Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004. DOI: 10.1056/NEJMoa1409077

(PDF updated December 2, 2014.)

Supplementary Appendix

Supplementary Appendix

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1. **Committees**

Executive Committee: John McMurray (Co-Chair), Milton Packer (Co-Chair), Jean Rouleau, Scott Solomon, Karl Swedberg, Michael Zile; sponsor representative (non-voting) Martin Lefkowitz.

National Leaders Committee: Argentina, Felipe Martinez ; Belgium, Johan Vanhaecke; Brazil, Felix Ramires; Bulgaria, Tzvetana Katova; Canada, Malcolm Arnold; China, Jun Huang; Colombia, Efrain Gomez; Czech Republic, Jan Belohlavek; Denmark, Jens Refsgaard (previously Ole Lederballe, retired); Dominican Republic, Angel Gonzalez; Ecuador, Yan Carlo Duarte; Estonia, Arvo Rosenthal; Finland Keijo Peuhkurinen; France, Alber-Alain Hagege; Germany, Michael Böhm; Guatemala, Juan Luis Arango; Hungary, Bela Merkely; Iceland, Karl Andersen; Italy, Michele Senni; Latvia, Andrejs Erglis; Lithuania, Zaneta Petrulioniene; Mexico, Edmundo Bayram Llamas; The Netherlands, Arend Mosterd; Peru, Walter Cabrera; Philippines, Antonio S. Sibulo Jr; Poland, Marta Negrusz-Kawecka; Portugal, José Silva-Cardoso; Romania, Dragos Vinereanu; Russia, Sergey Boytsov; Singapore, Raymond Wong; Slovakia, Andrej Dukat; South Africa, Lesley Burgess; South Korea, Kee-Sik Kim; Spain, Carlos Calvo; Sweden, Michael Fu; Taiwan, C-H Chen; Thailand, Songsak Kiatchoosakun; Turkey, Omer Kozan; UK, Iain Squire; USA, Randall Starling, John Teerlink; Venezuela, Ivan Mendoza.

Data Monitoring Committee: Henry Dargie, Golden Jubilee National Hospital Glasgow, Scotland, UK (Chair), Robert Foley, Chronic Disease Research Group Minneapolis, MN, USA; Gary S. Francis, University of Minnesota, Cardiovascular Division Minneapolis, MN, USA; Michel Komajda, Pitié-Salpêtrière, Institut de Cardiologie, Paris, France; Stuart Pocock, Department of Medical Statistics, London School of Hygiene and Tropical Diseases, London, UK.

Endpoint Adjudication Committee: Scott Solomon (Chair), Akshay S. Desai (Co-Chair); Ebrahim Barkoudah, Natalie Bello, Abdel Brahimi, David Charytan, Chau Duong, Peter Finn, Aidan Flynn, Mauro Gori, Howard Hartley, Pardeep Jhund, Rumen Kasabov, Kayode Odutayo, Vinutha Rajesh, Ali Vazir, Larry Weinrauch, Brigham and Women's Hospital Boston.

Angioedema Adjudication Committee: Allen P. Kaplan, Medical University of South Carolina Charleston, SC, USA, (Chair); Nancy Brown, Vanderbilt University School of Medicine, Nashville, TN, USA; Bruce Zuraw University of California, San Diego San Diego, CA, USA .

2. **Independent statistician:**

Nicola Greenlaw, Robertson Centre for Biostatistics, University of Glasgow.

3. **Angiotensin converting enzyme inhibitor and angiotensin receptor blocker doses at screening visit.**

The four ACE inhibitors and ARBs used most commonly along with the doses of these used at the screening visit are shown in the table below.

Four most commonly used ACE inhibitors at the screening visit - mean (±SD) daily dose (mg)	
Enalapril (n=2185)	16.4 ± 8.3
Ramipril (n=1871)	7.0 ± 3.1

Perindopril (n=1118)	5.9 ± 2.7
Lisinopril (n=576)	18.2 ± 12.1
Four most commonly used ARBs inhibitors at the screening visit - mean (±SD) daily dose (mg)	
Losartan (n=791)	67.1 ± 30.2
Valsartan (n=397)	181.5 ± 71.1
Telmisartan (n=196)	60.1 ± 23.9
Candesartan (n=188)	20.0 ± 9.6

Please note that these doses are only those that patients were taking 4 weeks before the screening visit and may not reflect the doses patients may have been taking long-term, before their consideration for the trial.

