

Predicting Outcome After Cardiac Resynchronization Therapy Defibrillator Implantation: The CRT-D Futility Score

Brief Title: CRT-D Futility Score

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Online Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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ONLINE TABLE 1. Codes in the 10th revision of the International Classification of Diseases (ICD-10) or in the classification commune des actes médicaux (CCAM, French classification for medical procedures) for diseases and comorbidities.

<i>Diseases and comorbidities</i>	<i>Codes in ICD-10 or CCAM</i>
Hypertension	I10, I11, I12, I13, I14, I15
Diabetes mellitus	E10, E11, E12, E13, E14
Heart failure	I50, I11.0, I13.0, I13.2, J81, R570, I42, I43, I25.5
History of pulmonary oedema	R570, J81
Aortic stenosis	I350, I352, I060, I062
Aortic regurgitation	I35.1
Mitral regurgitation	I34.0
Previous endocarditis	I330
Dilated cardiomyopathy	I42, I43
Coronary artery disease	I20, I21, I22, I23, I24, I25, Z955, DDAF006, DDAF001, DDAF003, DDAF004, DDAF007, DDAF008, DDAF009, DDAF010, Z951, DDMA003, DDMA004, DDMA005, DDMA006, DDMA007, DDMA008, DDMA009, DDMA011, DDMA012, DDMA013, DDMA015, DDMA016, DDMA017, DDMA018, DDMA019, DDMA020, DDMA021, DDMA022, DDMA023, DDMA024, DDMA025, DDMA026, DDMA027, DDMA028, DDMA029, DDMA030, DDMA031, DDMA032, DDMA033, DDMA034, DDMA035, DDMA036, DDMA037, DDMA038
Previous myocardial infarction	I21, I22, I23
Previous PCI	Z955, DDAF006, DDAF001, DDAF003, DDAF004, DDAF007, DDAF008, DDAF009, DDAF010
Previous CABG	Z951, DDMA003, DDMA004, DDMA005, DDMA006, DDMA007, DDMA008, DDMA009, DDMA011, DDMA012, DDMA013, DDMA015, DDMA016, DDMA017, DDMA018, DDMA019, DDMA020, DDMA021, DDMA022, DDMA023, DDMA024, DDMA025, DDMA026, DDMA027, DDMA028, DDMA029, DDMA030, DDMA031, DDMA032, DDMA033, DDMA034, DDMA035, DDMA036, DDMA037, DDMA038
Atrial fibrillation	I48
Left BBB	I447
Right BBB	I451
Vascular disease	I71, I790, I739, R02, Z958, Z959
Ischaemic stroke	I63
Intracranial bleeding	I60, I61, I62, S06.4, S06.5, S06.6
Smoker	I472
Dyslipidaemia	E78
Obesity	E65, E66
Alcohol-related diagnoses	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, P04.3, Q86.0, T51, Y90, Y91, Z50.2, Z71.4, Z72.1
Undernutrition	E41, E43, E44, E46, F508, K912, R636
Abnormal renal function	N18.3, N18.4, N18.5, T86.1, Z49, Z99.2
Lung disease	J40-J70, J96.1
Sleep apnoea syndrome	G47.3

COPD	J43, J44
Liver disease	K70-K77
Thyroid diseases	E0, E89.0
Inflammatory disease	M05-M14, M45, M46, K50, K51, K52
Anaemia	D50-D64
Previous cancer	C00-C97
Cognitive impairment	F00, F01, F02, F03, F106, F1073, F1173, F1273, F1373, F1473, F1573, F1673, F1773, F1873, F1973, G30, G310, G318, G938, I673

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention.

