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ORIGINAL RESEARCH ARTICLE

Prognostic value of reverse remodelling criteria in heart failure with reduced or mid-range ejection fraction

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Abstract

Aims Reverse remodelling (RR) is the recovery from left ventricular (LV) dilatation and dysfunction. Many arbitrary criteria for RR have been proposed. We searched the criteria with the strongest prognostic yield for the hard endpoint of cardiovascular death.

Methods and results We performed a systematic literature search of diagnostic criteria for RR. We evaluated their prognostic significance in a cohort of 927 patients with LV ejection fraction (LVEF) $<$ 50% undergoing two echocardiograms within 12 ± 2 months. These patients were followed for a median of 2.8 years (interquartile interval 1.3–4.9) after the second echocardiogram, recording 123 cardiovascular deaths. Two prognostic models were defined. Model 1 included age, LVEF, N-terminal pro-B-type natriuretic peptide, ischaemic aetiology, cardiac resynchronization therapy, estimated glomerular filtration rate, New York Heart Association, and LV end-systolic volume (LVESV) index, and Model 2 the validated Cardiac and Comorbid Conditions Heart Failure score. We identified 25 criteria for RR, the most used being LVESV reduction $\geq$15% (12 studies out of 42). In the whole cohort, two criteria proved particularly effective in risk reclassification over Model 1 and Model 2. These criteria were (i) LVEF increase $>$10 U and (ii) LVEF increase $\geq$1 category [severe (LVEF $\leq$ 30%), moderate (LVEF 31–40%), mild LV dysfunction (LVEF 41–55%), and normal LV function (LVEF $\geq$ 56%)]. The same two criteria yielded independent prognostic significance and improved risk reclassification even in patients with more severe systolic dysfunction, namely, those with LVEF $<$ 40% or LVEF $\leq$ 35%. Furthermore, LVEF increase $>$10 U and LVEF increase $\geq$1 category displayed a greater prognostic value than LVESV reduction $\geq$15%, both in the whole cohort and in the subgroups with LVEF $<$ 40% or LVEF $\leq$ 35%. For example, LVEF increase $>$10 U independently predicted cardiovascular death over Model 1 and LVESV reduction $\geq$15% (hazard ratio 0.40, 95% confidence interval 0.18–0.90, P = 0.026), while LVESV reduction $\geq$15% did not independently predict cardiovascular death (P = 0.112).

Conclusions Left ventricular ejection fraction increase $>$10 U and LVEF increase $\geq$1 category are stronger predictors of cardiovascular death than the most commonly used criterion for RR, namely, LVESV reduction $\geq$15%.

Keywords Reverse remodelling; Criteria; Prognosis; Heart failure

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Introduction

Heart failure (HF) is a progressive disease, as reflected by its clinical and pathophysiological classification into four stages, from Stage A (patients at risk for HF) to Stage D (patients with advanced, refractory HF). Similarly, left ventricular (LV) geometry and function change over time as the result of the combined effects of pressure or volume overload, myocardial insults, cardiac and systemic responses to injury, and guideline-directed drug and device therapy for HF.[1] In HF with reduced ejection fraction (HFrEF), four trajectories may be observed: a deterioration of LV geometry and function [adverse remodelling (AR)], a substantial stability over time, a trend towards recovery [reverse remodelling (RR)], or even a normalization (remission).[2] While AR has been associated with worsening clinical status and outcome, RR or remission predicts better prognosis, unless HF medications are withdrawn.[3] Nonetheless, none of these processes has a standardized definition, including the most intensively studied phenomenon, which is RR.[1] Indeed, studies have considered changes in LV end-systolic volume (LVESV), end-diastolic diameter or volume, or ejection fraction (either alone or in combination), and different, arbitrarily defined cut-offs.[1] The absence of a standardized definition makes estimates of RR incidence difficult. Indeed, existing studies suggest that the RR incidence can range from 29% to 60% across cohorts with different characteristics and also the widely heterogeneous criteria used to define RR.[1] The plethora of RR criteria might help explain the uncertainties regarding the frequency of RR, its predictors, and its impact on disease evolution.[1] The definition of RR should then be standardized, and RR could be preferentially defined through criteria that identify patients with a lower risk of adverse outcome, for example, cardiovascular mortality.

