/exp OR 'angiotensin converting enzyme inhibitors':ti,ab OR 'kininase ii inhibitors':ti,ab OR 'angiotensin i-converting enzyme inhibitors':ti,ab OR 'angiotensin i converting enzyme inhibitors':ti,ab OR 'antagonists, angiotensin-converting enzyme':ti,ab OR 'antagonists, angiotensin converting enzyme':ti,ab OR 'inhibitors, ace':ti,ab OR 'ace inhibitors':ti,ab OR 'inhibitors, angiotensin-converting enzyme':ti,ab OR 'enzyme inhibitors, angiotensin-converting':ti,ab OR 'inhibitors, angiotensin converting enzyme':ti,ab OR 'angiotensin-converting enzyme antagonists':ti,ab OR 'angiotensin converting enzyme antagonists':ti,ab OR 'angiotensin receptor antagonist'/exp OR 'antagonists, angiotensin receptor':ti,ab OR 'receptor antagonists, angiotensin':ti,ab OR 'angiotensin receptor blockers':ti,ab OR 'receptor blockers, angiotensin':ti,ab OR 'angiotensin ii receptor antagonists':ti,ab OR 'angiotensin ii receptor blockers':ti,ab OR 'angiotensin receptor antagonists':ti,ab

#4 'clinical trial (topic)'/exp OR 'drug therapy'/exp OR 'randomization'/exp OR 'random\*':ti,ab OR ('clinical':ti,ab AND 'trial':ti,ab) OR 'clinical trial':it

**#5 #1 AND #2 AND #3 AND #4      TOTAL 282**

**The Cochrane Library search strategy:**

**#1** MeSH descriptor: [Heart Failure, Systolic] explode all trees

**#2** MeSH descriptor: [Stroke Volume] explode all trees

**#3** MeSH descriptor: [Ventricular Dysfunction] explode all trees

**#4** ((cardi\*):ti,ab,kw OR (myocardi\*):ti,ab,kw OR (heart):ti,ab,kw) AND ((failure):ti,ab,kw OR (dysfunction):ti,ab,kw)

**#5** ("heart failure with reduced ejection fraction"):ti,ab,kw OR #1 OR #2 OR #3 OR #4

**#6** (LCZ696):ti,ab,kw OR (sacubitril-valsartan):ti,ab,kw OR (sacubitril):ti,ab,kw OR (LCZ-696):ti,ab,kw OR (entresto):ti,ab,kw OR (endopeptidase):ti,ab,kw OR (neutral endopeptidase):ti,ab,kw OR (neprilysin inhibitor):ti,ab,kw

**#7 (#5 AND #6) TOTAL 254**

**Web of Science search strategy:**

**#1** (TS=(LCZ696 OR entresto OR "sacubitril-valsartan" OR "neprilysin inhibitor"))

**#2** (TS=(heart OR myocardi\* OR cardio\* OR cardia\*))

**#3** (TS=(failure OR dysfunction))

**#4 #2 AND #3**

**#5** (TS=("systolic heart failure" OR "heart failure with reduced ejection fraction" OR "ventricular dysfunction"))

**#6 #4 OR #5**

**#7** Restrictive conditions: Language: English; Time period: 2010-2018; Article types: NOT reviews and letters **TOTAL 432**

**#8 #1 AND #6 AND #7**

**Table S1. Study population and quality assessment of included non-RCT**

<b>First Author</b>	<b>Study population</b>	<b>Selection</b>	<b>Comparability</b>	<b>Outcome</b>
<b>Almufleh<sup>1</sup> 2017</b>	Adult patients with a diagnosis of HFrEF treated with ARNI for more than 1 month, excluding patients with new diagnosis of HF within 1 year before starting ARNI	★★★	★★	★★★
<b>Nazzari<sup>2</sup> 2018</b>	Symptomatic patients with chronic HFrEF, who received ARNI on optimal medical treatment	★★	★★	★★
<b>De Diego<sup>3</sup> 2018</b>	Heart failure patients with 1) reduced LVEF<40%. 2) NYHA functional class II. 3) 6 months of optimal medical therapy with angiotensin inhibition (ACE inhibitor or ARB), BBK and MRA. 4) Then, ACE inhibitor or ARB was stopped and ARNI was tolerated	★★★★	★★	★★★
<b>Maurin<sup>4</sup> 2017</b>	systolic HF patients	★★★	★	★★★
<b>Canu<sup>5</sup> 2017</b>	systolic heart failure patients treated with ARNI; in stable hemodynamic condition with an optimized treatment before the switch.	★★★	★	★★★
<b>Murray<sup>6</sup> 2017</b>	Patients commencing ARNI therapy over an 18-month period were included, stable on angiotensin axis blockade prior to commencement. Patients were commenced on ARNI at the lowest dose and titrated upwards to either the maximum dose or to maximum tolerated dose	★★★	★	★★★
<b>Hlavata<sup>7</sup> 2018</b>	stable HF outpatients were in a clinically stable condition at least 1 month before S/V initiation (no deterioration in symptoms, no increase in diuretic dose, stable dose of ACEI/ARB and betablockers).	★★★★	★	★★★
<b>Beltrán<sup>8</sup> 2018</b>	stable symptomatic patients with HFrEF were eligible for ARNI according to current guidelines	★★★★	★	★★★
<b>Mantis<sup>9</sup> 2018</b>	patients with HFrEF who had symptoms despite receiving optimal medical therapy with a New York Heart Association (NYHA) functional class II-III.	★★★	★	★★★
<b>Fraille<sup>10</sup> 2018</b>	multimorbidity patients with severe symptomatic HFrEF diagnosis based on the guidelines of European Society of Cardiology on 2016 and who had dyspnea at rest or with minimal or slight limitation on physical activity.	★★★★	★	★★★
<b>Mercedes<sup>11</sup> 2018</b>	patients with chronic HF	★★★	★	★★★
<b>Marques<sup>12</sup> 2018</b>	patients with HFrEF assessed in our outpatient clinic, who started treatment with ARNI	★★★	★	★★★
<b>Groba-Marco<sup>13</sup> 2018</b>	patients with stable symptomatic HFrEF and optimized treatment after ANRI	★★★	★	★★★
<b>Kalantari<sup>14</sup> 2018</b>	patients on optimal guideline directed medical therapy were initiated on ARNI after an appropriate wash-out period from prior ACEI or ARB therapy	★★★	★	★★★
<b>Barrett<sup>15</sup> 2017</b>	Patients with HFrEF managed in a disease management programme, commencing ARNI therapy and achieving maximum tolerated dose	★★★	★	★★★
<b>Martens<sup>16</sup> 2018</b>	HFrEF patients with a class I indication (NYHA-class II-IV, LVEF < 35%, optimal dose with RAS-blocker)	★★★★	★	★★★

