

Supplementary Table 1. Factors associated with cardiovascular deaths in multivariable analysis considering RAASi prescription at baseline

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Potassium (in mmol/L) at baseline	<3 vs [4 – 5)	2.92 (0.66;12.82)	0.156
	[3 – 4) vs [4 – 5)	1.19 (0.89;1.59)	0.236
	[5 - 5.5) vs [4 – 5)	0.98 (0.71;1.34)	0.882
	≥5.5 vs [4 – 5)	1.08 (0.68;1.74)	0.735
ACEi at baseline	Yes vs No	0.64 (0.49;0.84)	0.001
ARB at baseline	Yes vs No	0.63 (0.45;0.87)	0.006
CRT-D	Yes vs No	1.42 (1.06;1.90)	0.017
MRA at baseline	Yes vs No	1.24 (0.98;1.58)	0.077
S3 gallop	Yes vs No	1.65 (1.12;2.44)	0.011
Age (in years)		1.03 (1.02;1.04)	<0.001
Aortic stenosis	Yes vs No	1.92 (1.29;2.85)	0.001
Atrial fibrillation	Yes vs No	1.35 (1.08;1.69)	0.009
BMI at baseline		0.96 (0.94;0.99)	0.002
Systolic BP (in mmHg) at baseline		0.98 (0.97;0.98)	<0.001
COPD	Yes vs No	1.28 (0.98;1.67)	0.073
Depression	Yes vs No	1.68 (1.22;2.31)	0.001
Diabetes class	Yes vs No	1.44 (1.14;1.82)	0.002
EF (%)	40-50 vs <40	0.94 (0.70;1.25)	0.651
	>50 vs <40	0.75 (0.51;1.09)	0.129
Primary Etiology	Ischemic heart disease vs Non-ischemic heart disease	1.15 (0.91;1.45)	0.249
Hepatic dysfunction	Yes vs No	1.42 (0.92;2.18)	0.110
Chronic kidney dysfunction	Yes vs No	1.82 (1.44;2.32)	<0.001
Peripheral vascular disease	Yes vs No	1.68 (1.29;2.18)	<0.001

Stroke/TIA	Yes vs No	1.36 (1.00;1.84)	0.050
Sex	Female vs Male	0.80 (0.61;1.05)	0.111
Beta blockers (Prior)	Yes vs No	0.61 (0.46;0.80)	<0.001
Mitral regurgitation	Yes vs No	1.16 (0.91;1.47)	0.232

Notes:

Number of patients in the analysis: 8173/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; HR=Hazard Ratio; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index; BP= Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; TIA= Transient Ischemic Attack; vs= versus.

Supplementary Table 2. Factors associated with cardiovascular deaths in multivariable analysis considering RAASi target doses prescription at baseline

Covariates	Multivariable		
	Comparison	HR (95% CI)	Pvalue
Potassium (in mmol/L) at baseline	<3 vs [4 – 5)	2.80 (0.63;12.39)	0.176
	[3 – 4) vs [4 – 5)	1.19 (0.88;1.61)	0.267
	[5 - 5.5) vs [4 – 5)	1.01 (0.72;1.41)	0.959
	≥5.5 vs [4 – 5)	0.97 (0.58;1.63)	0.908
Target dose ACEi	No ACE vs Inferior target dose	1.45 (1.06;1.97)	0.020
	Superior target dose vs Inferior target dose	0.75 (0.55;1.03)	0.077
Target dose ARB	No ARB vs Inferior target dose	1.59 (1.03;2.45)	0.037

