

Supplementary Table S1. Search strategies with appropriated key words and MeSH terms.

Database	Search
EMBASE	(('heart failure'/exp OR 'backward failure, heart' OR 'cardiac backward failure' OR 'cardiac decompensation' OR 'cardiac failure' OR 'cardiac incompetence' OR 'cardiac insufficiency' OR 'cardiac stand still' OR 'cardial decompensation' OR 'cardial insufficiency' OR 'chronic heart failure' OR 'chronic heart insufficiency' OR 'decompensatio cordis' OR 'decompensation, heart' OR 'heart backward failure' OR 'heart decompensation' OR 'heart failure' OR 'heart incompetence' OR 'heart insufficiency' OR 'insufficiencia cordis' OR 'myocardial failure' OR 'myocardial insufficiency') AND ('renin angiotensin aldosterone system'/exp OR 'angiotensin renin system' OR 'kidney pressor system' OR 'mechanism, renin angiotensin aldosterone' OR 'renin aldosterone system' OR 'renin angiotensin aldosterone mechanism' OR 'renin angiotensin aldosterone system' OR 'renin angiotensin mechanism' OR 'renin angiotensin system' OR 'renin-angiotensin system' OR 'system, renin angiotensin' OR 'system, renin angiotensin aldosterone' OR 'aliskiren'/exp OR 'aliskiren' OR 'aliskiren fumarate' OR 'aliskiren hemifumarate' OR 'aliskiren hydrochloride' OR 'enviage' OR 'rasilez' OR 'riprazo' OR 'tekturna' OR 'aliskiren plus valsartan'/exp OR 'aliskiren hemifumarate plus valsartan' OR 'aliskiren plus valsartan' OR 'aliskiren-valsartan' OR 'aliskiren/valsartan' OR 'valsartan plus aliskiren' OR 'valsartan plus aliskiren hemifumarate' OR 'valsartan-aliskiren' OR 'valsartan/aliskiren' OR 'valturna' OR 'angiotensin 1 receptor antagonist'/exp OR 'at1 antagonist' OR 'at1 blocker' OR 'at1 blocking agent' OR 'at1 receptor antagonist' OR 'at1 receptor blocker' OR 'at1 receptor blocking agent' OR 'angiotensin 1 receptor antagonist' OR 'angiotensin 1 receptor blocker' OR 'angiotensin 1 receptor blocking agent' OR 'angiotensin at1 antagonist' OR 'angiotensin at1 blocker' OR 'angiotensin at1 blocking agent' OR 'angiotensin at1 receptor antagonist' OR 'angiotensin at1 receptor blocker' OR 'angiotensin at1 receptor blocking agent' OR 'angiotensin ii type 1 receptor antagonist' OR 'angiotensin ii type 1 receptor blocker' OR 'angiotensin ii type 1 receptor blockers' OR 'angiotensin ii type 1 receptor blocking agent') AND ('mortality'/exp OR 'death'/exp OR 'death' OR 'mors' OR 'hospitalization'/exp OR 'heart stroke volume'/exp OR 'hypotension'/exp OR 'hyperkalemia'/exp OR 'glomerulus filtration rate'/exp OR 'proteinuria'/exp OR 'heart ventricle hypertrophy'/exp) AND ('randomized controlled trial'/exp OR 'controlled trial, randomized' OR 'pragmatic clinical trial' OR 'pragmatic clinical trials' OR 'randomised controlled study' OR 'randomised controlled trial' OR 'randomized controlled study' OR 'randomized controlled trial' OR 'trial, randomized controlled' OR 'controlled clinical trial'/exp)