ONLINE TABLE 2 Baseline Characteristics of Patients Implanted with CRT in French Hospitals (2010 to 2019) With at Least 1 Year of Follow-Up, According to CRT-P or CRT-D Device

	Total (n=36015)	CRT-P (n=12986)	CRT-D (n=23029)	p
Age, years	71.7±10.8	78.7±8.6	67.7±9.9	<0.0001
Sex (male)	26,615 (73.9)	8,459 (65.1)	18,156 (78.8)	<0.0001
Hypertension	22,183 (61.6)	8,734 (67.3)	13,449 (58.4)	<0.0001
Diabetes mellitus	11,375 (31.6)	3,747 (28.9)	7,628 (33.1)	<0.0001
History of hospitalization with congestion	29,218 (81.1)	10,457 (80.5)	18,761 (81.5)	0.03
History of pulmonary oedema	2,504 (7.0)	932 (7.2)	1,572 (6.8)	0.21
Dilated cardiomyopathy	23,127 (64.2)	7,144 (55.0)	15,983 (69.4)	<0.0001
Coronary artery disease	20,592 (57.2)	6,872 (52.9)	13,720 (59.6)	<0.0001
Previous myocardial infarction	3,176 (8.8)	1,021 (7.9)	2,155 (9.4)	<0.0001
Previous PCI	8,585 (23.8)	2,673 (20.6)	5,912 (25.7)	<0.0001
Previous CABG	3,846 (10.7)	1,163 (9.0)	2,683 (11.7)	<0.0001
Aortic stenosis	2,750 (7.6)	1,671 (12.9)	1,079 (4.7)	<0.0001
Aortic regurgitation	1,794 (5.0)	878 (6.8)	916 (4.0)	<0.0001
Mitral regurgitation	6,535 (18.1)	2,639 (20.3)	3,896 (16.9)	<0.0001
Atrial fibrillation	16,838 (46.8)	7,624 (58.7)	9,214 (40.0)	<0.0001
Left BBB	13,435 (37.3)	4,925 (37.9)	8,510 (37.0)	0.07
Right BBB	1,682 (4.7)	690 (5.3)	992 (4.3)	<0.0001
Vascular disease	11,209 (31.1)	3,642 (28.0)	7,567 (32.9)	<0.0001
Ischaemic stroke	1,226 (3.4)	449 (3.5)	777 (3.4)	0.67
Intracranial bleeding	321 (0.9)	140 (1.1)	181 (0.8)	0.005
Smoker	4,920 (13.7)	1,055 (8.1)	3,865 (16.8)	<0.0001
Dyslipidaemia	13,255 (36.8)	4,554 (35.1)	8,701 (37.8)	<0.0001
Obesity	7,510 (20.9)	2,381 (18.3)	5,129 (22.3)	<0.0001
Alcohol-related diagnoses	2,388 (6.6)	606 (4.7)	1,782 (7.7)	<0.0001
Undernutrition	1,970 (5.5)	1,072 (8.3)	898 (3.9)	<0.0001
Chronic kidney disease	4,303 (11.9)	2,102 (16.2)	2,201 (9.6)	<0.0001
Lung disease	6,670 (18.5)	2,553 (19.7)	4,117 (17.9)	<0.0001
Sleep apnoea syndrome	3,607 (10.0)	1,230 (9.5)	2,377 (10.3)	0.01
Liver disease	1,602 (4.4)	575 (4.4)	1,027 (4.5)	0.89
Thyroid diseases	3,865 (10.7)	1,740 (13.4)	2,125 (9.2)	<0.0001
Inflammatory disease	2,310 (6.4)	993 (7.6)	1,317 (5.7)	<0.0001
Anaemia	4,213 (11.7)	2,032 (15.6)	2,181 (9.5)	<0.0001
Previous cancer	3,742 (10.4)	1,749 (13.5)	1,993 (8.7)	<0.0001
Cognitive impairment	648 (1.8)	429 (3.3)	219 (1.0)	<0.0001

Values are n (%) or mean±SD. CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; BBB = bundle branch block; PCI = percutaneous coronary intervention; SD = standard deviation.