	Superior target dose vs Inferior target dose	0.96 (0.57;1.62)	0.883
CRT-D	Yes vs No	1.42 (1.05;1.92)	0.025
Target dose MRA	No MRA vs Inferior target dose	1.00 (0.60;1.66)	0.995
	Superior target dose vs Inferior target dose	1.30 (0.79;2.14)	0.292
S3 gallop	Yes vs No	1.75 (1.17;2.63)	0.007
Age (in years)		1.03 (1.02;1.04)	<0.001
Aortic stenosis	Yes vs No	1.99 (1.30;3.03)	0.001
Atrial fibrillation	Yes vs No	1.30 (1.03;1.65)	0.027
BMI at baseline		0.96 (0.93;0.98)	0.001
Systolic BP (in mmHg) at baseline		0.97 (0.97;0.98)	<0.001
COPD	Yes vs No	1.19 (0.89;1.58)	0.234
Depression	Yes vs No	1.70 (1.22;2.37)	0.002
Diabetes	Yes vs No	1.50 (1.17;1.92)	0.001
EF (%)	40-50 vs <40	0.97 (0.72;1.32)	0.861
	>50 vs <40	0.79 (0.53;1.18)	0.256
Primary Etiology	Ischemic heart disease vs Non-ischemic heart disease	1.20 (0.94;1.54)	0.145
Hepatic dysfunction	Yes vs No	1.45 (0.94;2.26)	0.096
Chronic kidney dysfunction	Yes vs No	1.78 (1.38;2.29)	<0.001
Peripheral vascular disease	Yes vs No	1.66 (1.26;2.18)	<0.001
Stroke/TIA	Yes vs No	1.25 (0.90;1.74)	0.187
Sex	Female vs Male	0.71 (0.53;0.95)	0.021
Beta blockers (Prior)	Yes vs No	0.62 (0.47;0.83)	0.001
Mitral regurgitation	Yes vs No	1.08 (0.84;1.40)	0.544

Notes:

Number of patients in the analysis: 7514/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; HR=Hazard Ratio; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme

inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index; BP= Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; TIA= Transient Ischemic Attack; vs= versus.

Supplementary Table 3. Factors associated with cardiovascular deaths in multivariable analysis considering RAAsi discontinuation during one-year follow-up

Multivariable			
Covariates	Comparison	HR (95% CI)	Pvalue
Potassium (in mmol/L) at baseline	<3 vs [4 – 5)	4.32 (0.97;19.19)	0.054
	[3 – 4) vs [4 – 5)	1.04 (0.75;1.43)	0.817
	[5 - 5.5) vs [4 – 5)	1.03 (0.73;1.46)	0.852
	≥5.5 vs [4 – 5)	0.91 (0.55;1.51)	0.725
	Discontinuation vs No Discontinuation	12.17 (8.06;18.37)	<0.001
ACEi	No ACEi vs No Discontinuation	6.95 (4.51;10.72)	<0.001
	Discontinuation vs No Discontinuation	8.13 (4.35;15.22)	<0.001
ARB	No ARB vs No Discontinuation	5.44 (3.00;9.88)	<0.001
	Discontinuation vs No Discontinuation	5.44 (3.00;9.88)	<0.001
CRT-D	Yes vs No	1.43 (1.05;1.96)	0.023
MRA	Discontinuation vs No Discontinuation	6.44 (4.45;9.33)	<0.001
	No MRA vs No Discontinuation	2.51 (1.71;3.68)	<0.001
	Discontinuation vs No Discontinuation	2.51 (1.71;3.68)	<0.001
S3 gallop	Yes vs No	1.54 (1.02;2.32)	0.040
Age (in years)		1.02 (1.01;1.03)	<0.001

Aortic stenosis	Yes vs No	1.51 (0.96;2.37)	0.072
Atrial fibrillation	Yes vs No	1.41 (1.11;1.80)	0.006
BMI at baseline		0.98 (0.95;1.00)	0.100
Systolic BP (in mmHg) at baseline		0.98 (0.97;0.99)	<0.001
COPD	Yes vs No	1.21 (0.91;1.62)	0.191
Depression	Yes vs No	1.39 (0.99;1.96)	0.059
Diabetes	Yes vs No	1.32 (1.02;1.70)	0.036
EF (%)	40-50 vs <40	0.95 (0.70;1.30)	0.756
	>50 vs <40	0.68 (0.45;1.04)	0.073
Ischemic heart disease			
vs			
Primary Etiology	Non-ischemic heart disease	1.34 (1.04;1.73)	0.023
Hepatic dysfunction	Yes vs No	1.156 (0.718;1.860)	0.551
Chronic kidney dysfunction	Yes vs No	1.380 (1.062;1.793)	0.016
Peripheral vascular disease	Yes vs No	1.755 (1.327;2.322)	<0.001
Stroke/TIA	Yes vs No	1.211 (0.871;1.684)	0.256
Sex	Female vs Male	0.852 (0.634;1.145)	0.288
Beta blockers (Prior)	Yes vs No	0.622 (0.462;0.837)	0.002
Mitral regurgitation	Yes vs No	1.158 (0.891;1.506)	0.273

Notes: Number of patients in the analysis: 7413/9222. RAASi= Renin-Angiotensin-Aldosterone System inhibitors; HR=Hazard Ratio; CI= Confidence Interval; ACEi= Angiotensin Converting Enzyme inhibitor; ARB= Angiotensin Receptor Blocker; CRT-D= Cardiac Resynchronization Therapy with defibrillator; MRA= Mineralocorticoid receptor antagonists; BMI= Body Mass Index;

BP= Blood Pressure; COPD= Chronic Obstructive Pulmonary Disease; EF= Ejection Fraction; TIA= Transient Ischemic Attack; vs= versus.

