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ORIGINAL ARTICLE

Real-world outcomes in cardiac resynchronization therapy patients: Primary results of the SMART registry

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Abstract

Aims Cardiac resynchronization therapy (CRT) is guideline recommended for the treatment of symptomatic heart failure (HF) with reduced left ventricular ejection fraction and prolonged QRS. However, patients with common comorbidities, such as persistent/permanent atrial fibrillation (AF), are often under-represented in clinical trials.

Methods The Strategic Management to Optimize Response to Cardiac Resynchronization Therapy (SMART) registry (NCT03075215) was a global, multicentre, registry that enrolled de novo CRT implants, or upgrade from pacemaker or implantable cardioverter defibrillator to CRT-defibrillator (CRT-D), using a quadripolar left ventricular lead in real-world clinical practice. The primary endpoint was CRT response between baseline and 12 month follow-up defined as a clinical composite score (CCS) consisting of all-cause mortality, HF-associated hospitalization, New York Heart Association (NYHA) class and quality of life global assessment.

Results The registry enrolled 2035 patients, of which 1558 had completed CCS outcomes at 12 months. The patient cohort was 33.0% female, mean age at enrolment was 67.5 ± 10.4 years and the mean left ventricular ejection fraction was 29.6 ± 7.9%. Notably, there was a high prevalence of mildly symptomatic patients (NYHA class I/II 51.3%), non-left bundle branch block (LBBB) morphology (38.0%), AF (37.2%) and diabetes mellitus (34.7%) at baseline. CCS at 12 months improved in 58.9% (n = 917) of patients; 20.1% (n = 313) of patients stabilized and 21.0% (n = 328) worsened. Several patient characteristics were associated with a lower likelihood of response to CRT including older age, ischaemic aetiology, renal dysfunction, AF, non-LBBB morphology and diabetes. Higher HF hospitalization ($P < 0.001$) and all-cause mortality ($P < 0.001$) were observed in patients with AF. These patients also had lower percentages of ventricular pacing than patients in sinus rhythm at baseline and follow-up ($P < 0.001$, both). A further association between AF and non-LBBB was observed with 81.4% of AF non-LBBB patients experiencing an HF hospitalization compared with 92.5% of non-AF LBBB patients ($P < 0.001$). Mortality between subgroups was also statistically significant ($P = 0.019$).

Conclusions This large, global registry enrolled a CRT-D population with higher incidence of comorbidities that have been historically underrepresented in clinical trials and provides new insight into factors influencing response to CRT. As defined by CCS, 58.9% of patients improved and 20.1% stabilized. Patients with AF had particularly worse clinical outcomes, higher HF hospitalization and mortality rates and lower percentages of ventricular pacing. High incidence of HF hospitalization in patients with AF and non-LBBB in this real-world cohort suggests that ablation may play an important role in increasing future CRT response rates.

Keywords atrioventricular optimization; cardiac resynchronization therapy; electrical delay; heart failure

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Introduction

Cardiac resynchronization therapy (CRT) has been a recommended therapy for over 20 years for appropriately selected patients with heart failure (HF), severe left ventricular (LV) systolic dysfunction and a prolonged QRS based on proven improvements in quality of life, LV reverse remodelling and reductions in HF-associated hospitalizations and total mortality.[1–7] Response to CRT has been measured by the clinical composite score (CCS) in previous clinical trials as a composite measure of all-cause mortality, HF events, New York Heart Association (NYHA) class and quality of life, as assessed by a patient global assessment instrument.[8] Response rates using CCS have varied from 50% to 75% depending upon the patient QRS morphology, underlying aetiology and the overall population enrolled in respective clinical trial.[9–19] However, clinical trials may not reflect the HF patients typically treated with CRT in real-world practice whose comorbidities who may be unrepresented due to the specific inclusion and exclusion criteria used.[20] In particular, only 11% and 13% of the recruited patients in MADIT-CRT and RAFT, respectively, had atrial fibrillation (AF).[21,22]

The SMART (Strategic Management to Optimize Response to Cardiac Resynchronization Therapy) registry (NCT03075215) was designed to assess real-world outcomes for patients receiving a CRT defibrillator (i.e., CRT-D) to understand the programming, optimization use, and effectiveness over a 12 month period. The specific design details and baseline demographics have been previously published.[23] Of note, as previously reported, 37% of the enrolled patients had AF at baseline.[23] This paper reports the 12 month results of the SMART registry.