In this study, we performed a systematic literature search for diagnostic criteria of RR, and we assessed how different definitions impacted on the prevalence of RR in a same cohort. We then searched which criteria of RR were most predictive of cardiovascular death over baseline variables or a prognostic score for chronic HF [the Cardiac and Comorbid Conditions Heart Failure (3C-HF) score].[4]

Methods

Study selection and data extraction

In October 2020, two investigators (AA and GG) performed a systematic search of PubMed and Embase to retrieve published studies evaluating RR in patients with HF and LV ejection fraction (LVEF) $<$ 50%, regardless of the imaging technique [transthoracic echocardiography (TTE), cardiac magnetic resonance, or nuclear imaging]. The search strategy is reported in Supporting Information, *Table S1*. Reference lists of selected articles were screened for other relevant articles. Only articles in English were selected. The process of study selection is reported in *Figure 1*. From the 42 studies selected, we extracted the diagnostic criteria for RR and the LVEF inclusion criterion (Supporting Information, *Table S2*).

Patient cohort to assess the prevalence and prognostic value of reverse remodelling criteria

The prevalence and prognostic value of RR were evaluated in a cohort of 927 stable outpatients with previously diagnosed chronic systolic HF (LVEF $<$ 50%, determined by TTE), evaluated at the Fondazione Toscana Gabriele Monasterio, Pisa, Italy, from 1999 to 2015, and undergoing two TTE examinations within 12 ± 2 months. Patients had received guideline-recommended therapy for HF and had undergone clinical follow-up examinations in a dedicated outpatient clinic every 3 to 6 months, as clinically indicated. Further details about this cohort are provided in a dedicated publication.[5] The endpoint was cardiovascular death.

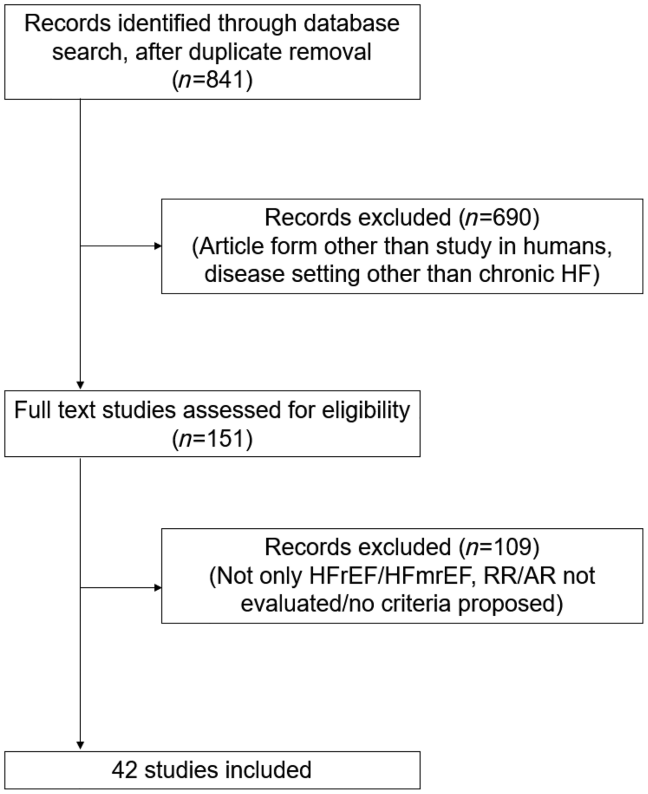
Cardiac and Comorbid Conditions Heart Failure score

The 3C-HF score included the following variables: age, New York Heart Association class III–IV vs. I–II, LVEF $<$ 20% vs. $\geq$20%, no renin–angiotensin–aldosterone system inhibitors, severe valve heart disease, atrial fibrillation, no beta-blockers, chronic kidney dysfunction (creatinine $>$ 2 mg/dL), diabetes with target organ damage (retinopathy, neuropathy, nephropathy, coronary artery disease, and peripheral artery disease), anaemia (haemoglobin $<$ 11 g/dL), and hypertension.[4,6] Score values were calculated at the time of first TTE examination; therapies prescribed after the same visit were considered.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (Version 22, 2013) and the R software (Version 3.4.4). Normal distribution was assessed through the Shapiro–Wilk test; all variables had non-normal distribution and were then expressed as median and interquartile interval. Missing data were discarded and not imputed. We evaluated the prevalence of RR in our cohort using the different criteria for RR. The prognostic value of RR criteria was evaluated through log-rank analysis on Kaplan–Meier survival curves and univariable and multivariate Cox regression analysis. Model 1 included all baseline variables with $P < 0.001$ at univariable Cox regression analysis: age, LVEF, N-terminal pro-B-type natriuretic

