

SUPPLEMENTAL MATERIAL

Table S1. List of covariates adjusted for in calculating hazard ratios (adjusted hazard ratios).

Source (First Author [PMID] ^{Ref.})*	Covariates
Boxer [20887617] ¹	Age, high-sensitivity C-reactive protein, interleukin-6
Cacciatore [16316247] ²	Age, sex, NYHA class, comorbidity, systolic and diastolic blood pressure, HF etiology (i.e. ischemic vs. others), use of diuretics, ACEI, digoxin and nitrates
Ferguson [27036952] ³	N/A (only unadjusted hazard ratio available)
Gastelurrutia [24820761] ⁴	Age, sex, HF duration, HF etiology, HF hospitalization, LVEF, NYHA class, number of comorbidities, history of implantable cardioverter defibrillator, use of beta-blockers, ACEI/ARB, mineralocorticoid receptor antagonist, loop diuretics and statin
Madan [26883168] ⁵	Age, sex, diabetes mellitus, Charlson comorbidity index
McNallan [23956958] ⁶	Age, sex, LVEF, incident and prevalent HF, estimated glomerular filtration rate, history of chronic obstructive pulmonary disease, diabetes mellitus and anemia
McNallan [24093859] ⁷	Age, sex, LVEF
Rodríguez-Pascual [28215465] ⁸	Age, sex, Charlson comorbidity index, LVEF \leq 45%, previous HF-related hospitalization other than the index admission, use of ACEI/ARB and beta-blocker
Vidán [27072307] ⁹	Age, sex, acute and chronic comorbidities, LVEF, NYHA class, N-terminal pro B-type natriuretic peptide level

ACEI, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; LVEF, left ventricular ejection fraction; N/A, not applicable; NYHA, New York Heart Association.

*See also References (Supplemental Material).

Table S2. Actual numbers of deaths and/or hospitalization episodes in chronic heart failure patients with and without frailty.

Source (First Author [PMID] ^{Ref.})*	Sample size, <i>n</i>	Follow-up duration, y	Mortality, % (<i>n</i>)			Hospitalization, % (<i>n</i>)		
			Total	Frail	Non-frail	Total	Frail	Non-frail
Boxer [20887617] ¹	59	4	33.9 (20/59)	60.0 (9/15)	25.0 (11/44)	N/A	N/A	N/A
Cacciatore [16316247] ²	120	12	64.2 (77/120)	89.6 (16/18)	59.8 (61/102)	N/A	N/A	N/A
Ferguson [27036952] ³	137	1	28.6 (24/84)	38.5 (20/52)	12.5 (4/32)	75.0 (63/84)	82.7 (43/52)	62.5 (20/32)
Gastelurrutia [24820761] ⁴	1314	3.6	47.6 (626/1314)	N/A	N/A	N/A	N/A	N/A
Madan [26883168] ⁵	40	1.24	25.5 (10/40)	30.8 (8/26)	14.3 (2/14)	N/A	N/A	N/A
McNallan [23956958] ⁶	448	2.0	N/A	N/A	N/A	N/A	N/A	N/A
McNallan [24093859] ⁷	223	2.4	28.3 (63/223)	N/A	N/A	N/A	N/A	N/A
Rodriguez-Pascual [28215465] ⁸	497	1	19.9 (99/497)	N/A	N/A	39.4 (165/419)	N/A	N/A
Vidán [27072307] ⁹	416	1	22.9 (93/406)	25.7 (79/307)	11.1 (11/99)	61.1 (248/406)	63.5 (195/307)	53.5 (53/99)

N/A, not applicable. PMID, PubMed identifier. Ref., reference number

*See also References (Supplemental Material)

Table S3. Quality assessment of studies using the Newcastle-Ottawa Scale*.