Methods

The SMART registry was a global, multicentre, prospective, observational, single-arm post-market study. Institutional review boards of all participating sites approved the protocol; all patients provided written informed consent prior to enrolment. Oversight and surveillance of study decisions, as well as final data interpretation and manuscript publication, were conducted by a physician steering committee.

The objective of the SMART registry was to characterize patient characteristics, clinical outcomes and response rates in a real-world CRT-D population. To reflect actual rates of comorbidities and patient characteristics that are often excluded in traditional clinical trials, inclusion criteria were broad. Enrolled patients were 18 years or older from the investigators' routine clinical practice and indicated for CRT-D implantation. Patients were implanted with a de novo or 'upgrade' to a Boston Scientific NG3 or NG4 CRT-D device integrated with a quadripolar LV lead from any manufacturer and enrolled within 21 days post-implant. 'Upgrades' were permitted from a single- or dual-chamber pacemaker or implantable cardioverter defibrillator as recommended by contemporary guidelines. Participating centres were chosen based on previous research experience, sufficient implant volume, presence and availability of necessary staff, no unresolved compliance issues and no concurrent conflicting study. Sites were encouraged but not required to enrol consecutive patients to reduce inclusion bias. Exclusion criteria were as follows: life expectancy less than 12 months, currently on the active heart transplantation list and/or implanted with an LV assist device, preexisting CRT device, current pregnancy or possibility of pregnancy at the time of study enrolment, enrolled in any concurrent clinical trial without prior written approval from a Boston Scientific and/or any contraindication to receive a CRT-D device.

Patients had in-clinic visits and were evaluated both at baseline and at 12 months. Clinical response at 12 months, defined by a CCS of all-cause mortality, HF-associated hospitalizations, NYHA class and quality of life as assessed by patient global assessment, categorized patients as either 'improved', 'stabilized' or 'worsened'. Patients with an improved CCS experienced an improvement by at least one NYHA class and/or improved patient global assessment while concurrently remaining alive and free of any HF-associated hospitalization. An HF-associated hospitalization was defined as an HF event with a primary cause of HF and either of the conditions below is met: (1) Patient is admitted and discharged with a calendar date change, or (2) patient is not hospitalized but received one or more IV medications including diuretics, inotropes, vasodilators, other parenteral therapy or aquapheresis. Worsened CCS consisted of experiencing either an HF-associated hospitalization, death due to any cause and/or worsening of the patient global assessment or worsening of at least one NYHA functional class. Patients were considered stabilized if they neither improved nor worsened after 12 months of follow-up.

The primary endpoint of CRT response was analysed when the last 12 month patient visit was completed. This analysis included the following to define response and nonresponse groupings, as based of the three CCS levels:

- Clinical endpoint 1: improved CCS versus stabilized or worsened CCS;
- Clinical endpoint 2: improved or stabilized CCS versus worsened CCS.

All patient visits and NYHA assessments were performed by qualified study staff at participating medical centres. A subset of the enrolled patients (n = 1189) utilized LATITUDE remote monitoring and had their atrial and ventricular pacing percentages calculated post-implant (i.e., between 1 and 21 days after CRT-D implantation) and at 12 months.

Prolonged LV delay (QRS-LV) and longer interventricular electrical delay (RV-LV) have been shown to be independent predictors of improved CRT response.[10,24] The QRS-LV was defined as the first deflection of the surface ECG to local intrinsic activation at the LV stimulation site. It was measured in sinus rhythm by taking measurements from surface lead II and the RV and LV leads simultaneously as the interval from the onset of QRS from the surface lead to the first large peak (positive or negative) of the LV electrogram. The RV-LV interval was defined as the difference in activation time as measured by the RV and LV leads. It was measured in sinus rhythm as the first major peaks of the RV and LV electrograms in a cardiac cycle. Leads were placed at the discretion of the implanting physician.