Figure 1 Flowchart of study selection. AR, adverse remodelling; HF, heart failure; HFmrEF, HF with mid-range ejection fraction; HFrEF, HF with reduced ejection fraction; RR, reverse remodelling.



peptide, ischaemic aetiology, cardiac resynchronization therapy, estimated glomerular filtration rate, New York Heart Association class III–IV, and LVESV index. Model 2 corresponded to the 3C-HF score. The Fine–Gray model was used to account for mutually exclusive endpoints (non-cardiovascular death vs. cardiovascular death). Multicollinearity was searched by calculating the variance inflation factor, with a conservative threshold of 3. The integrated discrimination improvement (IDI) and continuous net reclassification index (NRI) were calculated as metrics of risk reclassification. Two-tailed P values < 0.05 were deemed statistically significant.

Results

Diagnostic criteria for reverse remodelling from the literature

Forty-two studies fulfilled the search criteria (Supporting Information, *Table S2*).[5,7–47] Two of them evaluated exclusively AR,[46,47] and two other studies assessed AR together with RR.[8,9] Because of the limited number of these studies and the heterogeneous criteria for AR, we focused on diagnostic criteria for RR. Twenty-five criteria were identified. The most common definition of RR was an LVESV reduction ≥15% (12 studies), followed by an LVESV reduction ≥30% (three studies). All other criteria were considered in two studies at most (Supporting Information, *Table S2*).

Patient characteristics and outcome in our cohort

Our cohort included 927 patients [median age 70 years (interquartile interval 61–77), 73% men, ischaemic aetiology in 52%, baseline LVEF 35% (30–43%), N-terminal pro-B-type natriuretic peptide 1658 ng/L (577–4634)]. When stratifying patients according to the date of baseline evaluation, 16% were studied from 1999 to 2005, 44% from 2006 to 2010, and 40% from 2011 to 2015. Two-thirds of patients (66%) had HFrEF at baseline, and 57% had an LVEF ≤ 35%. The 3C-HF could be calculated in 485 patients (52%); the comparison with the other patients is provided in Supporting Information, *Table S3*. Median score value was −2.92 (−3.75 to −1.81). The characteristics of patients with baseline LVEF < 40% or ≤35% are provided in *Table 1*.

Table 1 Population characteristics

	LVEF < 50% *n* = 927		LVEF < 40% *n* = 610 (66%)	LVEF ≤ 35% *n* = 530 (57%)
	n of missing variables (0%)			
Age (years)	70 (61–77)	0 (0%)	70 (61–77)	69 (61–76)
Men, *n* (%)	677 (73)	0 (0%)	457 (75)	37 (75)
Ischaemic aetiology, *n* (%)	486 (52)	0 (0%)	322 (53)	275 (52)
HF duration (years)	2 (0–7)	0 (0%)	3 (0–8)	3 (0–8)
eGFR (mL/min/1.73 m^2)	60 (48–74)	6 (0%)	65 (51–80)	65 (41–80)
NT-proBNP (ng/L)	1658 (577–4634)	4 (0%)	1807 (806–4377)	1845 (855–4757)
NYHA III–IV, *n* (%)	230 (25)	0 (0%)	184 (30)	172 (33)
LBBB, *n* (%)	158 (17)	3 (0%)	137 (23)	127 (24)
Anaemia, *n* (%)	293 (36)	77 (4%)	195/543 (36)	168/478 (35)
Hypertension, *n* (%)	478 (58)	107 (12%)	297/541 (55)	254/463 (55)
Diabetes with organ damage, *n* (%)	195 (27)	204 (22%)	115/427 (27)	102/365 (28)
Atrial fibrillation, *n* (%)	204 (22)	0 (0%)	132 (22)	113 (21)
Baseline TTE				
LVEF (%)	35 (30–43)	0 (0%)	30 (25–35)	28 (24–32)
LVESVi (mL/m^2)	60 (46–81)	0 (0%)	71 (58–92)	75 (61–95)
LVEDVi (mL/m^2)	89 (70–108)	0 (0%)	101 (85–123)	105 (88–128)
LVMI (g/m^2)	131 (113–158)	0 (0%)	138 (119–164)	140 (120–166)
Severe valve disease, *n* (%)	82 (12)	257 (28%)	63/414 (15)	57/357 (16)
3C-HF score	−2.92 (−3.75 to −1.81)	440 (48%)	−2.75 (−3.61 to −1.57)	−2.70 (−3.54 to −1.55)
Therapy after baseline examination				
Beta-blockers, *n* (%)	853 (92)	1 (0%)	573 (94)	496 (94)
ACEi/ARB, *n* (%)	814 (88)	1 (0%)	549 (90)	477 (90)
MRA, *n* (%)	711 (77)	1 (0%)	491 (81)	428 (81)
Furosemide, *n* (%)	711 (77)	0 (0%)	509 (83)	449 (85)
CRT, *n* (%)	315 (34)	0 (0%)	182 (30)	163 (31)