Source (First Author [PMID] ^{Ref.}) [‡]	Year	Total Score	Selection					Comparability		Outcome			
			Score Subtotal	Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure to implants	Demonstrate that outcome of interest was not present at start of study	Score Subtotal	Comparability of cohorts on the basis of design or analysis (variables)	Score Subtotal	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of follow-up of cohorts
Boxer [20887617] ¹	2010	8	3	0	1	1	1	2	Frailty (age, interleukin-6, high-sensitivity C-reactive protein)	3	1	1	1
Cacciatore [16316247] ²	2005	9	4	1	1	1	1	2	Frailty (age, sex, NYHA, blood pressure, comorbidity, HF etiology, use of ACEI, digoxin, diuretics and/or nitrates)	3	1	1	1
Ferguson [27036952] ³	2017	7	4	1	1	1	1	0	Not applicable	3	1	1	1
Gastelurrutia [24820761] ⁴	2014	9	4	1	1	1	1	2	Fragility [†] (age, sex)	3	1	1	1
Madan [26883168] ⁵	2016	8	3	1	1	1	0	2	Frailty (age, sex, DM, Charlson comorbidity index)	3	1	1	1
McNallan [23956958] ⁶	2013	8	3	1	1	1	0	2	Frailty (age, sex, LVEF, incident HF and prevalence of HF, estimated glomerular filtration rate, chronic obstructive pulmonary disease, DM, anemia)	3	1	1	1
McNallan	2013	9	4	1	1	1	1	2	Frailty (age, sex, LVEF)	3	1	1	1

[24093859] ⁷													
Rodríguez-Pascual [28215465] ⁸	2017	9	4	1	1	1	1	2	Frailty (age, sex, Charlson index, LVEF ≤45%, previous HF-related hospitalization other than the index admission, use of ACEI or angiotensin receptor blocker and β-blocker)	3	1	1	1
Vidán [27072307] ⁹	2016	9	4	1	1	1	1	2	Frailty (age, sex, acute and chronic comorbidities, LVEF, NYHA, NT-proBNP levels)	3	1	1	1

ACEI, angiotensin converting enzyme inhibitor; DM, diabetes mellitus; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain (B-type) natriuretic peptide; NYHA, New York Heart Association functional class.

*Newcastle-Ottawa Scale categorizes the quality of a study based on summed total points: low, 0 to 3 points; intermediate, 4 to 6 points; high, 7 to 9 points.

†Fragility is synonymous with frailty in this study.

*See also References (Supplemental Material).