Statistical analysis

Baseline demographics and clinical characteristics are presented as mean ± standard deviation (*SD*); categorical values presented as counts (% of total patients). Patients were stratified according to CCS outcome, specifically, Improved, stabilized or worsened. Differences in continuous and categorical demographics between the three CCS outcome groups were assessed via an F test and a χ^2 or exact test, respectively.

CRT response, quantified by CCS, was calculated in the full SMART registry patient population, as well as in selected subgroups. Clinical endpoint 1 categorized responders as the patients with Improved CCS. Clinical endpoint 2 characterized responders as either improved or stabilized CCS. Multivariable analyses were performed through logistic regression models on prespecified and unspecified variables on the primary endpoint and included both a priori and post-hoc analysis. No adjustments to the significance level (alpha) were made for multiple tests. Results interpretation was based on the biological plausibility of the result along with consistency of findings from external sources.

Prespecified variables were chosen based on known subgroup associations with CRT response based on data from previous clinical studies.[2,4,10,24] Per protocol, these variables included ischaemic aetiology (ischaemic vs. non-ischaemic), bundle branch block morphology [left bundle branch block (LBBB) vs. non-LBBB], NYHA class (I/II vs. III/IV), presence of AF (yes vs. no), diabetes mellitus (yes vs. no), sex (male vs. female), age (<65 vs. ≥65 years), RV-LV (<70 vs. ≥70 ms), QRS-LV at the implantation site and QRS width (<150 vs. ≥150 ms).

Time to event analysis compared HF-associated hospitalization and all-cause mortality across AF versus non-AF groups using Kaplan–Meier methodology. Patients followed through 12 months or who had a primary endpoint even (HF hospitalization or death) were considered to have complete data. Patients withdrawn during the follow-up period without experiencing an endpoint event were considered to have missing data. Due to COVID-19, data from remote follow-up visits were considered equal to data from onsite visits. Patients that died or withdrew from the study without experiencing HF-associated hospitalization before the 12 month visit were censored on the death date or withdraw date; P values were from the log-rank test and hazard ratios from the univariate Cox proportional hazard regression model.

To obtain a two-sided 95% confidence interval of the CRT response rate that did not exceed 5%, a total of 2000 enrolments were required. It was expected that, with a total of 2000 enrolments, each subgroup analysis would include approximately 50 subjects. No formal hypotheses were tested for the primary endpoint.

Results

Patient disposition and characteristics

The registry enrolled 2035 patients from April 2017 until August 2019 at 137 sites from the United States, Europe, Canada and Australia. Of those, 2005 subjects met all the inclusion and none of the exclusion criteria. These subjects were followed per standard of care for 12 months (average ± *SD*: 12.0 ± 3.5 months as of last data snapshot on 2 June 2022). The majority (77.4%) of 12 month follow-up visits were performed prior to the COVID-19 pandemic. The follow-up visit compliance (i.e., number of completed follow-up visits relative to the number of scheduled follow-up visits) was 79.1%. During the pandemic, there was an increase in late visits (post- vs. pre-pandemic: 26% vs. 13%), as well as missed visits/withdrawals (25% vs. 18%).

Patients were predominately male (77.0%) and White (61.3%). The average LV ejection fraction (LVEF) was 29.6 ± 7.9%, and age at enrolment was 67.5 ± 10.4 years. Although the average QRS width was 150.2 ± 27.5 ms, only 62.0% had LBBB QRS morphology at baseline (*Table* 1). Non-specific interventricular conduction delay (NSIVCD) and right bundle branch block (RBBB) were noted in 24.8% and 13.1% of patients, respectively. There was a relatively high combined prevalence of asymptomatic (NYHA class I: 5.4%)

Table 1 SMART registry baseline demographics and clinical characteristics.