3C-HF, Cardiac and Comorbid Conditions Heart Failure; ACEi/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; LBBB, left bundle branch block; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVMI, left ventricular mass index; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
Therapy introduction during baseline examination and drug/device therapies after this examination are reported.

Over a median 2.8 year follow-up after the second TTE (1.3–4.9), 123 cardiovascular deaths were recorded (13%), 102 events (83%) occurring in patients with baseline LVEF < 40%, and 90 events (73%) in those with LVEF ≤ 35%. No patient from this cohort underwent heart transplantation or LV assist device implantation.

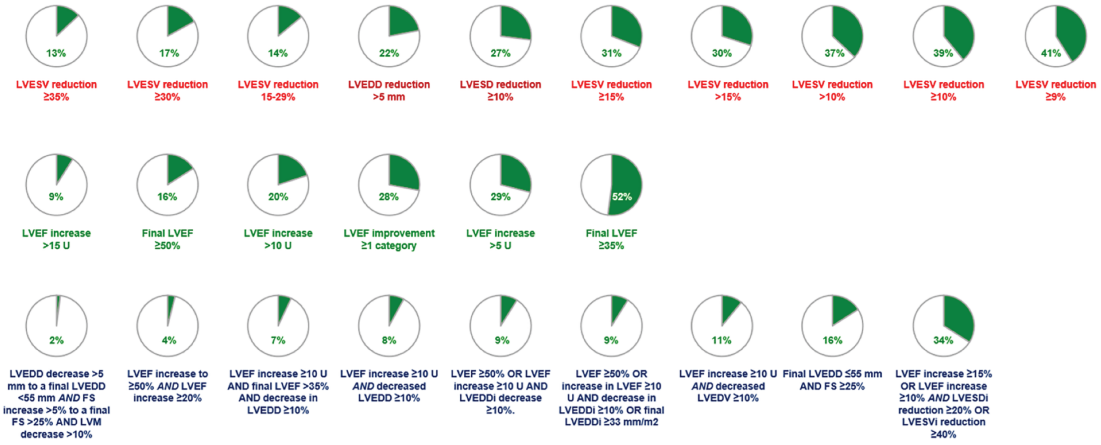
Prevalence of reverse remodelling according to the different criteria

The estimated prevalence of RR varied widely when using different criteria for RR (*Figure 2* and Supporting Information, *Table S4*). In the whole cohort, as many as 52% of patients had RR when using the criterion 'final LVEF > 35%' (although 43% of patients had a baseline LVEF > 35%), and just 2% when using an elaborate criterion (left ventricular end-diastolic diameter decrease >5 mm to a final left ventricular end-diastolic diameter < 55 mm AND fractional shortening increase >5% to a final fractional shortening > 25% AND LV mass decrease >10%). When the most common criterion for RR (LVESV reduction ≥15%) was applied, 31% of patients were categorized as having RR. Patients with more depressed systolic function (baseline LVEF < 40% or ≤35%) had often higher rates of RR, except when specific LVEF thresholds were considered to define RR (>50% or ≥35%; *Table 2*).

