Supplementary data materials

Temporal trends in mortality and readmission after acute heart failure: A systematic review and meta-regression in the past four decades

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Please open the Table S1.csv in "data" directory on https://osf.io/cxv5k/?view_only=770ba512f61a4153aec88e35b40300f8 Table S2: Baseline clinical characteristics in acute heart failure studies according to four periods of times. Proportions for each study period were calculated as back-transformed adjusted means from the model.

		Total		1981-2000		2001-2005	:	2006-2010		2011-2015	
Reported characteristics	n	% (95%CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	p-value
Demography	-										
Age ≥ 74 years old	300	50 (44-56)	64	64 (51-76)	62	47 (34-60)	102	50 (40-60)	72	40 (29-53)	0.0451
Male ratio	315	53 (51-55)	68	50 (45-54)	64	54 (50-58)	107	54 (51-58)	76	54 (49-58)	0.3599
Medical history											
Heart failure	114	50 (47-53)	30	39 (33-45)	22	56 (47-63)	35	52 (46-59)	27	60 (52-67)	<0.0001
Coronary artery disease	173	44 (41-46)	41	38 (33-44)	38	48 (42-54)	58	44 (39-49)	36	45 (39-52)	0.0866
Hypertension	229	61 (59-63)	51	41 (37-46)	49	62 (57-67)	78	69 (65-73)	51	71 (65-76)	<0.0001
Atrial fibrillation	174	35 (32-37)	31	27 (22-33)	35	33 (27-39)	64	39 (35-44)	44	35 (29-40)	0.0158
Diabetes mellitus	254	36 (34-38)	50	29 (25-34)	53	37 (32-41)	88	37 (33-41)	63	40 (35-45)	0.0122
Chronic respiratory disease	157	25 (23-27)	30	26 (21-31)	34	31 (26-36)	53	20 (16-24)	40	24 (19-29)	0.0107
Treatment at admission											
ACEi and/or ARB	117	56 (53-60)	16	55 (45-63)	27	65 (58-72)	53	55 (50-60)	21	49 (41-58)	0.0396
Loop diuretics	94	71 (67-74)	11	73 (62-81)	24	72 (64-78)	43	71 (65-76)	16	66 (56-75)	0.7573
Beta-blockers	117	52 (49-56)	13	26 (19-36)	29	55 (48-62)	54	58 (53-63)	21	53 (44-61)	<0.0001
Digoxin	66	25 (21-29)	10	44 (34-56)	17	27 (20-36)	30	18 (14-24)	9	18 (10-30)	0.0001
Clinical characteristics at admission											
Systolic blood pressure ≥ 135 mmHg	145	50 (42-59)	13	54 (25-81)	30	60 (41-77)	53	55 (40-68)	49	39 (25-54)	0.2395
Heart rate ≥ 87 bpm	117	50 (40-59)	11	64 (31-89)	23	48 (27-69)	43	51 (35-67)	40	45 (29-62)	0.7347
Ejection fraction < 40%	110	44 (34-53)	11	27 (6-61)	23	39 (20-61)	39	46 (30-63)	37	49 (32-66)	0.6321

Table S3: Summary table for the differences among continents in the temporal trend for each outcome. Oddsratio (CI) using a 10-year increment and p-value for each continent, as well as the p-value of the interaction between year of recruitment and continent are presented.

Variable	Continent	Number of studies	Odds Ratio (Confidence interval)	р	p inter
30-day death					0.2705
-	Asia	23	0.56 (0.3-1.05)	0.0706	
	Europe	63	0.67 (0.52-0.86)	0.0015	
	North-America	48	0.9 (0.64-1.28)	0.5637	
One-year death					0.7764
-	Asia	29	0.99 (0.72-1.36)	0.9553	
	Europe	75	0.88 (0.74-1.06)	0.1766	
	North-America	82	0.87 (0.74-1.03)	0.1153	
30-day readmission			· · ·		0.418
•	Asia	16	0.92 (0.53-1.58)	0.762	
	Europe	35	1.17 (0.93-1.47)	0.1798	
	North-America	49	1.35 (1.02-1.78)	0.0375	
One-year readmission			· · ·		0.0774
	Asia	12	1.17 (0.44-3.08)	0.7501	
	Europe	20	0.4 (0.2-0.78)	0.0075	
	North-America	23	0.94 (0.53-1.68)	0.8441	

Table S4: Summary table for the effect of oral cardiovascular medications at admission on 30-day death. Oddsratio (CI), calculated using a 10% increment, and p-value for the effects of treatment at admission on one-year all-cause death. RAASi: renin-angiotensin-aldosterone system inhibitors

	One-year de	ath
Treatment	Odds Ratio (Confidence interval)	p-value
RAASi	0.8 (0.7-0.91)	0.001
Diuretics	1 (0.86-1.16)	0.995
Beta-blockers	0.9 (0.81-0.99)	0.033
Digoxin	1.03 (0.77-1.37)	0.888

For all analyses, year of recruitment was added as a moderator.