Measurement	*N*	Overall	Improved	Stabilized	Worsened	*P* value
Mean age at enrolment ± SD, years (range)	2005	67.5 ± 10.4 (24.0–92.0)	66.9 ± 10.2 (24.0–92.0)	68.9 ± 10.1 (32.0–87.0)	69.1 ± 10.4 (30.0–90.0)	<0.001
Sex, *n* (%)	2005					0.12
Male		1543 (77.0%)	699 (76.1%)	252 (80.8%)	264 (80.2%)	
Female		462 (23.0%)	219 (23.9%)	60 (19.2%)	65 (19.8%)	
Race, *n* (%)	2005					0.96
White		1230 (61.3%)	582 (63.4%)	207 (66.3%)	207 (62.9%)	
Black		86 (4.3%)	46 (5.0%)	13 (4.2%)	15 (4.6%)	
Other		17 (0.8%)	5 (0.5%)	1 (0.3%)	2 (0.6%)	
Race not disclosed		672 (33.5%)	285 (31.0%)	91 (29.2%)	105 (31.9%)	
NYHA class, *n* (%)	1943					<0.001
Class I		104 (5.4%)	36 (3.9%)	8 (2.6%)	42 (13.0%)	
Class II		892 (45.9%)	420 (45.8%)	184 (59.0%)	116 (35.8%)	
Class III		907 (46.7%)	446 (48.6%)	116 (37.2%)	157 (48.5%)	
Class IV		40 (2.1%)	16 (1.7%)	4 (1.3%)	9 (2.8%)	
Left ventricular ejection fraction ± *SD*, % (range)	336	29.6 ± 7.9 (9.0–60.0)	29.3 ± 7.6 (14.0–55.0)	30.6 ± 8.3 (9.0–51.0)	30.2 ± 7.6 (10.0–48.0)	0.53
Ischaemic aetiology	2004	1005 (50.1%)	426 (46.4%)	177 (56.7%)	188 (57.1%)	<0.001
PR interval ± *SD*, ms (range)	907	166.0 ± 47.2 (0.0–648.0)	163.7 ± 41.4 (0.0–296.0)	166.3 ± 40.5 (3.0–280.0)	172.2 ± 63.0 (0.0–648.0)	0.16
QRS width ± *SD*, ms (range)						
Intrinsic	693	150.2 ± 27.5 (50.0–269.0)	149.2 ± 28.5 (50.0–269.0)	148.2 ± 24.4 (65.0–208.0)	151.0 ± 25.9 (72.0–200.0)	0.75
Paced	564	151.1 ± 27.7 (56.0–322.0)	151.4 ± 27.6 (70.0–259.0)	152.6 ± 28.0 (56.0–244.0)	151.4 ± 26.9 (74.0–250.0)	0.93
QRS morphology (bundle branch block morphology), *n* (%)	1051					0.023
Left bundle branch block		652 (62.0%)	322 (64.3%)	84 (56.4%)	96 (54.2%)	
Right bundle branch block		138 (13.1%)	55 (11.0%)	29 (19.5%)	30 (16.9%)	
Non-specific interventricular conduction delay		261 (24.8%)	124 (24.8%)	36 (24.2%)	51 (28.8%)	
Sinus rhythm, *n* (%)	1304	517 (39.6%)	250 (40.6%)	65 (34.9%)	80 (35.9%)	0.25
Bradycardia, *n* (%)	2004	623 (31.1%)	282 (30.7%)	109 (34.9%)	114 (34.7%)	0.24
Atrial fibrillation, *n* (%)	746					0.30
Paroxysmal		332 (44.5%)	135 (44.1%)	58 (52.3%)	65 (40.1%)	
Persistent		191 (25.6%)	82 (26.8%)	23 (20.7%)	50 (30.9%)	
Permanent		223 (29.9%)	89 (29.1%)	30 (27.0%)	47 (29.0%)	
Diabetes mellitus, *n* (%)	1983	689 (34.7%)	290 (31.8%)	121 (39.0%)	139 (42.5%)	<0.001
Chronic pulmonary disease, *n* (%)	1957	314 (16.0%)	140 (15.6%)	43 (14.1%)	70 (21.8%)	0.015
Renal dysfunction, *n* (%)	2004	470 (23.5%)	198 (21.6%)	75 (24.0%)	120 (36.5%)	<0.001
Medications, *n* (%)						
Angiotensin-converting enzyme (ACE) inhibitors	2005	880 (43.9%)	413 (45.0%)	144 (46.2%)	125 (38.0%)	0.057
Angiotensin II receptor blockers (ARB) inhibitors)	2005	365 (18.2%)	160 (17.4%)	57 (18.3%)	55 (16.7%)	0.87
ARB/ACE	1994	1244 (62.4%)	573 (62.8%)	201 (64.6%)	180 (55.2%)	0.025
Angiotensin receptor neprilysin inhibitor (ARNI)	1994	417 (20.9%)	215 (23.5%)	56 (18.0%)	67 (20.6%)	0.10
ACE/ARB/ARNI	1994	1654 (82.9%)	785 (61.0%)	255 (19.8%)	246 (19.1%)	<0.001
Beta blockers	2005	1746 (87.1%)	811 (88.3%)	269 (86.2%)	280 (85.1%)	0.27
Mineralocorticoid receptor antagonists	1994	1004 (50.4%)	493 (54.0%)	148 (47.6%)	144 (44.2%)	0.005
Diuretics	2005	1406 (70.1%)	632 (68.8%)	211 (67.6%)	262 (79.6%)	0.001
Digoxin	2005	128 (6.4%)	55 (6.0%)	22 (7.1%)	28 (8.5%)	0.29
CRT Implant, *n* (%)	2002					<0.001
De novo		1578 (78.8%)	755 (82.2%)	240 (76.9%)	236 (71.7%)	
Upgrade		422 (21.1%)	163 (17.8%)	71 (22.8%)	93 (28.3%)	
Replace		2 (0.1%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	