A maximum of 4 stars for selection, 2 for comparability and 3 for outcome.

**Table S2.** Functional exercise capacity before and after treatment of ARNI.

Study	NYHA functional class		6-min walking test (m)	
	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI
Nazzari <sup>2</sup>	2.1±0.6	1.9±0.7	NR	NR
De Diego <sup>3</sup>	2.4±0.4	1.5±0.7	NR	NR
Canu <sup>5</sup> 1M	2.3±0.5	2.1±0.4	461±120.5	511±120.5
Canu <sup>5</sup> 3M	2.3±1.3	1.9±0.5	472±125.6	516±125.6
Hlavata <sup>7</sup>	2.7±0.7	2.5±0.8	390.8±77.1	440.8±72.9
Beltrán <sup>8</sup> 1M	NR	NR	300±6.2	341.2±5.8
Beltrán <sup>8</sup> 3M	NR	NR	274±69.8	335±69.8
Mantis <sup>9</sup> 2018	NR	NR	298±35	306±49
Fraile <sup>10</sup> 2018	3.7±0.5	2.6±0.7	223±93.6	279±104.8
Mercedes <sup>11</sup>	NR	NR	274±102	335±102
Marques <sup>12</sup>	2.5±0.5	2.1±0.6	NR	NR
Kalantari <sup>14</sup>	NR	NR	428±105	451±115
Solomon <sup>17</sup> 9M	2.2±0.4	2±0.5	NR	NR

ARNI, Angiotensin-receptor neprilysin inhibitor; NYHA, New York Heart Association; NR,

Not reported.

**Table S3.** Remodeling parameters after taking ARNI from baseline.

Study	LVEF (%)		LVESV (mL)		LVEDV (mL)		LVESD (mm)		LVEDD (mm)		LVMI (g/m <sup>2</sup> )		LAV (ml)	
	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI
Almufleh <sup>1</sup>	25.33±7.8	30.14±8	165.0±91.5	143.7±91.5	221.4±3546	207.5±3546	56.3±6.5	52.9±6.5	65.8±3.4	63.15±3.4	128.1±16.4	113.7±16.4	NR	63.8±22.6
Nazzari <sup>2</sup>	27.4±6.9	36.4±12.4	NR	NR	NR	NR	NR	NR	67.6±4.2	65.2±4.2	NR	NR	NR	
De Diego <sup>3</sup>	31±6	36.5±8	NR	NR	141±17	119±15	NR	NR	62±6	60±6	NR	NR	NR	60.7±22.1
Maurin <sup>4</sup>	28.4±7.7	31.9±8.2	158.9±68.0	142.7±70.1	218.8±79.1	204.1±79.3	NR	NR	67.2±8.6	64.8±10.9	NR	NR	69.9±24.3	
Groba-Marco <sup>13</sup>	30±7.9	35.5±10.3	NR	NR	NR	NR	NR	NR	66.42±6.7	62.42±7.5	NR	NR	NR	
Kalantari <sup>14</sup>	32±7	35±7	170±58	148±50	247±68	222±58	53±9	49±10	62±8	60±8	NR	NR	96±39	NR
Martens <sup>16</sup>	29.6±5.9	34.8±6.2	147±57	129±55	206±71	197±72	NR	NR	NR	NR	NR	NR	NR	
Solomon <sup>17</sup> 3M	58.2±7.6	59.3±7	46.5±15.7	43.2±15	110±26.4	107±25.9	NR	NR	NR	NR	77.4±20.7	76.2±21.1	67±23.2	
Solomon <sup>17</sup> 9M	58.3±7.7	61.0±7	46.9±15.8	40±15.5	112±26.3	101±25.9	NR	NR	NR	NR	76.6±19.8	73.8±20.2	65.3±22.5	NR
Schmieder <sup>18</sup> 3M	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	72.1±18	65.74±16	NR	63.2±22.2
Schmieder <sup>18</sup> 13M	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	72.1±18	65.27±15.8	NR	NR
Kang DH <sup>19</sup>	34.9±7.1	37.7±8.1	122.9±43.7	105.2±51.1	186.4±54.5	164.4±60	NR	NR	NR	NR	NR	NR	NR	NR