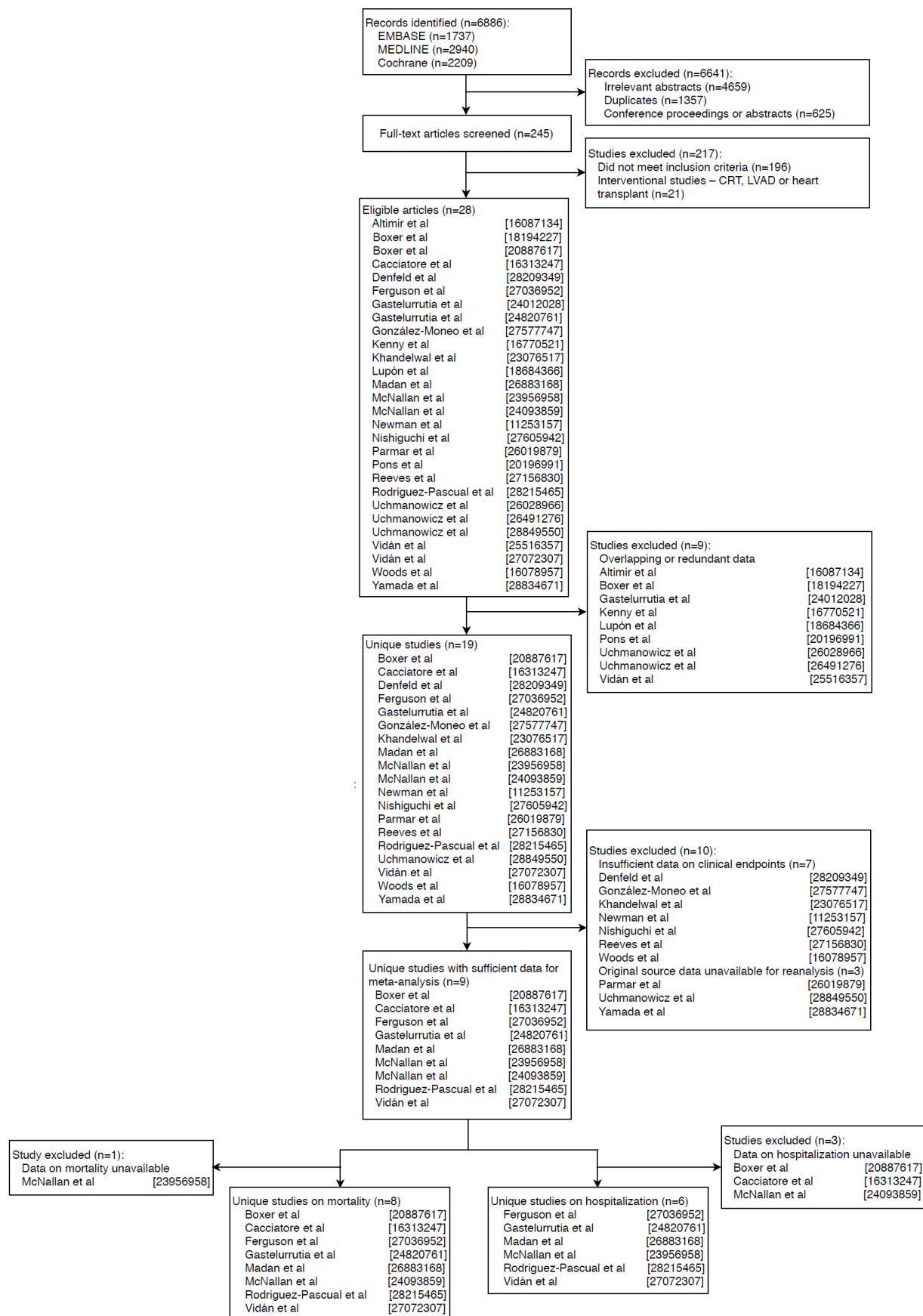


Figure S1. Detailed CONSORT-style flow diagram. PubMed unique identifiers shown in squared brackets.