(*Continues*)

Table 1 (continued)

Measurement	*N*	Overall	Improved	Stabilized	Worsened	*P* value
Pacing Chamber, *n* (%)	2002					0.97
BiV		1700 (84.9%)	776 (84.5%)	265 (84.9%)	277 (84.2%)	
LV-only		302 (15.1%)	142 (15.5%)	47 (15.1%)	52 (15.8%)	
Atrial pacing ± *SD*, % (range)	839	27.0 ± 33.2 (0.1–100.0)	25.7 ± 32.7 (0.1–100.0)	30.7 ± 33.1 (0.1–100.0)	29.2 ± 36.1 (0.1–100.0)	0.28
Ventricular pacing ± *SD*, % (range)	1189	94.2 ± 14.0 (0.1–100.0)	94.7 ± 13.2 (1.2–100.0)	95.4 ± 9.9 (21.5–100.0)	91.9 ± 17.1 (0.1–100.0)	0.022
QRS-LV Site, *n* (%)	1440					0.42
Apical		91 (6.3%)	43 (6.3%)	9 (4.0%)	15 (6.4%)	
Middle		281 (19.5%)	122 (17.9%)	36 (16.0%)	49 (20.8%)	
Basal		1068 (74.2%)	518 (75.8%)	180 (80.0%)	172 (72.9%)	

Note: Continuous values presented as mean ± *SD* and range (minimum–maximum); categorical values presented as number of patients (% of total). Patients may contribute to more than one category for some variables. Clinical composite score, categorized as either improved (n = 917), stabilized (n = 313) or worsened (n = 328), was assessed at the 12 month follow-up visit in 1560 patients. Differences in patient baseline demographics were stratified across CCS groups. Ventricular pacing (%) assessed at the initial post-implant clinic visit. *P* values for continuous and categorical variables are from *F*-test and χ^2 test, respectively.

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BiV; biventricular; CCS, clinical composite score; HF, heart failure; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; NSIVCD, non-specific interventricular conduction delay; NYHA, New York Heart Association; RBBB, right bundle branch block.

and mildly symptomatic (NYHA class II: 45.9%) patients, as well as high prevalence of diabetes mellitus (34.7%) and AF (37.2%) at baseline. Of the 746 patients in AF, 44.5% had paroxysmal, 25.6% had persistent and 29.9% had permanent AF.

Of the total cohort, 1,578 (78.8%) patients underwent a de novo implant procedure, and 422 (21.1%) patients underwent an 'upgrade' procedure. Patients could be programmed to biventricular pacing or pacing of only the LV, for example where the physician wished to preserve intrinsic stimulation. Of the patients, 1710 (84.9%) were programmed to biventricular pacing at the baseline visit, and 302 patients (15.1%) had LV-only pacing. The initial post-implant percentage of ventricular pacing was only 94.2 ± 14.0% in the total cohort while the average atrial pacing was 27.0 ± 33.2%.