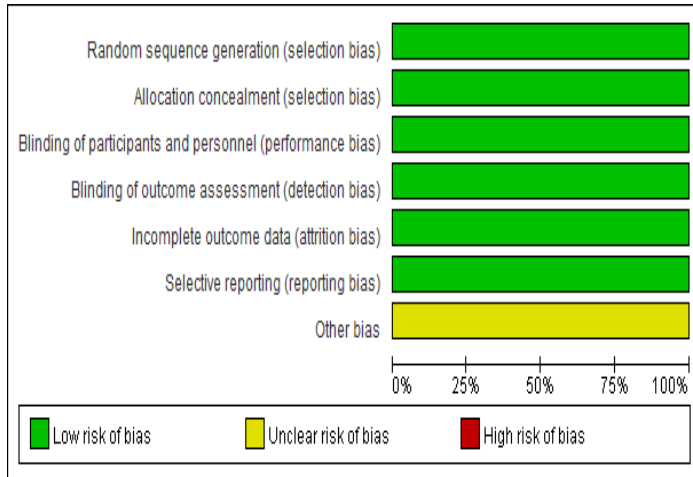
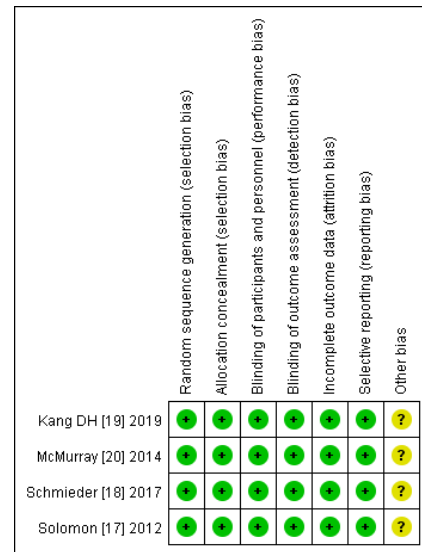
ARNI, Angiotensin-receptor neprilysin inhibitor; LVEF, Left ventricular ejection fraction; ESV, End-systolic volume; EDV, End-diastolic volume; ESD, End-systolic dimension; EDD, End-diastolic dimension; LVMI, Left ventricular mass index; LAV, Left atrial volume; NR, Not reported.