Supplementary Table 4. three mediation analyses (for ACEi, or ARB, or MRA discontinuation, respectively), using multivariable* Cox models for the outcomes: all-cause death and cardiovascular death

	All-cause death				Cardiovascular death			
	Type 3 tests	Parameter estimate			Type 3	Parameter estimate		
	Potassium level (in mmol/L) at baseline (natural indirect effect via drug discontinuation mediation)	Potassium level (in mmol/L) at baseline (natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via drug discontinuation mediation)	Potassium level (in mmol/L) at baseline (natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via drug discontinuation mediation)	Potassium level (in mmol/L) at baseline (natural direct effect	Potassium level (in mmol/L) at baseline (natural indirect effect via drug discontinuation mediation)	
Models considering ACEI discontinuation	P<0.001	[5; 5.5) vs. [4; 5): HR (CI) 1.03 [0.92;	[5; 5.5) vs. [4; 5): 1.03 [0.91; 1.16] P=0.658	<0.044	0.009	[5; 5.5) vs. [4; 5): 0.89 [0.76; 1.05] P=	[5; 5.5) vs. [4; 5): 1.03 [0.88; 1.21] P=0.703	

			1.15]				0.171	
			P=					
			0.636					
			>5.5	>5.5 vs. [4;			>5.5	>5.5 vs. [4;
			vs. [4;	5)			vs. [4;	5)
			5)	1.12 [1.00;			5)	1.12 [0.96;
			1.20	1.26]			0.97	1.32]
			[0.99;	P= 0.059			[0.74;	P= 0.151
			1.44]				1.27]	
			P=				P=0.81	
			0.057				4	
Models	P<0.00	P=0.480	[5; 5.5)	[5; 5.5) vs.	<0.001	0.734	[5; 5.5)	[5; 5.5) vs.
considering	1		vs. [4;	[4; 5):			vs. [4;	[4; 5):
ARB			5):	1.00 [0.90;			5):	1.00[0.86;
discontinua			1.08	1.12]			1.04	1.17]
tion			[0.98;	P=0.953			[0.90;	P=0.974
			1.20]				1.20]	
			P=				P=0.62	
			0.136				3	
			>5.5	>5.5 vs. [4;			>5.5	>5.5 vs. [4;
			vs. [4;	5)			vs. [4;	5)
			5)	1.09 [0.97;			5)	1.09 [0.93;
			1.36	1.22]			1.03	1.27]
			[1.15;	P= 0.136			[0.79;	P= 0.285
			1.60]				1.34]	
			P<0.00				P=0.82	
			1				7	
Models	P<0.00	P<0.001	[5; 5.5)	[5; 5.5) vs.	0.008	<0.001	[5; 5.5)	[5; 5.5) vs.
considering	1		vs. [4;	[4; 5):			vs. [4;	[4; 5):
MRA			5):	1.03 [0.92;			5):	1.03 [0.88;
discontinua			1.09	1.16]			0.99	1.21]
tion			[0.98;	P=0.609			[0.85;	P=0.689
			1.22]				1.15]	
			P=0.10				P=0.89	
			9				3	

>5.5	>5.5 vs. [4;	>5.5	>5.5 vs. [4;
vs. [4;	5)	vs. [4;	5)
5)	1.18 [1.04;	5)	1.15 [0.98;
1.21	1.32]	0.85	1.36]
[1.03;	P= 0.007	[0.66;	P= 0.080
1.43]		1.10]	
P=		P=	
0.024		0.213	

*Age, aortic stenosis, systolic blood pressure at baseline, ejection fraction, primary etiology, chronic kidney dysfunction, peripheral vascular disease, prior beta blockers as covariates in each of the multivariable models