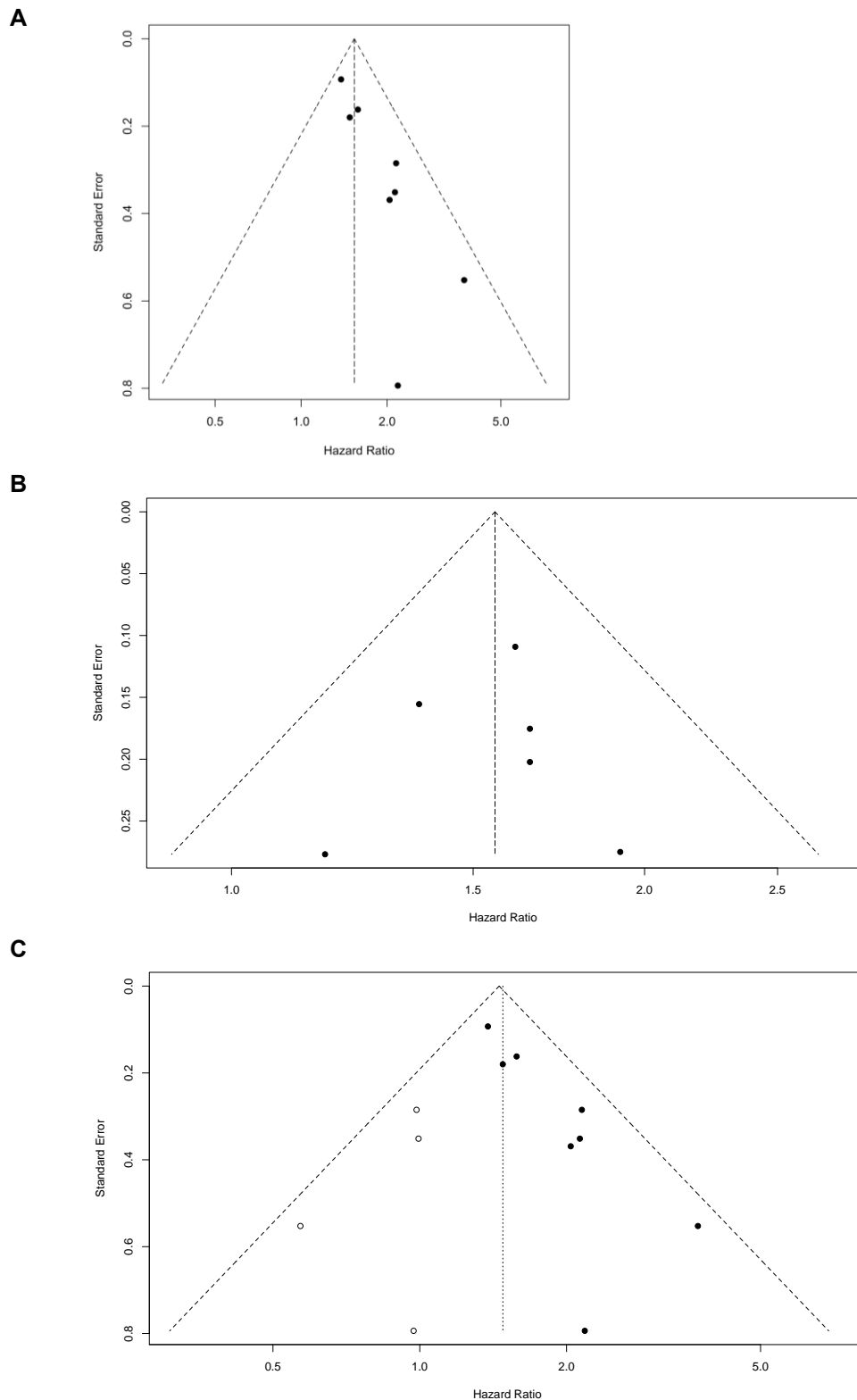


Figure S2. Funnel plots assessing for publication bias in the meta-analyses of frailty on (A) all-cause mortality and (B) incident hospitalization in patients with chronic heart failure. (C) Data on all-cause mortality were further subjected to the Duval-Tweedie's trim and fill test, demonstrating virtually unchanged effect size estimates and statistical significance (adjusted hazard ratio, 1.48; 95% confidence interval 1.25–1.75, $P < 0.001$).

Supplemental References:

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3. Ferguson C, Inglis SC, Newton PJ, Middleton S, Macdonald PS, Davidson PM. Multi-morbidity, frailty and self-care: important considerations in treatment with anticoagulation drugs. Outcomes of the AFASTER study. *Eur J Cardiovasc Nurs.* 2017; 16:113-124.
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5. Madan SA, Fida N, Barman P, Sims D, Shin J, Verghese J, Pina I, Jorde U, Patel SR. Frailty Assessment in Advanced Heart Failure. *J Card Fail.* 2016; 22:840-844.
6. McNallan SM, Singh M, Chamberlain AM, Kane RL, Dunlay SM, Redfield MM, Weston SA, Roger VL. Frailty and healthcare utilization among patients with heart failure in the community. *JACC Heart Fail.* 2013; 1:135-141.
7. McNallan SM, Chamberlain AM, Gerber Y, Singh M, Kane RL, Weston SA, Dunlay SM, Jiang R, Roger VL. Measuring frailty in heart failure: a community perspective. *Am Heart J.* 2013; 166:768-774.
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