**Table S4.** Changes of biomarkers from baseline with ARNI.

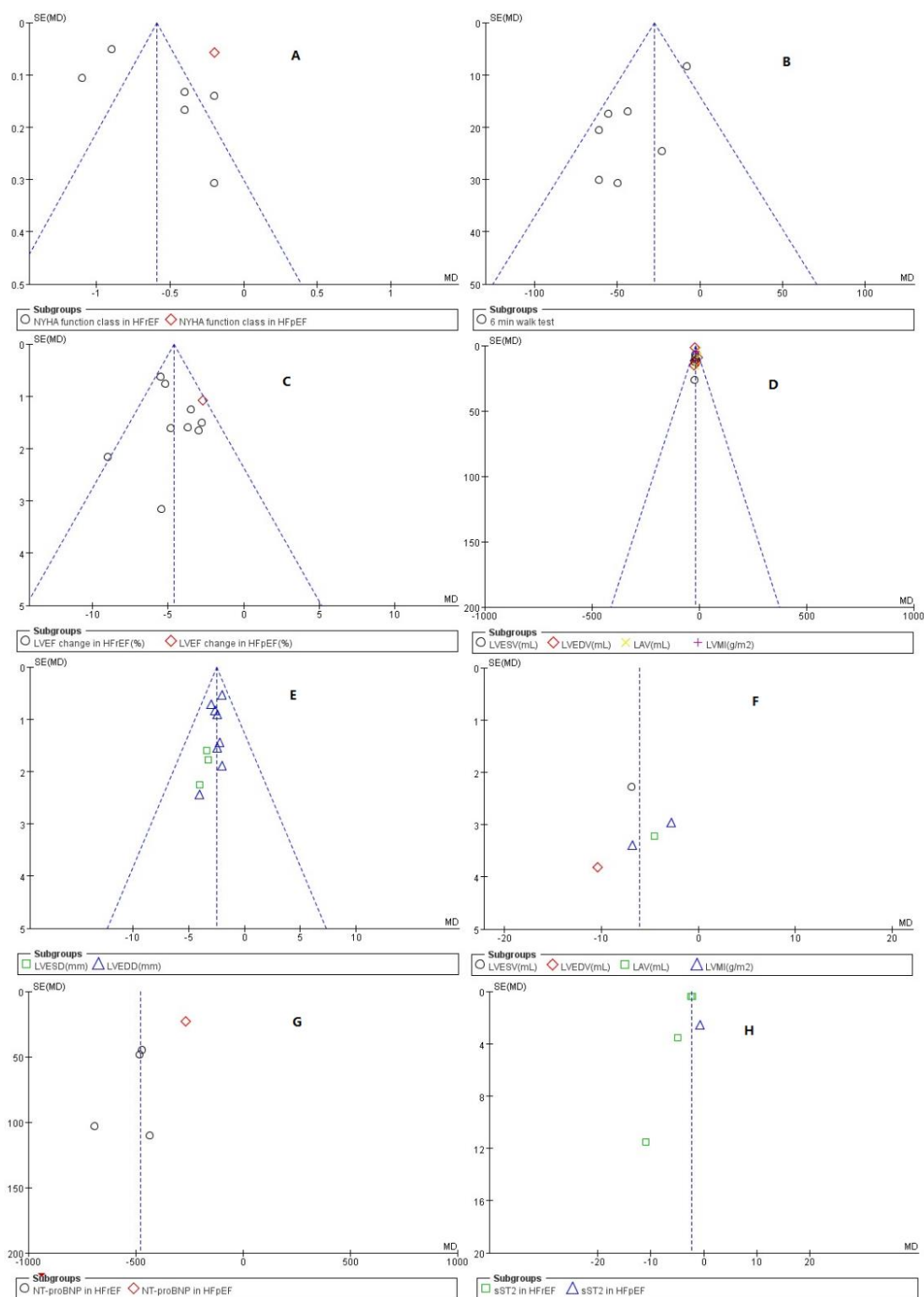
Study	NT-proBNP (pg/ml)		sST2 (ng/ml)	
	Pre-ARNI	Post-ARNI	Pre-ARNI	Post-ARNI
De Diego <sup>3</sup>	1851±1410	1160±815	NR	NR
ICD/ICD-CRT <sup>3</sup>	1971±1530	1172±955	NR	NR
Murray <sup>6</sup>	1951±822	1516±822	43±26.5	38±26.5
Hlavata <sup>7</sup>	1528.9±2310.6	551.2±574.4	NR	NR
Barrett <sup>15</sup>	1592±1912.2	655±1912.2	58.3±63.3	47.3±63.3
Solomon <sup>17</sup> 3M	783±180.7	605±149.6	32.2±17.4	29.8±16.7
Solomon <sup>17</sup> 9M	763±188.9	496±157	32.2±17.4	31.4±19.9
McMurray <sup>20</sup> 1M	1485±1186.6	1014.7±809	33.2±11.9	31±0.8
McMurray <sup>20</sup> 8M	1485±1186.6	1005.7±938.8	33.2±11.9	30.7±0.8

ARNI, Angiotensin-receptor neprilysin inhibitor; NR, Not reported.



**A****B**

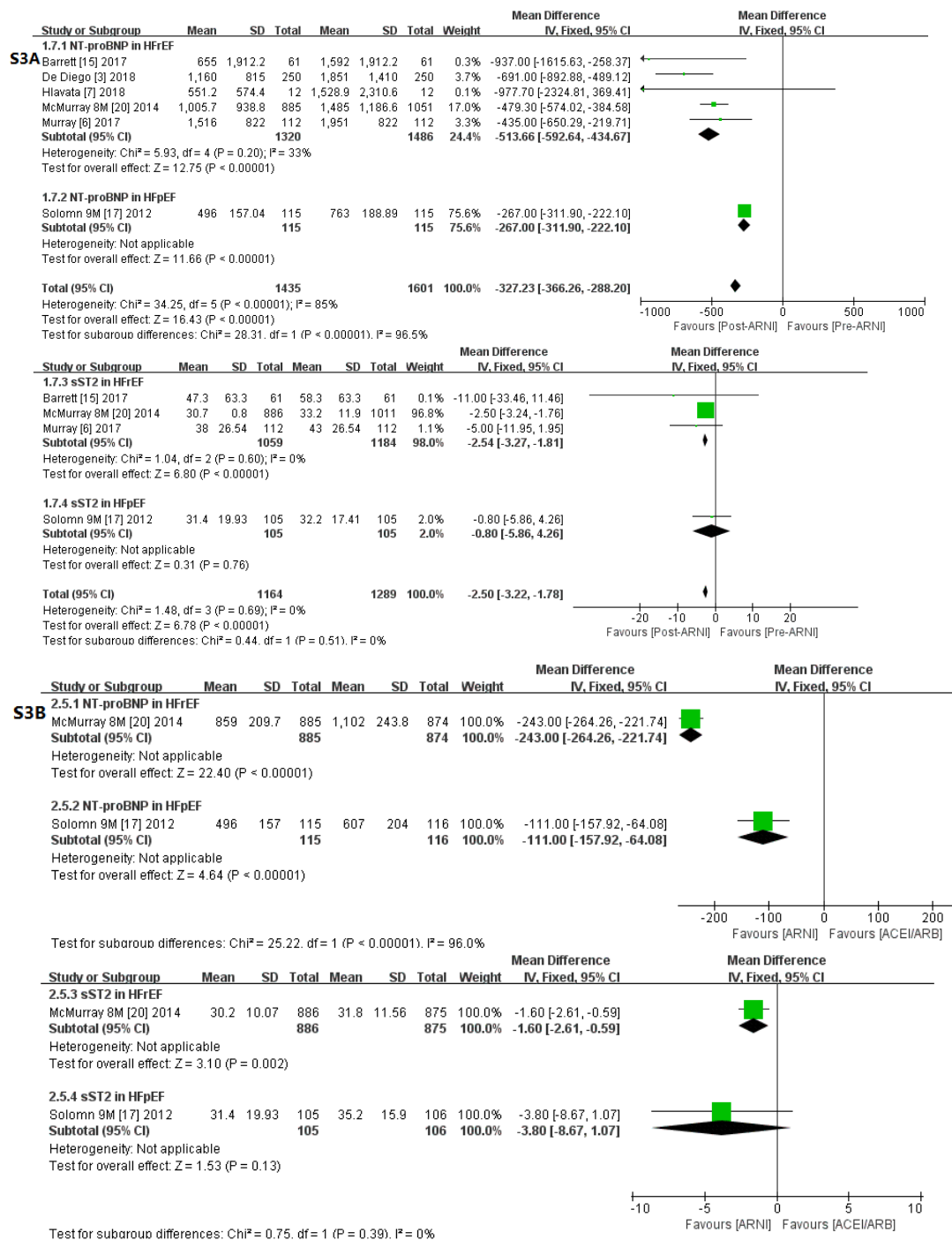
**Figure S1.** (A) Methodological quality graph: reviewer author's judgments about each methodological quality item presented as percentage across all included studies; (B) Methodological quality summary: review authors' judgments about each methodological quality.