4. **Urinary cyclic guanosine monophosphate (cGMP)**

The signature response to activation of natriuretic peptides is an increase in their second messenger cyclic GMP. The table below shows change in urinary cGMP from the randomization visit to the follow-up visits at 4 weeks and 8 months later. Please note that at the randomization visit all patients had been taking LCZ696 i.e. had stimulated cGMP production. Thereafter, half of the patients switched to enalapril and half continued on LCZ696. The table shows that in the LCZ696 group cGMP levels did not change much after randomization whereas, in the enalapril group urinary, cGMP fell to approximately 60% of the baseline level.

Change in urinary cyclic guanosine monophosphate (cGMP) from randomization visit to week 4 and month 8

	LCZ696	**Enalapril**	**LCZ696 vs. enalapril**	**P value**[†]
	Ratio of follow-up visit value to baseline value*	**Ratio of follow-up visit value to baseline value***	**Ratio of ratios (LCZ696/enalapril)**	
4 weeks	1.00 (0.96, 1.04) n = 939	0.59 (0.06, 0.62) n = 952	1.69 (1.59,1.79)	< 0.0001
8 months	0.95 (0.90, 0.99) n = 846	0.60 (0.57, 0.63) n = 848	1.58 (1.48, 1.68)	< 0.0001

Note: At randomization visit all patients had been taking LCZ696. *Geometric means (95% CI)
[†]P values from ANCOVA model for log-scaled response with treatment, region, visit and treatment-by-visit interaction as fixed-effect factors and logarithmic baseline cGMP value as a covariate.

5. **Serious adverse events**

Most common serious adverse events (>=1% of patients in any group) during double-blind period regardless of study drug relationship, by preferred term and treatment group (note: this is the safety set). All SAEs that were a possible trial endpoint were submitted for blinded adjudication. Some SAE numbers may therefore differ from endpoint numbers.

Preferred term	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Number of patients with at least one SAE	1937 (46.09)	2142 (50.65)	4079 (48.38)
Cardiac failure	588 (13.99)	649 (15.35)	1237 (14.67)
Pneumonia	155 (3.69)	181 (4.28)	336 (3.98)
Cardiac failure chronic	112 (2.66)	135 (3.19)	247 (2.93)
Cardiac failure congestive	112 (2.66)	140 (3.31)	252 (2.99)
Atrial fibrillation	108 (2.57)	113 (2.67)	221 (2.62)
Cardiac death	85 (2.02)	114 (2.70)	199 (2.36)
Renal failure acute	74 (1.76)	79 (1.87)	153 (1.81)
Cerebrovascular accident	71 (1.69)	72 (1.70)	143 (1.70)
Acute myocardial infarction	69 (1.64)	68 (1.61)	137 (1.62)
Cardiac failure acute	67 (1.59)	93 (2.20)	160 (1.90)
Sudden cardiac death	67 (1.59)	69 (1.63)	136 (1.61)
Sudden death	66 (1.57)	78 (1.84)	144 (1.71)
Ventricular tachycardia	66 (1.57)	85 (2.01)	151 (1.79)
Myocardial infarction	65 (1.55)	72 (1.70)	137 (1.62)
Hypotension	59 (1.40)	68 (1.61)	127 (1.51)
Death	56 (1.33)	78 (1.84)	134 (1.59)
Angina pectoris	55 (1.31)	62 (1.47)	117 (1.39)
Angina unstable	53 (1.26)	51 (1.21)	104 (1.23)
Dyspnoea	51 (1.21)	57 (1.35)	108 (1.28)
Renal impairment	46 (1.09)	57 (1.35)	103 (1.22)
Renal failure	43 (1.02)	54 (1.28)	97 (1.15)
Syncope	43 (1.02)	68 (1.61)	111 (1.32)
Chronic obstructive pulmonary disease	40 (0.95)	46 (1.09)	86 (1.02)
Anaemia	31 (0.74)	47 (1.11)	78 (0.93)
Cardiac arrest	30 (0.71)	56 (1.32)	86 (1.02)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Preferred terms are sorted in descending order of frequency as reported in LCZ696 column.