ONLINE TABLE 3 Baseline Characteristics of Patients Implanted with CRT-D in French Hospitals (2010 to 2019) With at Least 1 Year of Follow-Up in the Derivation and Validation Samples.

	Total (n=23,029)	Derivation Cohort (n=11,514)	Validation Cohort (n=11,515)	p
Age, years	67.7±9.9	67.8±9.9	67.5±10.0	0.02
Sex (male)	18,156 (78.8)	9,098 (79.0)	9,058 (78.7)	0.51
Hypertension	13,449 (58.4)	6,747 (58.6)	6,702 (58.2)	0.54
Diabetes mellitus	7,628 (33.1)	3,802 (33.0)	3,826 (33.2)	0.74
History of hospitalization with congestion	18,761 (81.5)	9,393 (81.6)	9,368 (81.4)	0.66
History of pulmonary oedema	1,572 (6.8)	807 (7.0)	765 (6.6)	0.27
Dilated cardiomyopathy	15,983 (69.4)	7,990 (69.4)	7,993 (69.4)	0.97
Coronary artery disease	13,720 (59.6)	6,904 (60.0)	6,816 (59.2)	0.23
Previous myocardial infarction	2,155 (9.4)	1,103 (9.6)	1,052 (9.1)	0.25
Previous PCI	5,912 (25.7)	2,980 (25.9)	2,932 (25.5)	0.47
Previous CABG	2,683 (11.7)	1,369 (11.9)	1,314 (11.4)	0.26
Aortic stenosis	1,079 (4.7)	552 (4.8)	527 (4.6)	0.43
Aortic regurgitation	916 (4.0)	480 (4.2)	436 (3.8)	0.14
Mitral regurgitation	3,896 (16.9)	1,977 (17.2)	1,919 (16.7)	0.31
Atrial fibrillation	9,214 (40.0)	4,652 (40.4)	4,562 (39.6)	0.22
Left BBB	8,510 (37.0)	4,275 (37.1)	4,235 (36.8)	0.58
Right BBB	992 (4.3)	502 (4.4)	490 (4.3)	0.7
Vascular disease	7,567 (32.9)	3,806 (33.1)	3,761 (32.7)	0.52
Ischaemic stroke	777 (3.4)	387 (3.4)	390 (3.4)	0.91
Intracranial bleeding	181 (0.8)	84 (0.7)	97 (0.8)	0.33
Smoker	3,865 (16.8)	1,970 (17.1)	1,895 (16.5)	0.19
Dyslipidaemia	8,701 (37.8)	4,295 (37.3)	4,406 (38.3)	0.13
Obesity	5,129 (22.3)	2,508 (21.8)	2,621 (22.8)	0.07
Alcohol-related diagnoses	1,782 (7.7)	873 (7.6)	909 (7.9)	0.38
Undernutrition	898 (3.9)	471 (4.1)	427 (3.7)	0.13
Chronic kidney disease	2,201 (9.6)	1,108 (9.6)	1,093 (9.5)	0.74
Lung disease	4,117 (17.9)	2,067 (18.0)	2,050 (17.8)	0.77
Sleep apnoea syndrome	2,377 (10.3)	1,189 (10.3)	1,188 (10.3)	0.98
Liver disease	1,027 (4.5)	515 (4.5)	512 (4.4)	0.92
Thyroid diseases	2,125 (9.2)	1,047 (9.1)	1,078 (9.4)	0.48
Inflammatory disease	1,317 (5.7)	683 (5.9)	634 (5.5)	0.16
Anaemia	2,181 (9.5)	1,100 (9.6)	1,081 (9.4)	0.67
Previous cancer	1,993 (8.7)	990 (8.6)	1,003 (8.7)	0.76
Cognitive impairment	219 (1.0)	113 (1.0)	106 (0.9)	0.63

Values are n (%) or mean±SD. CABG = coronary artery bypass graft; CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; BBB = bundle branch block; PCI = percutaneous coronary intervention; SD = standard deviation.