**Figure S2.** Funnel plot estimating publication bias for changes of main parameters following ARNI.

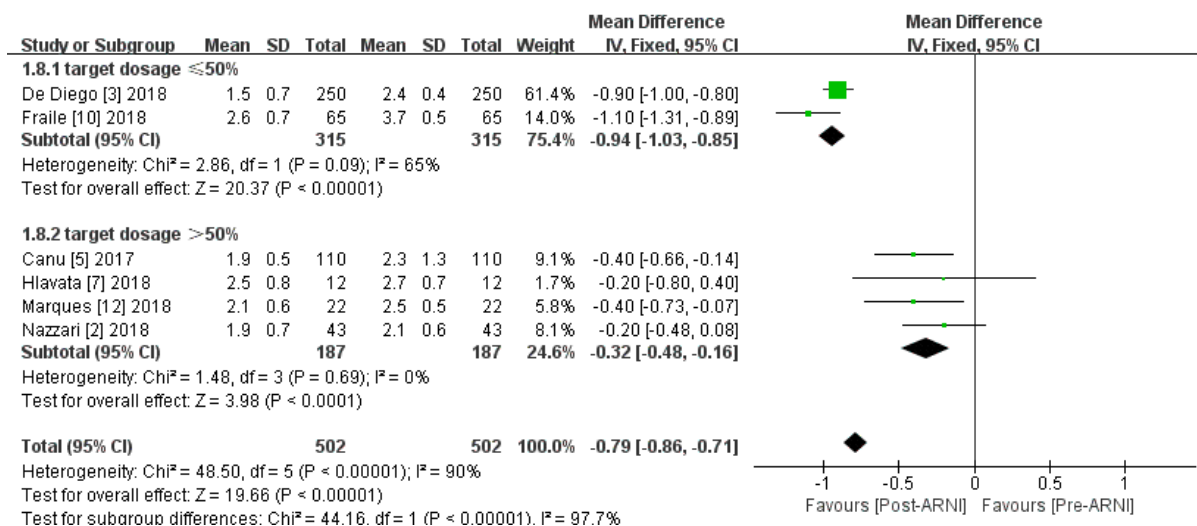
(A) New York Heart Association (NYHA) functional class, (B) 6-minute walking distance (6MWD), (C) Left ventricular ejection fraction (LVEF), (D) and (E) remodeling indexes in patients of heart failure

with reduced ejection fraction (HFrEF), (F) remodeling indexes in patients of heart failure with preserved ejection fraction (HFpEF), (G) and (H) biomarkers including NT-proBNP and sST2.