CCS

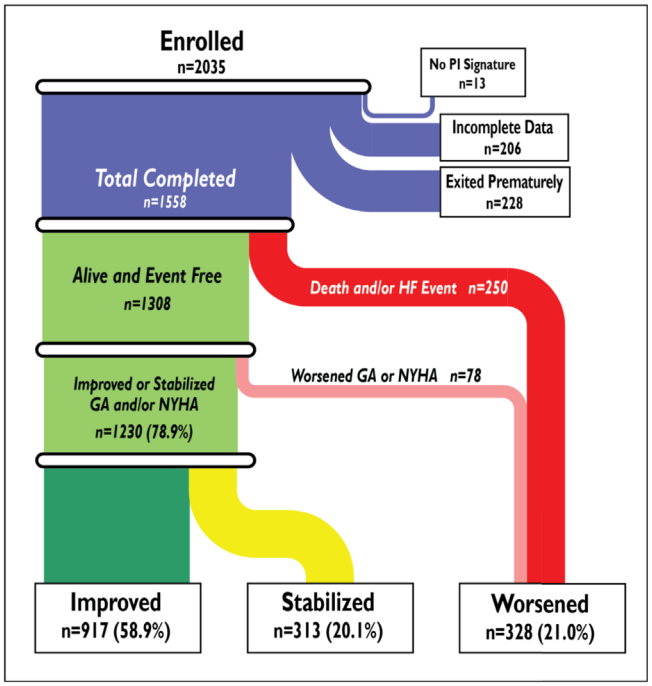
There were 1558 patients with completed CCS outcomes. Of the patients, 917 (58.9%) had improved CCS outcomes at 12 months; 313 (20.1%) and 328 (21.0%) patients stabilized and worsened, respectively (*Figure* 1). Among the improved CCS patients, 375 patients (24.1%) improved in both patient global assessment and NYHA class. Of the patients, 359 (23.0%) exclusively had improvements in the patient global assessment; 184 patients (11.8%) had improved NYHA class only. Worsened CCS predominately reflected clinical events (250 patients, 76.2%): specifically, HF hospitalization alone (119 patients, 7.6%), death without antecedent worsening of HF (87 patients, 5.6%) or death preceded by an HF hospitalization (44 patients, 2.8%). The remaining 78 patients (5.0%) remained event-free, but experienced either worsening NYHA class (71 patients, 4.6%), worsening global assessment (4 patients, 0.3%), or both (3 patients, 0.2%).

There were no significant differences across the three CCS groups with regard to sex (P = 0.12), race (P = 0.96), LVEF (P = 0.53), intrinsic QRS width (P = 0.75), and baseline PR interval (P = 0.16) (*Table* 1). QRS morphology was different across the CCS groups (P = 0.02); specifically, patients with LBBB conduction had a higher likelihood of improved CCS (64.3%) as compared with RBBB (11.0%) and NSIVCD (24.8%). As expected, patients with Worsened CCS outcomes also had lower (P = 0.02) percentages of ventricular pacing at the initial post-implant clinic visit (91.9 ± 17.1%) as compared with patients with Improved (94.7 ± 13.2%) and Stabilized (95.4 ± 9.9%) CCS outcomes (*Table 1*; Supplemental Information, *Table 1*).

Clinical endpoints and defining CRT response—Improved CCS

When analysing CCS as defined by Clinical endpoint 1, 58.9% of patients were CRT responders with improved CCS, and

Figure 1 SMART registry enrolment. GA, global assessment; HF, heart failure; NYHA, New York Heart Association; PI, principal investigator.