Table S5: Combined effect of RAASi and BBs at admission on 30-day and one-year all-cause death. For these analyses, four-class variable describing the combination of high and low (i.e. above and below the median, respectively) percentages of prescription of RAASi and BBs was created. Odds-ratios and 95% CI are represented. P-values for the comparison between each class and the reference class (low RAASi & low BBs) and sample sizes are given, as well as the overall p-value for the effect of the four-class variable.

		30-day death Overall p= 0.037			One-year death Overall p= 0.047	
Group	Ν	OR (CI)	P-value	Ν	OR (CI)	P-value
low RAASi & low BBs	14	1 (1 - 1)	NA	23	1 (1 - 1)	NA
high RAASi & low BBs	13	0.59 (0.35 - 1)	0.049	11	1.16 (0.79 - 1.68)	0.451
low RAASi & high BBs	13	0.59 (0.35 - 1.01)	0.054	11	0.81 (0.55 - 1.18)	0.268
high RAASi & high BBs	13	0.46 (0.27 - 0.8)	0.006	23	0.72 (0.53 - 0.98)	0.036

Table S6: Summary table for the effect of oral cardiovascular therapies at admission on 30-day and one-year readmission. Odds-ratio (CI), calculated using a 10% increment, and p-value for the effects of treatment at admission on 30-day and 1-year all-cause readmission. RAASi: renin-angiotensin-aldosterone system inhibitors

-	30-day readmis	sion	One-year readmiss	ion
Treatment	OR (CI)	P-value	OR (CI)	P-value
RAASi	0.92 (0.63-1.35)	0.56	1.03 (0.87-1.22)	0.69
Diuretics	0.98 (0.63-1.51)	0.877	0.99 (0.78-1.27)	0.961
Beta-blockers	0.91 (0.66-1.26)	0.45	0.97 (0.81-1.16)	0.71
Digoxin	0.96 (0.18-5.25)	0.937	1.15 (0.81-1.64)	0.369

For all analyses, year of recruitment was included as a moderator.

Table S7: Subgroup analyses for 30-day all-cause death. Odds-ratios (CI) and p-values for the effects of year of recruitment (10-year increment) on 30-day all-cause death in subgroups from clinically relevant variables accounting for severity of AHF. SBP: systolic blood pressure, HR: heart rate, EF: ejection fraction

Variable	Group	Number of studies	Odds Ratio (Confidence interval)	p-value	p-value interaction
Age			-		0.589
	Age < 74 years old	62	0.92 (0.65-1.29)	0.6138	
	Age ≥ 74 years old	73	0.82 (0.65-1.03)	0.0876	
Male ratio					0.2526
	Male ratio < 52%	76	0.72 (0.56-0.92)	0.0092	
	Male ratio ≥ 52%	66	0.92 (0.66-1.28)	0.6099	
Systolic blood pressure					0.1506
	SBP < 135 mmHg	29	1.16 (0.66-2.04)	0.6092	
	SBP ≥ 135 mmHg	37	0.68 (0.41-1.11)	0.1199	
Heart rate					0.1901
	HR < 87 bpm	27	1.33 (0.7-2.53)	0.3755	
	HR ≥ 87 bpm	29	0.81 (0.52-1.26)	0.3418	
Ejection fraction					0.416
	EF < 40%	21	0.72 (0.34-1.5)	0.3752	
	EF ≥ 40%	20	1.12 (0.49-2.57)	0.7877	

Table S8: Subgroup analyses for one-year all-cause death. Odds-ratios (CI) and p-values for the effects of year of recruitment (10-year increment) on one-year all-cause death in subgroups from clinically relevant variables accounting for severity of AHF. SBP: systolic blood pressure, HR: heart rate, EF: ejection fraction