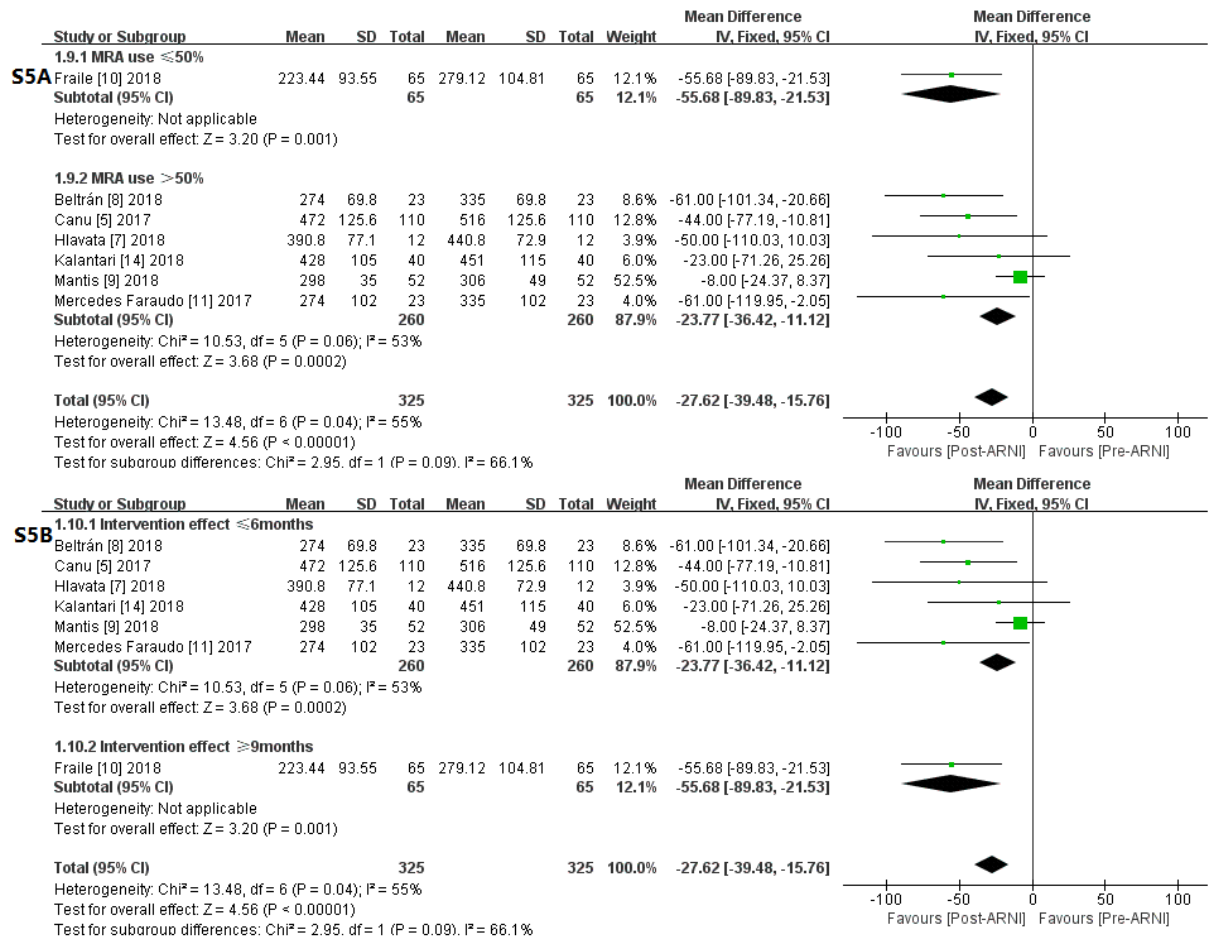


**Figure S3.** Forest plots for effect of ARNI on remodeling biomarkers (A) in contrast with ACEIs/ARBs

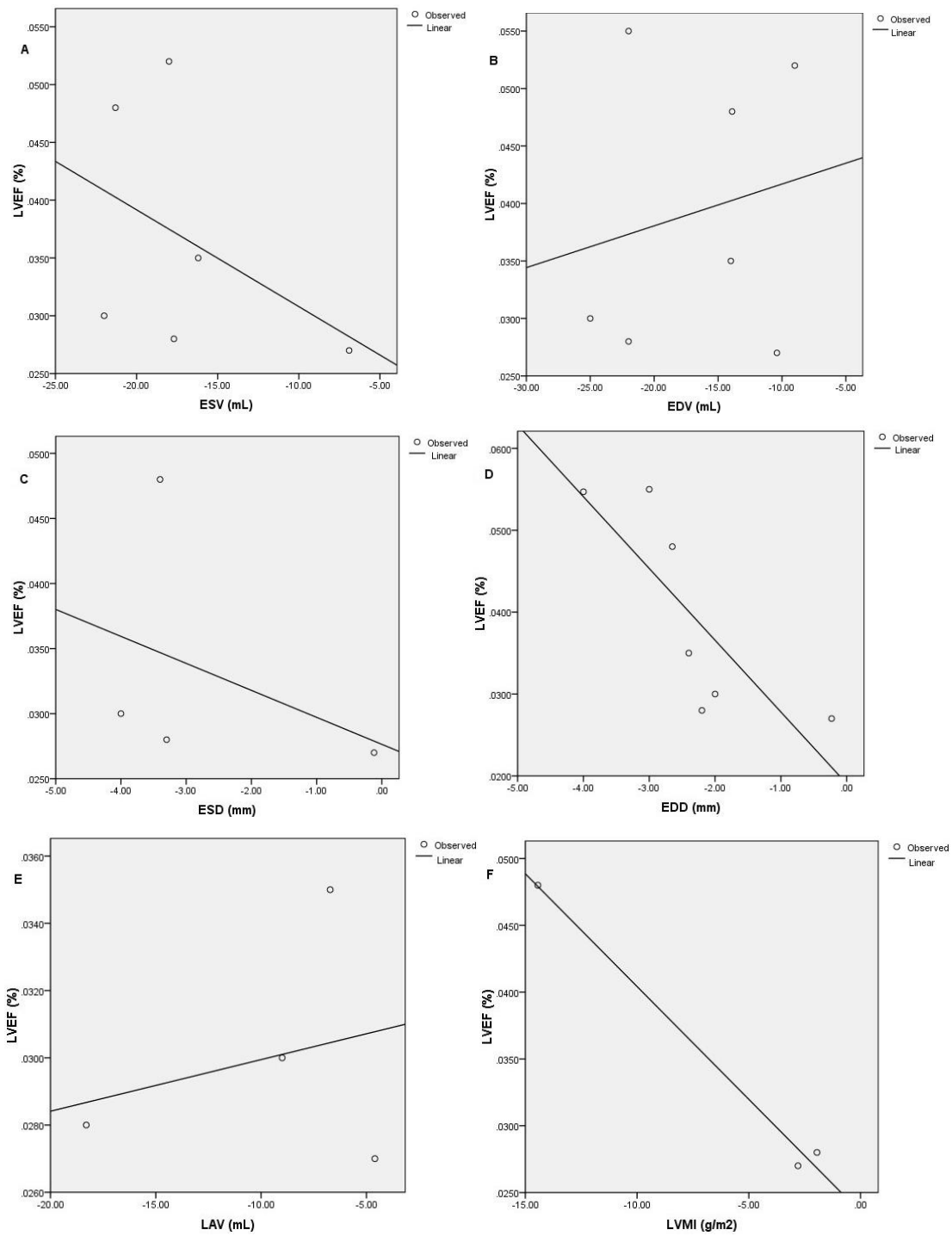
(B).



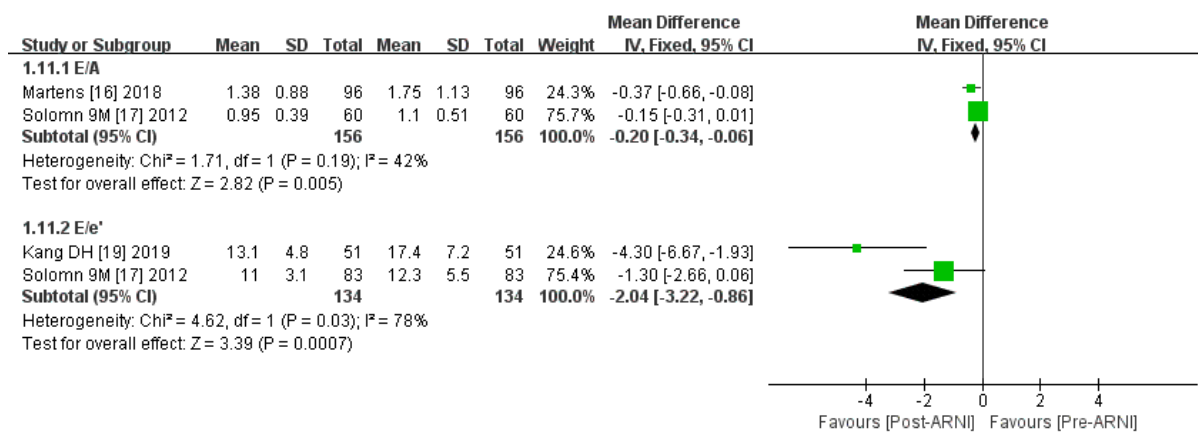
**Figure S4.** Subgroup analysis of ARNI effects on NYHA functional class according to different proportions of patients reaching target dosage of ARNI.



**Figure S5.** Subgroup analysis of ARNI effects on 6MWD according to different (A) proportions of patients with MRA use and (B) follow-up periods.



**Figure S6** .Correlation analyses of LVEF and CRR indices, except LVEF, (A) LVESV, (B) LVEDV, (C) LVESD, (D) LVEDD, (E) LAV, (F) LVMI, respectively in patients following ARNI.