LILACS	(tw:((tw:((mh:("Heart Failure")) OR (mh:("Insuficiência Cardíaca")) OR (mh:("Insuficiencia Cardíaca")) OR (mh:("Insuficiência Cardíaca Congestiva"))))) OR (tw:((tw:((tw:("Heart Failure")) OR (tw:("Insuficiência Cardíaca")) OR (tw:("Insuficiencia Cardíaca")) OR (tw:("Insuficiência Cardíaca Congestiva")))))))) AND (tw:((tw:((mh:("Angiotensin-Converting Enzyme Inhibitors")) OR (mh:("Inibidores da Enzima Conversora de Angiotensina")) OR (mh:("Inhibidores de la Enzima Convertidora de Angiotensina")) OR (mh:("Inibidores da ACE")) OR (mh:("Angiotensin II Type 1 Receptor Blockers")) OR (mh:("Bloqueadores do Receptor Tipo 1 de Angiotensina II")) OR (mh:("Bloqueadores del Receptor Tipo 1 de Angiotensina II")) OR (mh:("Bloqueador do Receptor Tipo 1 de Angiotensina II")) OR (mh:("Aliskiren")) OR (mh:("Alisquireno"))))) OR (tw:((tw:("Angiotensin-Converting Enzyme Inhibitors")) OR (tw:("Inibidores da Enzima Conversora de Angiotensina")) OR (tw:("Inhibidores de la Enzima Convertidora de Angiotensina")) OR (tw:("Inibidores da ACE")) OR (tw:("Angiotensin II Type 1 Receptor Blockers")) OR (tw:("Bloqueadores do Receptor Tipo 1 de Angiotensina II")) OR (tw:("Bloqueadores del Receptor Tipo 1 de Angiotensina II")) OR (tw:("Bloqueador do Receptor Tipo 1 de Angiotensina II")) OR (tw:("Aliskiren")) OR (tw:("Alisquireno"))))))))
Cochrane CENTRAL	MeSH descriptor: [Heart Failure AND (Renin-Angiotensin System OR Angiotensin II Type 1 Receptor Blockers OR Angiotensin-Converting Enzyme Inhibitors OR aliskiren) AND (Mortality OR Death OR Hospitalization OR Glomerular Filtration Rate)] explode all trees
PubMed	(((((Heart Failure[mh] OR "Heart Failure" OR "Cardiac Failure" OR "Heart Decompensation" OR "Right-Sided Heart Failure" OR "Right Sided Heart Failure" OR "Myocardial Failure" OR "Congestive Heart Failure" OR "Left-Sided Heart Failure" OR "Left Sided Heart Failure" OR "Chronic heart failure")) AND ((Renin-Angiotensin System[mh] OR "Renin Angiotensin System" OR Angiotensin II Type 1 Receptor Blockers[mh] OR "Angiotensin II Type 1 Receptor Antagonists" OR "Type 1 Angiotensin Receptor Blockers" OR "Angiotensin receptor blocker" OR "Angiotensin 2 Type 1 Receptor Antagonists" OR "Type 1 Angiotensin Receptor Antagonists" OR "Selective Angiotensin II Receptor Antagonists" OR "Sartans" OR Angiotensin-Converting Enzyme Inhibitors[mh] OR "Angiotensin-Converting Enzyme Inhibitors" OR "Angiotensin Converting Enzyme Inhibitors" OR "Kininase II Inhibitors" OR "Angiotensin I-Converting Enzyme Inhibitors" OR "Angiotensin I Converting Enzyme Inhibitors" OR "ACE-inhibitor" OR "ACE Inhibitors" OR "Angiotensin-Converting Enzyme

	Antagonists" OR "Angiotensin Converting Enzyme Antagonists" OR Aliskiren OR "rasilez" OR "Tekturna" OR "direct renin inhibitor" OR "Renin inhibitor")) AND ((mortality[mh] OR "mortality" OR "death" hospitalization[mh] OR "hospitalization" OR "hospitalizations" OR stroke volume[mh] OR "ventricular ejection fractions" OR hypertrophy[mh] OR "hypertrophy" OR "hypertrophies" OR "hypotension"[mh] OR "hypotension" OR "hyperkalemia"[mh] OR "hyperkalemia" OR "hyperpotassemia" OR "proteinuria"[mh] OR "proteinuria" OR potassium[mh] OR glomerular filtration rate[mh] OR "glomerular filtration rate")) AND ((randomized controlled trial[pt] OR "randomized controlled trial" OR controlled clinical trial[pt] OR randomized [tiab] OR clinical trials as topic [mesh: noexp]))
Web of Science	TS=(((((((“Heart Failure” OR “Cardiac Failure” OR “Heart Decompensation” OR “Right-Sided Heart Failure” OR “Right Sided Heart Failure” OR “Myocardial Failure” OR “Congestive Heart Failure” OR “Left-Sided Heart Failure” OR “Left Sided Heart Failure” OR “Chronic heart failure”)))) AND (((“Renin Angiotensin System” OR “Angiotensin II Type 1 Receptor Antagonists” OR “Type 1 Angiotensin Receptor Blockers” OR “Angiotensin receptor blocker” OR “Angiotensin 2 Type 1 Receptor Antagonists” OR “Type 1 Angiotensin Receptor Antagonists” OR “Selective Angiotensin II Receptor Antagonists” OR “Sartans” OR “Angiotensin-Converting Enzyme Inhibitors” OR “Angiotensin Converting Enzyme Inhibitors” OR “Kininase II Inhibitors” OR “Angiotensin I-Converting Enzyme Inhibitors” OR “Angiotensin I Converting Enzyme Inhibitors” OR “ACE-inhibitor” OR “ACE Inhibitors” OR “Angiotensin-Converting Enzyme Antagonists” OR “Angiotensin Converting Enzyme Antagonists” OR Aliskiren OR “rasilez” OR “Tekturna” OR “direct renin inhibitor” OR "Renin inhibitor")))) AND ((("mortality" OR "hospitalization" OR "hospitalizations" OR "ventricular ejection fractions" OR "hypertrophy" OR "hypertrophies" OR "hypotension" OR "hyperkalemia" OR "hyperpotassemia" OR "proteinuria" OR "glomerular filtration rate")))) AND ((("randomized controlled trial" OR “controlled clinical trial”)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=All years
International Clinical Trials Registry Platform (ICTRP)	heart failure AND “Angiotensin II Type 1 Receptor Blockers” OR “Angiotensin I-Converting Enzyme Inhibitors” OR aliskiren