Prognostic value of criteria for reverse remodelling

In the whole cohort, several cut-offs of per cent LVESV changes displayed an independent prognostic value for cardiovascular death from Model 1. An LVESV reduction ≥15% independently predicted a 49% lower risk of cardiovascular death (hazard ratio 0.51, 95% confidence interval 0.32–0.80, *P* = 0.004), with an improvement in risk reclassification as

Figure 2 Prevalence of reverse remodelling in the whole cohort using diagnostic criteria from the literature. FS, fractional shortening; LVEDD(i), left ventricular end-diastolic diameter (index); LVEF, left ventricular ejection fraction; LVESD(i), left ventricular end-systolic diameter (index); LVESV, left ventricular end-systolic volume; LVM, left ventricular mass.



measured through NRI. Most other criteria based on LVESV changes displayed an independent prognostic value. Two RR criteria proved particularly effective in risk reclassification, as demonstrated by improvement in both IDI and NRI: LVEF increase ≥1 category [severe (LVEF ≤ 30%), moderate (LVEF 31–40%), mild LV dysfunction (LVEF 41–55%), and normal LV function (LVEF ≥ 56%)] and LVEF increase >10 U (*Table 2*). The same two criteria improved IDI and NRI even when added to Model 2 (Supporting Information, *Table S5*).

In the subgroup with LVEF < 40%, LVESV reduction ≥15% did not yield independent prognostic significance (P = 0.086). Among independent predictors, LVEF increase ≥1 category improved NRI with a trend towards better IDI (P = 0.075), and LVEF increase >10 U improved both IDI and NRI (Supporting Information, *Table S6*). Both criteria improved IDI and NRI over Model 2 (Supporting Information, *Table S7*).

In the subset with LVEF ≤ 35%, LVESV reduction ≥15% yielded borderline independent prognostic significance for cardiovascular mortality (P = 0.052). LVEF increase ≥1 category improved the NRI, with a trend towards better IDI, while LVEF increase >10 U improved both IDI and NRI. Both criteria improved IDI and NRI over Model 2 (data not shown).

Left ventricular ejection fraction-based criteria vs. left ventricular end-systolic volume reduction ≥15%

Left ventricular ejection fraction increase ≥1 category and LVEF increase >10 U were then compared (one at the time) with the most used criterion for RR, that is, LVESV reduction ≥15%, on the background of Model 1 and Model 2. Although not always achieving independent statistical significance, LVEF increase ≥1 category and LVEF increase >10 U displayed a stronger prognostic value than LVESV reduction ≥15%, both in the whole population and in the subsets with LVEF < 40% or ≤35% (*Table 3*).

Discussion

In this study, we searched all proposed diagnostic criteria for RR and we identified which ones were most predictive of cardiovascular death. We found a substantial heterogeneity in the criteria for RR, variably considering changes in LV volumes or LVEF, resulting in a large variability in the estimated prevalence of RR. The most commonly used criterion for RR was LVESV reduction ≥15%. When added to a prognostic model including several patient variables, or to a validated prognostic score, LVESV reduction ≥15% proved less effective in risk reclassification than the two LVEF-based criteria: LVEF increase ≥1 category [severe (LVEF ≤ 30%), moderate (LVEF 31–40%), mild LV dysfunction (LVEF 41–55%), and normal LV function (LVEF ≥ 56%)] and LVEF increase >10 U (Central Illustration). Similar results were found in the whole cohort (LVEF < 50%) and in subgroups with more severe systolic dysfunction: LVEF < 40% and ≤35%. We conclude that LVEF-based criteria should be preferentially used to define RR, given their stronger association with a lower risk of cardiovascular death.

To our knowledge, this is the first attempt to retrieve all published criteria for RR. We found as many as 25 criteria, most of them arbitrarily selected, and proposed in patient cohorts with varying degrees of LV dilatation and dysfunction. While the original studies employed multiple imaging techniques, we decided to apply these criteria in a cohort of patients with baseline LVEF < 50% undergoing serial echocardiograms. The percentages of patients categorized as

Table 2 Prognostic value of criteria for reverse remodelling in the whole cohort (left ventricular ejection fraction < 50%)