**Figure S7.** Forest plots for effects of ARNI on main LV diastolic function indices.



### Supplemental References:

1. Almufleh A, Marbach J, Chih S, Stadnick E, Davies R, Liu P, Mielniczuk L. Ejection fraction improvement and reverse remodeling achieved with Sacubitril/Valsartan in heart failure with reduced ejection fraction patients. *Am J Cardiovasc Dis.* 2017; 7:108-113.
2. Nazzari H, Yeung M, Marceau A, Luong M, Clark C, Ahuja S, Knoll J, Koscal M, Ignaszewski A, Virani S, Toma M. Left Ventricular Function Improves in Heart Failure Patients Treated with Sacubitril-Valsartan. *Can J Cardiol.* 2017; 33: S163.
3. De Diego C, González-Torres L, Núñez JM, Centurión ER, De Lara G, Macias M. Angiotensin-neprilysin inhibition further reverses cardiac remodeling as compared to angiotensin inhibition in reduced heart failure patients. *Europace.* 2018; 20: i139.
4. Maurin V, Canu A, Bernard A, Lafitte S, Picard F. Early reverse remodeling and improvement of echo parameters after introduction of sacubitril/valsartan in 80 stable and well treated HF<sub>r</sub>EF patients. *Eur J Heart Fail.* 2017; 19:296.
5. Canu A, Hebert M, Gachet A, Arabucki F, Maurin V, Picard F, Dos Santos P. Results of a single center experience on 110 consecutive patients treated with Entresto (sacubitril/valsartan). *Archives of Cardiovascular Diseases Supplements.* 2017; 9:33.
6. Murray G, Barrett M, Earls S, Hammond M, Campbell P, O'Hanlon R, McDonald K. THE USE OF SACUBITRIL/VALSARTAN: A REALWORLD EXPERIENCE IN A HIGH VOLUME SPECIALIST HEART FAILURE SERVICE. *Heart.* 2017; 103: A8-A9.
7. Hlavata K, Hoskova L, Franekova J, Jabor A, Kautzner J, Melenovsky V, Benes J. Transition from angiotensin-converting enzyme inhibitor/angiotensin-II-receptor-blocker to sacubitril/valsartan in

- chronic heart failure patients: Initial experiences in clinical practice. *Cor et Vasa*. 2018; 60: e209 - e214.
8. Beltrán P, Palau P, Domínguez E, Faraudo M, Nunez E, Guri O, Mollar A, Sanchis J, Bayes-Genis A, Nunez J. Sacubitril/valsartan and short-term changes in the 6-minute walk test: A pilot study. *Int J Cardiol*. 2018; 252:136-139.
  9. Mantis C, Anadiotis A, Patsilidakos S. Impact of sacubitril/valsartan on functional exercise capacity and quality of life in patients with heart failure with reduced ejection fraction. *European Journal of Preventive Cardiology*. 2018; 25: S73.
  10. Rodil Fraile R, Malafarina V, Tiberio Lopez G. Sacubitril-valsartan in heart failure and multimorbidity patients. *ESC Heart Failure*. 2018; 5:957-960.
  11. Mercedes Faraudo M, Beltran P, Freixa R, Guri O, Mena E, Contra A, Ceresuela L, Masip J. How does sacubitril/valsartan improve submaximal functional capacity measured through six-minute walk test? *Eur J Heart Fail*. 2017; 19:307.
  12. Rafael Bravo Marques R, Torres Calvo F, Lopez Tejero S, Valle Alberca A, Corona Barrio C, Chinchurreta Capote PA, Siles Rubio JR, Mesa Prado FE, Milan Pinilla AC, Perez Cabeza AI, Moreno Sanjuan D, Ruiz Mateas F. Initial experience using LCZ696 in real life: tolerability and clinical evolution in a short term. *Eur J Heart Fail*. 2017; 19:290-291.
  13. Groba-Marco M, Singh M, Galvan Ruiz M, Fernandez-De-Sanmamed-Giron M, Montiel Quintero R, Perez-Nogales E, Medina Gil JM, Blanco-Nuez M, Caballero Dorta E, Ortega Trujillo JR, Menduina Gallego I, Morales Gonzalez J, Quevedo Nelson V, Mendoza Lemes H, Antonio Garcia Quintana A. Early left ventricular reverse remodeling after sacubitril/valsartan treatment in clinical practice. *Eur J Heart Fail*. 2017; 20:225.

14. Kalantari S, Medvedofsky DM, Grinstein JG, Tayazime ST, Kim GK, Sarswat NS, Raikelkhar JR, Smith BS, Maffessanti FM, Beiser DB, Ward PW, Uriel NU. Remodel: Demonstration of Reverse Remodeling Effects of sacubitril/valsartan. *Eur J Heart Fail.* 2017; 20:36-37.
15. Barrett MJ, Hammond M, Zhou S, Hanlon RO, Campbell P, McDonald K. Effect of sacubitril/valsartan therapy on risk stratification biomarkers in a real-world heart failure population. *Eur J Heart Fail.* 2018; 19:585-586.
16. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. *Cardiovascular Therapeutics.* 2018; 36: e12435.
17. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomized controlled trial. *Lancet.* 2012; 380:1387-1395.
18. Schmieder RE, Wagner F, Mayr M, Delles C, Ott C, Keicher C, Hrabak-Paar M, Heye T, Aichner S, Khder Y, Yates D, Albrecht D, Langenickel T, Freyhardt P, Janka R, Bremerich J. The effect of sacubitril/valsartan compared to olmesartan on cardiovascular remodeling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study. *Eur Heart J.* 2017; 38:3308-3317.
19. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, Yun SC, Song JM, Park SW, Kim JJ. Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation. *Circulation.* 2019; 139:1354-1365.

20. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz M, Rizkala AR, Rouleau JL, Shi VC, Solomon S, Swedberg K, Zile MR, Kardos A. PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med.* 2014; 371:993–1004.