41.1% were non-responders with either stabilized or worsened CCS. Unadjusted odds of Improved CCS are presented in *Figure* 2A. Younger age (i.e., <65 years old; $P = 0.004$) and LBBB QRS morphology ($P = 0.01$) were associated with increased odds of Improved CCS. Increased odds of either worsened or stabilized CCS were associated with male sex ($P = 0.04$), diabetes mellitus ($P < 0.001$), ischaemic aetiology ($P < 0.001$), AF ($P < 0.001$) and renal dysfunction ($P < 0.001$). In multivariable analysis, LBBB QRS morphology ($P = 0.02$) was associated with increased odds of improved CCS. NYHA class I/II ($P = 0.004$), diabetes mellitus ($P = 0.04$) and ischaemic aetiology ($P = 0.004$) had lower odds of Improved CCS (*Table* 2).

Clinical endpoints and defining CRT response—Improved or stabilized CCS

When analysing CCS as defined by Clinical endpoint 2, 79.0% were CRT responders with either improved or stabilized CCS, and 21.0% were non-responders with worsened CCS. Younger age ($P = 0.04$) and LBBB QRS morphology ($P = 0.05$) were associated with higher odds of improved or stabilized CCS. Significantly lower odds of improved or stabilized CCS were associated with diabetes mellitus ($P = 0.003$), ischaemic aetiology ($P = 0.008$), AF ($P < 0.001$), RV-LV electrical delay <70 ms ($P = 0.02$) and renal dysfunction ($P < 0.001$) (*Figure* 2B). With multivariable adjustment, lower odds of improved or stabilized CCS persisted for ischaemic aetiology ($P = 0.01$), AF ($P = 0.03$) and renal dysfunction ($P = 0.02$) (*Table* 2).

Time-to-event analysis—HF-associated hospitalizations and all-cause mortality rates

The HF hospitalization-free rate at 12 months was 91.6% (95% CI: 90.3%, 92.8%) using Kaplan–Meier methodology. *Table* 3 presents univariate factors associated with HF hospitalization. The presence of comorbidities such as diabetes mellitus ($P < 0.001$) and AF ($P < 0.001$) were associated with increased HF hospitalization rates, as was heart disease of ischaemic aetiology ($P = 0.036$). Patients with intrinsic RV-LV intervals <70 ms ($P = 0.009$), non-LBBB QRS morphology ($P = 0.013$) and NYHA class III/IV ($P < 0.001$) were also associated with an increased likelihood of HF hospitalization.

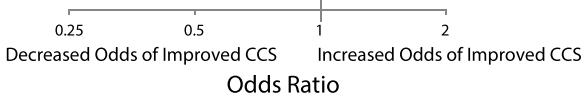
There were 131 deaths from all causes that occurred during the initial 12 months of follow-up (until the visit window close date). All-cause survival at 12 months was estimated at 93.4% (95% CI: 92.2%, 94.4%). Male sex ($P = 0.018$), NYHA class III/IV ($P < 0.0001$), diabetes mellitus ($P = 0.006$), AF ($P < 0.001$) and ischaemic aetiology ($P = 0.003$) were associated with worsened survival (*Table* 3).

Figure 2 (A) Impact of specific individual baseline risk factors on Clinical endpoint 1—improved CCS. (B) Impact of specific individual baseline risk factors on Clinical endpoint 2—improved/stabilized CCS. AF, atrial fibrillation; CCS, clinical composite score; LBBB, left bundle branch block.

A

Clinical Endpoint 1

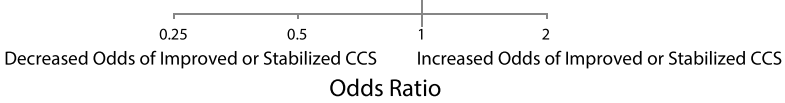
Comparison	OR	95% CI	P-value
Age <65 (vs >= 65)	1.38	(1.11-1.71)	0.004
Sex Male (vs Female)	0.77	(0.60-0.99)	0.043
NYHA Class I/II (vs III/IV)	0.80	(0.66-0.98)	0.035
Diabetes Present (vs Absent)	0.67	(0.55-0.83)	<.001
Ischemic Etiology Present (vs Absent)	0.65	(0.53-0.80)	<.001
LBBB (vs Non-LBBB)	1.38	(1.07-1.78)	0.012
AF (vs Non-AF)	0.67	(0.55-0.83)	<.001
QRS Width <150ms (vs >=150ms)	0.95	(0.66-1.34)	0.754
RV-LV Electrical Delay <70ms (vs >=70ms)	0.70	(0.48-1.02)	0.063
QRS-LV Site Basal/Middle (vs Apical)	0.82	(0.49-1.37)	0.442
Renal Dysfunction Present (vs Absent)	0.63	(0.50-0.79)	<.001