Variable	Group	Number of studies	Odds Ratio (Confidence interval)	p-value	p-value interaction
Age		-			0.8849
	Age < 74 years old	87	0.93 (0.78-1.11)	0.411	
	Age ≥ 74 years old	94	0.94 (0.82-1.09)	0.4168	
Male ratio					0.5731
	Male ratio < 52%	93	0.91 (0.77-1.06)	0.2285	
	Male ratio ≥ 52%	95	0.85 (0.72-1)	0.0506	
Systolic blood pressure					0.2232
	SBP < 135 mmHg	46	1 (0.73-1.37)	0.9967	
	SBP ≥ 135 mmHg	42	0.73 (0.49-1.1)	0.1284	
Heart rate					0.8904
	HR < 87 bpm	29	0.84 (0.57-1.25)	0.3935	
	HR ≥ 87 bpm	38	0.88 (0.61-1.26)	0.4758	
Ejection fraction					0.2509
	EF < 40%	41	0.81 (0.58-1.13)	0.2173	
	EF ≥ 40%	32	1.13 (0.7-1.8)	0.6192	

Table S9: Subgroup analyses for 30-day all-cause readmission. Odds-ratios (CI) and p-values for the effects of year of recruitment (10-year increment) on 30-day all-cause readmission in subgroups from clinically relevant variables accounting for severity of AHF. SBP: systolic blood pressure, HR: heart rate, EF: ejection fraction

Variable	Group	Number of studies	Odds Ratio (Confidence interval)	p-value	p-value interaction
Age				-	0.3613
	Age < 74 years old	41	1.09 (0.82-1.43)	0.5578	
	Age ≥ 74 years old	54	1.28 (1.02-1.59)	0.0308	
Male ratio					0.7202
	Male ratio < 52%	59	1.17 (0.93-1.47)	0.1745	
	Male ratio ≥ 52%	41	1.25 (0.93-1.67)	0.1362	
Systolic blood pressure					0.2009
	SBP < 135 mmHg	14	1.13 (0.58-2.2)	0.7237	
	SBP ≥ 135 mmHg	17	0.69 (0.44-1.07)	0.0932	
Heart rate					0.0595
	HR < 87 bpm	19	1.18 (0.66-2.1)	0.5788	
	HR ≥ 87 bpm	7	0.57 (0.32-1.01)	0.0536	
Ejection fraction					0.3368
	EF < 40%	13	1.09 (0.76-1.55)	0.6448	
	EF ≥ 40%	13	0.76 (0.38-1.54)	0.4523	

Table S10: Subgroup analyses for all-cause one-year readmission. Odds-ratios (CI) and p-values for the effects of year of recruitment (10-year increment) on one-year all-cause readmission in subgroups from clinically relevant variables accounting for severity of AHF. SBP: systolic blood pressure, HR: heart rate, EF: ejection fraction

Variable	Group	Number of studies	Odds Ratio (Confidence interval)	р	p interaction
Age	-	-	-	-	0.1962
	Age < 74 years old	24	0.55 (0.33-0.91)	0.0212	
	Age ≥ 74 years old	27	0.88 (0.52-1.51)	0.6434	
Male ratio					0.9801
	Male ratio < 52%	29	0.76 (0.43-1.34)	0.3479	
	Male ratio ≥ 52%	26	0.77 (0.45-1.33)	0.349	
Systolic blood pressure					0.9156
	SBP < 135 mmHg	14	0.9 (0.43-1.91)	0.7921	
	SBP ≥ 135 mmHg	7	0.97 (0.29-3.32)	0.9652	
Heart rate					0.8495
	HR < 87 bpm	9	0.86 (0.4-1.87)	0.7035	
	HR ≥ 87 bpm	7	0.98 (0.3-3.16)	0.9686	
Ejection fraction					0.7554
	EF < 40%	9	0.7 (0.41-1.2)	0.1963	
	EF ≥ 40%	5	0.83 (0.27-2.49)	0.7354	

Figures

Figure S1: Flow chart * In studies that included independent cohorts, each cohort was presented separately



Figure S2: Temporal trends in reported clinical characteristics in AHF studies. Proportions at the beginning and at the end of the study period were calculated as back-transformed adjusted means from the model.





Figure S4: Sensitivity analysis according to study characteristics.

The effect of year of recruitment found in the global population has been compared with the effect in subgroups (using a model with interaction between group variable and year of recruitment): survey vs. trial, mono- vs. multicentric, outcomes assessed from discharge vs. from admission, without Medicare studies. The effect of year of recruitment will be expressed as an odds ratio for a 10-year increment with Cl. P-values are for the interaction between year of recruitment and the variable tested. In all models heterogeneity statistic l² was > 99%.



Figure S5: Assessment of study quality.