	Kaplan–Meier analysis		Univariate Cox analysis	Multivariate Cox analysis: age, LVEF, NT-proBNP, ischaemic HF, CRT, eGFR, NYHA III–IV, and LVESVi			Reclassification analysis: IDI			Reclassification analysis: NRI		
Criterion	*P*	Log-rank	*P*	*P*	HR	95% CI	*P*	IDI	95% CI	*P*	NRI	95% CI
LVESV reduction ≥35%	**0.004**	8.5	**0.005**	**0.031**	0.45	0.21–0.93	0.956	—	—	0.353	—	—
LVESV reduction ≥30%	**0.001**	11.4	**0.001**	**0.008**	0.41	0.21–0.79	0.670	—	—	0.812	—	—
LVESV reduction 15–29%	0.736	—	0.709	—	—	—	—	—	—	—	—	—
LVESV reduction ≥15%	**0.002**	9.7	**0.002**	**0.004**	0.51	0.32–0.80	0.347	—	—	**0.020**	0.21	0.03–0.39
LVESV reduction >15%	<**0.001**	13.4	<**0.001**	**0.001**	0.45	0.27–0.73	0.235	—	—	**0.005**	0.25	0.07–0.42
LVESV reduction ≥10%	**0.001**	11.3	**0.001**	**0.005**	0.54	0.35–0.83	0.726	—	—	**0.028**	0.22	0.02–0.41
LVESV reduction >10%	**0.001**	12.4	**0.001**	**0.002**	0.50	0.32–0.79	0.402	—	—	**0.021**	0.23	0.03–0.42
LVESV reduction ≥9%	**0.001**	11.1	**0.001**	**0.007**	0.56	0.36–0.85	0.732	—	—	**0.024**	0.23	0.03–0.42
LVESD reduction ≥10%	**0.001**	12.2	**0.001**	0.070	—	—	—	—	—	—	—	—
LVEDD reduction >5 mm	0.656	—	0.657	—	—	—	—	—	—	—	—	—
Final LVEF ≥ 50%	**0.001**	10.3	**0.002**	**0.005**	0.18	0.06–0.59						
Final LVEF ≥ 35%	<**0.001**	30.3	<**0.001**	**0.037**	0.59	0.36–0.97	—	—	—	—	—	—
LVEF increase ≥1 category: severe (LVEF ≤ 30%), moderate (LVEF 31–40%), mild LV dysfunction (LVEF 41–55%), and normal LV function (LVEF ≥ 56%)	**0.001**	10.6	**0.001**	**0.003**	0.45	0.27–0.77	0.027	0.01	0.01–0.01	**0.007**	0.23	0.06–0.40
LVEF increase >5 U	**0.010**	6.7	**0.011**	**0.006**	0.50	0.30–0.82	0.724	—	—	0.053	—	—
LVEF increase >10 U	**0.003**	8.6	**0.002**	**0.003**	0.32	0.15–0.67	<**0.001**	0.01	0.01–0.01	**0.005**	0.20	0.05–0.32
LVEF increase >15 U	0.107	—	0.109	—	—	—	—	—	—	—	—	—
LVEF ≥ 50% *OR* increase in LVEF ≥ 10 U *AND* decrease in LVEDDi ≥ 10%	**0.023**	5.2	**0.030**	0.248	—	—	—	—	—	—	—	—
LVEF ≥ 50% *OR* increase in LVEF ≥ 10 U *AND* decrease in LVEDDi ≥ 10% *OR* final LVEDDi ≥ 33 mm/m^2	0.128	—	0.736	—	—	—	—	—	—	—	—	—
LVEF increase ≥10 U *AND* final LVEF > 35% *AND* decrease in LVEDD ≥ 10%	**0.031**	4.6	**0.043**	0.346	—	—	—	—	—	—	—	—
LVEF increase ≥10 U *AND* decreased LVEDD ≥ 10%	**0.035**	4.5	**0.044**	0.248	—	—	—	—	—	—	—	—
LVEF increase ≥10 U *AND* decreased LVEDV ≥ 10%	**0.011**	6.4	**0.015**	0.134	—	—	—	—	—	—	—	—

(*Continues*)

Table 2 (continued)