ONLINE TABLE 4 Comparison of C-Statistics (95% CIs) for Different Risk Scoring Systems Predicting 1-Year All-Cause Death in Patients Treated With CRT-D in the Derivation and Validation Samples

	C-statistics (95% CI)	p Value*	p Value†
Derivation sample (n=11,514)			
Goldenberg score	0.649 (0.631–0.668)		<0.0001
EAARN score	0.683 (0.665–0.700)	<0.0001	
CRT-D Futility score	0.716 (0.698–0.734)	<0.0001	<0.0001
Validation sample (n=11,515)			
Goldenberg score	0.637 (0.618–0.656)		<0.0001
EAARN score	0.667 (0.649–0.686)	<0.0001	
Futility CRT-D score	0.692 (0.673–0.710)	<0.0001	<0.0001

*p value for the DeLong test vs. the Goldenberg score. †p value for the DeLong test vs. the EAARN score. CI = confidence interval; CRT-D = cardiac resynchronization therapy defibrillator EAARN = Ejection fraction, Age, Atrial fibrillation, Renal dysfunction, New York Heart Association class IV.

ONLINE TABLE 5 Sensitivity and Specificity for Different Risk Strata of the CRT-D Futility Score

Cut point	Sensitivity	Specificity	Correctly classified	LR+	LR-
Low	100.0%	0.0%	7.0%	1	
Medium low	95.9%	17.4%	22.9%	1.161	0.236
Medium high	76.6%	52.7%	54.3%	1.618	0.445
High	37.8%	85.7%	82.4%	2.650	0.725

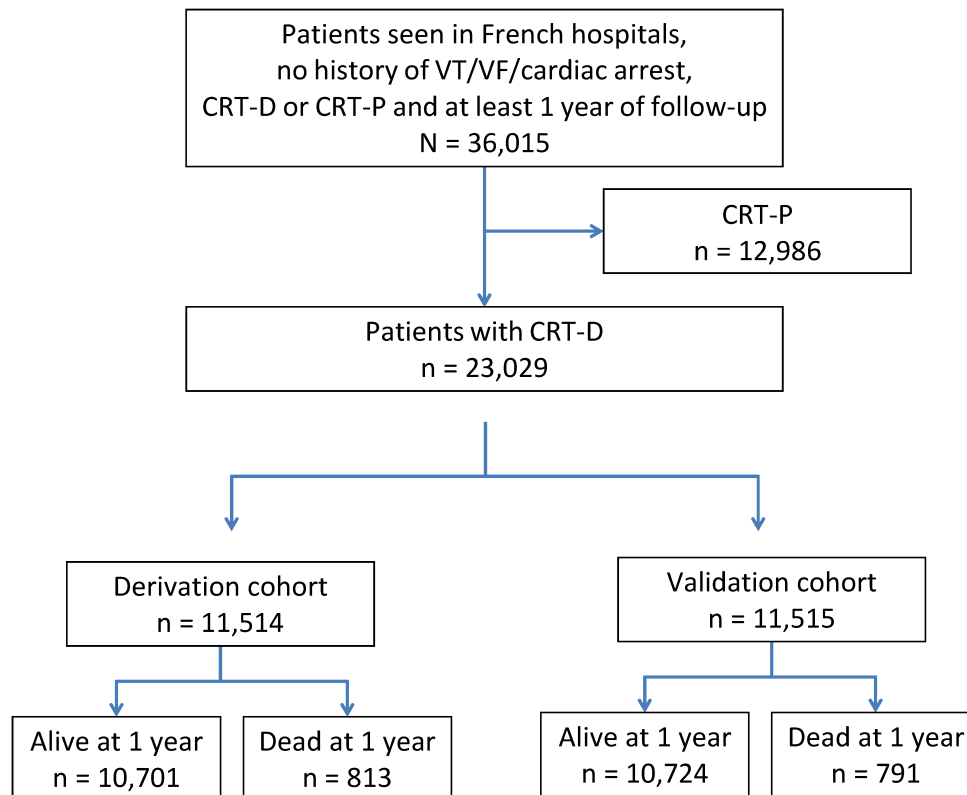
For the CRT-D Futility score, risk was defined as: Low = score 0–3; Medium low = score 4–7; Medium high = score 8–11; and High = score ≥ 12 . LR+ = positive likelihood ratio; LR- = negative likelihood ratio.