6. **Adverse events**

Most common adverse events (>=2% of patients in any group), during the double-blind period regardless of study drug relationship, by preferred term and treatment group (note: this is the safety set). Certain AEs (e.g. hypotension, cough) were assessed at each study visit using specific questions on the case report form. These are reported in Table 3 of the main results paper.

Preferred term	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Number of patients with at least one AE	3419 (81.35)	3503 (82.83)	6922 (82.09)
Hypotension	740 (17.61)	506 (11.97)	1246 (14.78)
Cardiac failure	730 (17.37)	832 (19.67)	1562 (18.52)
Hyperkalaemia	488 (11.61)	592 (14.00)	1080 (12.81)
Renal impairment	426 (10.14)	487 (11.52)	913 (10.83)
Cough	369 (8.78)	533 (12.60)	902 (10.70)
Dizziness	266 (6.33)	206 (4.87)	472 (5.60)
Atrial fibrillation	251 (5.97)	236 (5.58)	487 (5.78)
Pneumonia	227 (5.40)	237 (5.60)	464 (5.50)
Oedema peripheral	215 (5.12)	213 (5.04)	428 (5.08)
Dyspnoea	213 (5.07)	306 (7.24)	519 (6.16)
Nasopharyngitis	204 (4.85)	175 (4.14)	379 (4.49)
Upper respiratory tract infection	203 (4.83)	201 (4.75)	404 (4.79)
Urinary tract infection	199 (4.73)	195 (4.61)	394 (4.67)
Diarrhoea	194 (4.62)	189 (4.47)	383 (4.54)
Bronchitis	183 (4.35)	224 (5.30)	407 (4.83)
Angina pectoris	172 (4.09)	170 (4.02)	342 (4.06)
Anaemia	168 (4.00)	201 (4.75)	369 (4.38)
Back pain	164 (3.90)	138 (3.26)	302 (3.58)
Influenza	159 (3.78)	132 (3.12)	291 (3.45)
Hypokalaemia	139 (3.31)	107 (2.53)	246 (2.92)
Cardiac failure chronic	135 (3.21)	155 (3.67)	290 (3.44)
Cardiac failure congestive	133 (3.16)	167 (3.95)	300 (3.56)
Arthralgia	126 (3.00)	119 (2.81)	245 (2.91)
Hypertension	126 (3.00)	193 (4.56)	319 (3.78)
Fatigue	125 (2.97)	129 (3.05)	254 (3.01)
Diabetes mellitus	123 (2.93)	134 (3.17)	257 (3.05)
Gout	121 (2.88)	120 (2.84)	241 (2.86)
Renal failure	112 (2.66)	144 (3.41)	256 (3.04)
Hyperuricaemia	108 (2.57)	151 (3.57)	259 (3.07)
Ventricular tachycardia	108 (2.57)	137 (3.24)	245 (2.91)

Preferred term	LCZ696 N=4203 n (%)	Enalapril N=4229 n (%)	Total N=8432 n (%)
Noncardiac chest pain	106 (2.52)	122 (2.88)	228 (2.70)
Headache	103 (2.45)	106 (2.51)	209 (2.48)
Renal failure acute	95 (2.26)	93 (2.20)	188 (2.23)
Syncope	94 (2.24)	114 (2.70)	208 (2.47)
Chronic obstructive pulmonary disease	93 (2.21)	106 (2.51)	199 (2.36)
Insomnia	92 (2.19)	92 (2.18)	184 (2.18)
Pain in extremity	92 (2.19)	100 (2.36)	192 (2.28)
Asthenia	88 (2.09)	78 (1.84)	166 (1.97)
Nausea	88 (2.09)	100 (2.36)	188 (2.23)
Cardiac death	86 (2.05)	114 (2.70)	200 (2.37)
Constipation	86 (2.05)	124 (2.93)	210 (2.49)
Pyrexia	78 (1.86)	85 (2.01)	163 (1.93)
Cardiac failure acute	72 (1.71)	100 (2.36)	172 (2.04)
Vomiting	71 (1.69)	85 (2.01)	156 (1.85)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- Preferred terms are sorted in descending order of frequency as reported in LCZ696 column.

7. **Systolic blood pressure during run-in and after randomization.**