	Kaplan–Meier analysis		Univariate Cox analysis	Multivariate Cox analysis: age, LVEF, NT-proBNP, ischaemic HF, CRT, eGFR, NYHA III–IV, and LVESVi			Reclassification analysis: IDI			Reclassification analysis: NRI		
Criterion	*P*	Log-rank	*P*	*P*	HR	95% CI	*P*	IDI	95% CI	*P*	NRI	95% CI
LVEF increase ≥50% *AND* LVEF increase ≥20%	0.450	—	0.466	—	—	—	—	—	—	—	—	—
LVEF increase ≥15% *OR* LVEF increase ≥10% *AND* reduction of LVESDi ≥ 20% *OR* LVESVi reduction ≥40%	**0.005**	7.9	**0.006**	**0.001**	0.48	0.31–0.75	0.462	—	—	**0.038**	0.20	0.01–0.39
LVEDD decrease >5 mm to a final LVEDD < 55 mm *AND* FS increase >5% to a final FS > 25% *AND* LVM decrease >10%	0.075	—	0.239	—	—	—	—	—	—	—	—	—
LVEDD ≤ 55 mm *AND* FS ≥ 25%	**0.001**	12.0	**0.001**	0.099	—	—	—	—	—	—	—	—

CI, confidence interval; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; FS, fractional shortening; HF, heart failure; HR, hazard ratio; IDI, integrated discrimination improvement; LVEDD(i), left ventricular end-diastolic diameter (index); LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV(i), left ventricular end-systolic volume (index); LVM, left ventricular mass; NRI, net reclassification index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

The prognostic models for multivariate Cox regression analysis included age, LVEF, NT-proBNP, ischaemic aetiology, CRT, eGFR, NYHA, and LVESVi, all adjudicated at the time of the first transthoracic examination. Reverse remodelling criteria were evaluated on the background of the same model in reclassification analysis. Significant p values were reported in bold characters.

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Table 3 Comparison between different criteria for reverse remodelling

	Multivariate Cox analysis: age, LVEF, NT-proBNP, ischaemic HF, CRT, eGFR, NYHA, and LVESVi																	
	LVEF < 50%			LVEF < 40%			LVEF ≤ 35%			LVEF < 50%			LVEF < 40%			LVEF ≤ 35%		
	P	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI
LVEF increase ≥1 category	0.050	—	—	0.101	—	—	0.090	—	—									
LVEF increase >10 U										**0.026**	0.40	0.18–0.90	**0.042**	0.42	0.18–0.97	0.082	—	—
LVESV reduction ≥15%	0.087	—	—	0.147	—	—	0.144	—	—	0.112	—	—	0.659	—	—	0.117	—	—
	Multivariate Cox analysis: 3C-HF																	
	LVEF < 50%			LVEF < 40%			LVEF ≤ 35%			LVEF < 50%			LVEF < 40%			LVEF ≤ 35%		
	P	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI
LVEF increase ≥1 category	0.050	—	—	**0.017**	0.19	0.05–0.74	**0.046**	0.23	0.05–0.98									
LVEF increase >10 U										0.053	—	—	0.080	—	—	0.150	—	—
LVESV reduction ≥15%	0.412	—	—	0.803	—	—	0.793	—	—	0.354	—	—	0.633	—	—	0.693	—	—

CI, confidence interval; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVESV(i), left ventricular end-systolic volume (index); NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
The prognostic models for multivariate Cox regression analysis included age, LVEF, NT-proBNP, ischaemic aetiology, CRT, eGFR, NYHA, and LVESVi, all adjudicated at the time of the first transthoracic examination. Reverse remodelling criteria were evaluated on the background of the same model in reclassification analysis. Significant p values were reported in bold characters.