ONLINE TABLE 6 Net reclassification after adding the CRT-D Futility Score for 1-year risk of all-cause death.

	Cases, n=1,604		Non cases, n=21,425		NRI	SE	Z	p
	Up	Down	Up	Down				
Goldenberg	249	11	1,013	80	0.105	0.010	10.308	<0.0001
EAARN	134	32	554	220	0.048	0.008	5.899	<0.0001

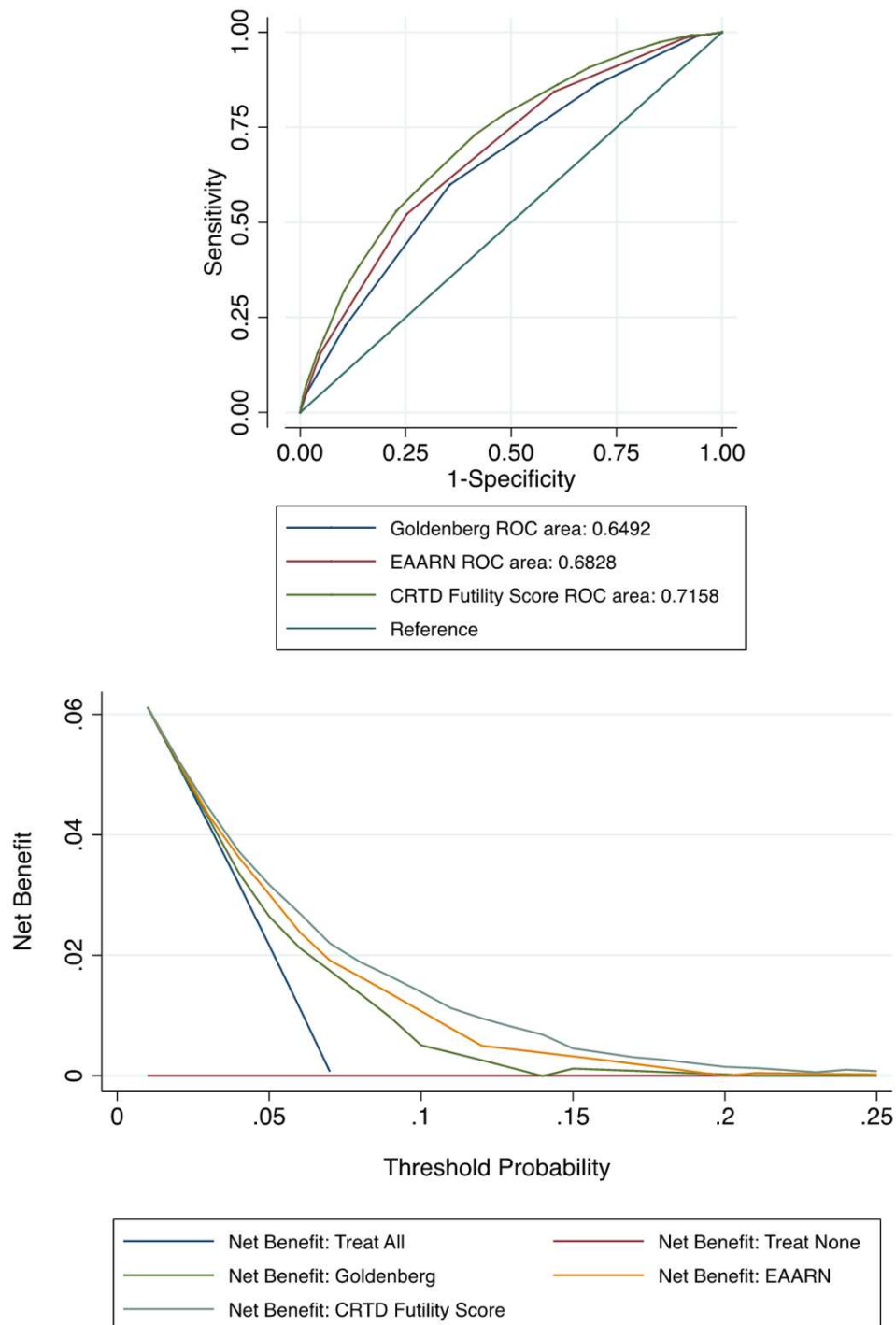
We assessed the categorical net reclassification improvement of the new score at the clinically relevant 15% risk threshold compared with the Goldenberg and EAARN scores. The new score substantially improved net reclassification. NRI=net reclassification improvement; SE =standard error.