Clinicaltrials.gov (NCT) Open Grey	“Heart failure” AND “Angiotensin II Type 1 Receptor Blockers” OR “Angiotensin I-Converting Enzyme Inhibitors” OR aliskiren
Google Scholar Filters: 1)Relevance First 100 citation AND 2)Year(2018) First 80 citation	heart failure AND "angiotensin ii type 1 receptor" OR "angiotensin Converting Enzyme Inhibitors" OR aliskiren

Supplementary Table S2. Excluded articles and reasons for exclusion (n=38).

(1) Review (n =4);

(2) Monotherapy (n = 2);

(3) Studies that has excluded HF (n =7);

(4) Intervention with spironolactone (mineralocorticoid receptor antagonist) or other medicinal or medical procedures (n = 2);

(5) Triple therapy (n=0);

(6) Insufficient data (n =23).

Reference number	Author/Year	Reason for exclusion
1.	Palevsky, P. M., et al. 2016.	3
2.	Miura M, et al. 2016.	6
3.	Damman K,et al. 2016.	6
4.	Jhund PS, et al. 2015.	6
5.	Lonn EM, et al. 2014	6
6.	Heerspink HJ, et al. 2014	3
7.	Damman K, et al. 2014	3
8.	Ohsawa M, et al. 2013	3
9.	Redon J, et al. 2012	6
10.	Parving H , et al. 2012	3
11.	Aleksova A ,et al. 2012	6
12.	Tobe SW, et al. 2011	6

13.	Solomon SD, et al. 2011	6
14.	Pitt B, et al. 2011	6
15.	Jackson CE, et al. 2011	6
16.	Cice G, et al. 2010	4
17.	Verdecchia P, et al. 2009	6
18.	Sleight P, et al. 2009	1
19.	Berns JS, et al. 2009	1
20.	Yusuf S, et al. 2008	3
21.	Weir RA, et al. 2008	6
22.	Parving HH, et al. 2008	3
23.	Kum LC, et al. 2008	6
24.	Cohn JN, et al. 2008	1
25.	Anavekar NS, et al. 2008	6
26.	Seed A, et al. 2007	6
27.	Desai AS, et al. 2007	6
28.	Yan RT,et al. 2007	6
29.	Demers C, et al. 2005	6
30.	Solomon SD,et al. 2006	6
31.	Azizi M, 2004	1
32.	Anavekar NS, et al. 2004	6
33.	Pfeffer MA, et al. 2003	6
34.	Gremmler B, et al. 2003	6
35.	Carson P, et al. 2003	6
36.	Yusuf S, et al. 2000	2
37.	Pitt B, P, et al. 2000	2
38.	Houghton AR, et al. 2000	4

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5. Lonn EM, Rambihar S, Gao P, et al. Heart rate is associated with increased risk of major cardiovascular events, cardiovascular and all-cause death in patients with stable chronic cardiovascular disease: an analysis of ONTARGET/TRANSCEND. *Clinical research in cardiology*. 2014;103(2):149-159.
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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Death						
7	randomised trials	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ HIGH
Death according to the estimated glomerular filtration rate.						
2	randomised trials	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ HIGH
Cardiovascular death or hospitalization for heart failure						
4	randomised trials	serious ^a	not serious	not serious	not serious	⊕⊕⊕○ MODERATE
Cardiovascular death or hospitalization for heart failure according to the estimated glomerular filtration rate.						
3	randomised trials	serious ^a	not serious	not serious	not serious	⊕⊕⊕○ MODERATE
Renal impairment						
5	randomised trials	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ HIGH
Renal impairment - Discontinuation of treatment						
8	randomised trials	not serious	not serious ^b	not serious	not serious	⊕⊕⊕⊕ HIGH
Hyperkalemia						
6	randomised trials	not serious	serious ^b	not serious	not serious	⊕⊕⊕○ MODERATE
Hyperkalemia - Discontinuation of treatment						

5	randomised trials	not serious	serious ^c	not serious	not serious	⊕⊕⊕○ MODERATE
Hypotension						
6	randomised trials	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ HIGH
Hypotension - Discontinuation of treatment						
7	randomised trials	not serious	not serious	not serious	not serious	⊕⊕⊕⊕ HIGH

Table S3 - Summary of the evaluation of the quality of evidence, according to GRADE (Grading of Recommendations Assessment, Development and Evaluation). a. The risk of bias in the report of high selective outcome for the Val-HeFT study. b. Meta-analysis with moderate heterogeneity $I^2 = 53\%$; c. Meta-analysis with substantial heterogeneity $I^2 = 61\%$.