experiencing RR varied widely (from 2% to up to 52%). We report that definitions using changes in a single variable (such as LVESV or LVEF) are usually more predictive than combined criteria. Therefore, there does not seem to be a trade-off between ease of calculation and prognostic value. Among single-variable criteria, volumetric changes were used in a greater number of studies, but a recovery from LV dilation seemed less predictive than a relief from systolic dysfunction, expressed in terms of changes between LVEF categories, or absolute increase in LVEF by 10 units. The finding that positive changes in LVEF over time are predictive of better outcome is in agreement with previous studies. In addition to studies using changes in LVEF criteria to define RR (Supporting Information, *Table S1*), we may cite an analysis of the Swedish Heart Failure Registry, where transition from HFrEF to HF with mid-range ejection fraction (HFmrEF) or (to a lesser extent) from HFmrEF to HF with preserved ejection fraction was associated with a lower risk of mortality and/or HF hospitalization.[48] In a specular fashion, a transition from HF with preserved ejection fraction to HFmrEF or from HFmrEF to HFrEF predicted a higher risk of death and/or hospitalization,[48] and a decline in LVEF was found to precede death in a large cohort of HF outpatients.[49] LVEF decrease follows LV dilation and denotes the failure of LV dilation as a compensatory mechanism to sustain systolic LV function.[50] It is then reasonable to speculate that HF therapy may cause a decrease in LV volumes and then a recovery in LV function and that patients achieving a substantial increase in LVEF (such as a change in LVEF category or an increase by more than 10 units) have also a better long-term outcome. The magnitude of risk reduction is substantial: for example, patients with baseline LVEF $<$ 50% and LVEF increase $\geq$1 category had a 72% lower risk of cardiovascular death over a 3 year follow-up, beyond a validated prognostic model such as the 3C-HF score. These considerations support the assessment of RR for risk stratification of outpatients with systolic HF (baseline LVEF $<$ 50%, $<$40%, or $\leq$35%) and suggest that LVEF-based criteria are preferentially used over volume-based definitions.

Several limitations must be acknowledged. First, this was a single-centre study with a comparatively small number of patients, and the most predictive criteria for RR might depend on the characteristics of the current study cohort. This study was also retrospective in nature, with no prespecified hypothesis. We evaluated RR criteria regardless of the imaging technique and the inclusion criteria of the original studies; the latter point led, for example, to widely different estimates of the rate of RR. Furthermore, the assessment of RR did not take into account therapeutic interventions (medical therapy alone, myocardial revascularization, or heart valve repair, including the Mitra Clip procedure), which underlie different pathophysiology and different effects on cardiac remodelling; on the other hand, our focus was on the definition of RR, which prescinds from the specific therapeutic strategies. HF therapies drastically changed over the period covered in this study. While the specific drugs of each class and their doses might impact on the clinical course of RR, this information was not available. Additionally, changes in medication usage over time might represent another considerable confounder, but were not evaluated in this analysis. Furthermore, the retrospective data collection did not allow to retrieve all the information needed to calculate the 3C-HF score in as many as 48% of patients, although this score includes commonly acquired variables. Changes in diastolic function over time might accompany RR and predict cardiovascular outcomes,[51] but these changes could be evaluated just in a minority of patients, again because of missing data. As for the prognostic analysis, we focused on the hard endpoint of cardiovascular death, rather than HF hospitalization, either alone or as part of a composite endpoint, although RR is an important risk factor for the prediction of HF development. The refinement in risk stratification was evaluated in terms of NRI and IDI, which are commonly used yet suboptimal metrics, because they can have inflated false positive rates.[52,53] Finally, we examined proposed criteria for RR rather than deriving the best prognostic criterion based on our data. A possible perspective for future studies is to search for the most predictive criterion for RR among a wide spectrum of variables, possibly including echocardiographic and cardiac magnetic resonance data, advanced imaging modalities (such as 2D speckle tracking or 3D echocardiography), and also variables exploring the left atrium and the right heart.

In conclusions, LVEF increase $\geq$1 category and LVEF increase $>$10 U reclassify the risk of cardiovascular death more effectively than the most used criterion for RR (i.e. LVESV reduction $\geq$15%). RR defined by these LVEF-based criteria should be considered as an additive tool for risk stratification in outpatients with HF.

Conflict of interest

None declared.

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None.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Search strategy.
Table S2. Selected studies.

Table S3. Comparison between patients with or without the 3C-HF score data.

Table S4. Prevalence of reverse remodelling (RR) according to the different criteria.

Table S5. Prognostic value of criteria for reverse remodeling (RR) in the whole cohort (left ventricular ejection fraction [LVEF] $<$ 50%) vs. the cardiac and comorbid conditions (3C-HF) score.

Table S6. Prognostic value of criteria for reverse remodelling (RR) in patients with heart failure and reduced ejection fraction (left ventricular ejection fraction [LVEF] $<$ 40%).

Table S7. Prognostic value of criteria for reverse remodeling (RR) in patients with heart failure and reduced ejection fraction (left ventricular ejection fraction [LVEF] $<$ 40%) vs. the cardiac and comorbid conditions (3C-HF) score.

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