ONLINE FIGURE 1 Flow Chart

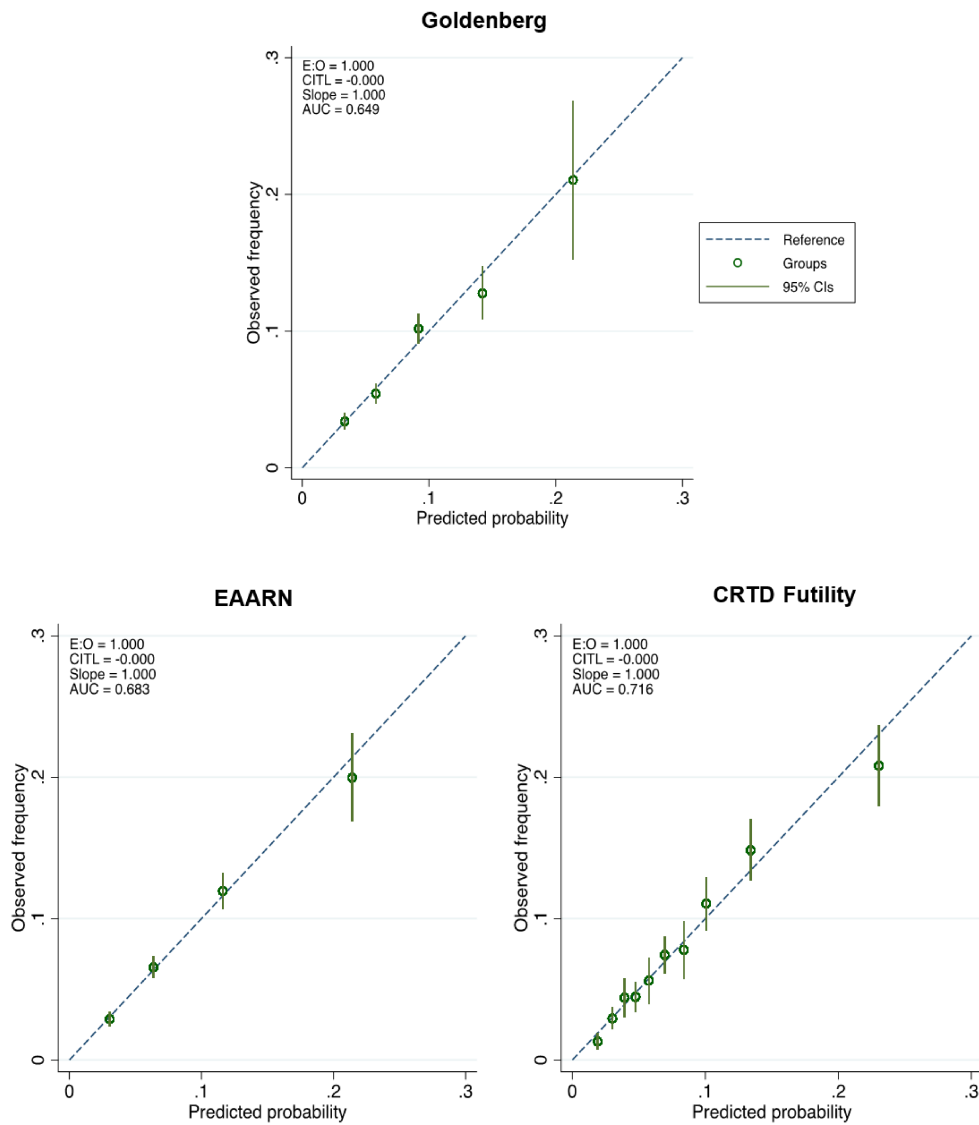


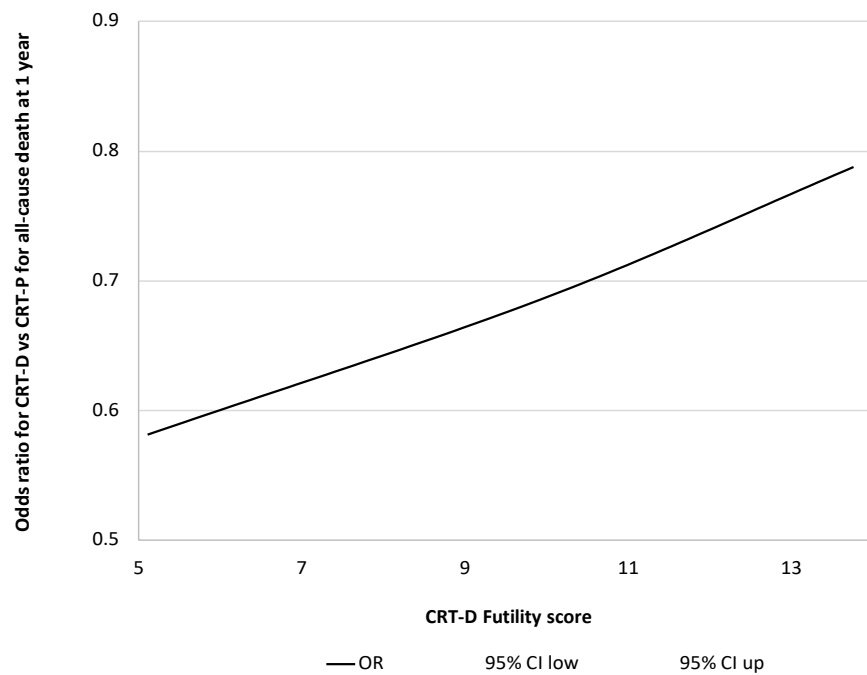
CRT-D = cardiac resynchronization therapy defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; VF = ventricular fibrillation; VT = ventricular tachycardia.

ONLINE FIGURE 2: Upper panel: Area Under the Curve for the 3 Scores in Predicting Death at 1 Year for Patients With CRT-D Implantation, in the derivation cohort. Lower panel: Decision Curve Analysis: Net Number of True Positives Gained Using Different Models Compared With No Model at a Range of Threshold Probabilities



ONLINE FIGURE 3. Calibration Plots of the 3 Scores Predicting Risk of All-Cause Death During the First Year After CRT-D Implantation in the derivation Cohort Using the Goldenberg Score (Upper Panel), EAARN Score (Lower Left Panel) or CRT-D Futility Score (Lower Right Panel). The diagonal line represents perfect calibration. Vertical bars represent 95% CIs. Abbreviations as in Tables 1 and 2.



ONLINE FIGURE 4 Odds Ratio for All-Cause Death at 1 Year in Patients Treated With CRT-D Versus CRT-P, Stratified by CRT-D Futility Score.

Abbreviations as in Online Table 2.