B

Clinical Endpoint 2

Comparison	OR	95% CI	P-value
Age <65 (vs >= 65)	1.32	(1.01-1.72)	0.042
Sex Male (vs Female)	0.84	(0.62-1.14)	0.267
NYHA Class I/II (vs III/IV)	1.16	(0.91-1.49)	0.228
Diabetes Present (vs Absent)	0.68	(0.53-0.87)	0.003
Ischemic Etiology Present (vs Absent)	0.72	(0.56-0.92)	0.008
LBBB (vs Non-LBBB)	1.35	(1.00-1.82)	0.050
AF (vs Non-AF)	0.53	(0.41-0.67)	<.001
QRS Width <150ms (vs >=150ms)	1.22	(0.80-1.84)	0.353
RV-LV Electrical Delay <70ms (vs >=70ms)	0.57	(0.36-0.91)	0.018
QRS-LV Site Basal/Middle (vs Apical)	1.12	(0.62-2.02)	0.714
Renal Dysfunction Present (vs Absent)	0.49	(0.38-0.64)	<.001



Post hoc analysis—Hospitalizations, all-cause mortality and ventricular pacing in AF patients

Patients with and without AF were stratified into LBBB and non-LBBB status and CCS was assessed (Supporting Information, *Table* 3 and *Figure* 3). LBBB patients without AF had lower rates of a Worsened CCS (16.4%) over LBBB or non-LBBB patients with AF (25.0% or 27.4%). Kaplan–Meier curves for HF-associated hospitalizations and all-cause mortality across AF versus non-AF groups are presented in *Figure* 4A,B, as well as AF and non-AF stratified by LBBB status in *Figure* 4C,D. Of LBBB patients without AF, 92.5% were free of HF-associated hospitalization compared with 81.4% of non-LBBB patients with AF ($P < 0.001$). Mortality was also significantly different between subgroups with 94.7% of LBBB non-AF patients and 89.9% of non-LBBB AF patients surviving at the end of the 12 month follow-up period ($P = 0.019$).

The worsening clinical outcomes in patients in AF could be attributable to, in part, lower percentages of ventricular pacing ($P < 0.001$) as compared with patients in sinus rhythm at both baseline and at the 12 month follow-up visit (Supporting Information, *Table* 2). Significant differences in percentages of ventricular pacing were observed irrespective of AF pattern ($P < 0.001$), but patients with persistent/permanent AF had the lowest percentage of ventricular pacing (87.2 ± 21.8%); ventricular pacing for paroxysmal AF was 94.4 ± 14.7% ($P < 0.001$).

Table 2 Multivariable modelling—odds of CRT response.

Clinical endpoint 1—Improved CCS versus stabilized or worsened CCS					
Multivariable modelling—*a priori analysis*	OR (95% CI)	*P* value	Multivariable modelling—*post-hoc analysis*	OR (95% CI)	*P* value
NYHA class (class I/II vs. class III/IV)	0.69 (0.53, 0.89)	0.004	NYHA class (class I/II vs. class III/IV)	0.64 (0.49, 0.83)	<0.001
Diabetes (yes vs. no)	0.75 (0.57, 0.99)	0.041	Diabetes (yes vs. no)	0.74 (0.56, 0.98)	0.034
Ischaemic aetiology (ischaemic vs. non-ischaemic)	0.68 (0.52, 0.88)	0.004	Ischaemic aetiology (ischaemic vs. non-ischaemic)	0.69 (0.53, 0.90)	0.006
Left bundle branch block (LBBB vs. non-LBBB)	1.36 (1.05, 1.76)	0.019	Left bundle branch block (LBBB vs. non-LBBB)	1.37 (1.05, 1.78)	0.019
Renal dysfunction (yes vs. no)	0.78 (0.58, 1.06)	0.12	Renal dysfunction (yes vs. no)	—	—
Mineralocorticoid receptor antagonists (yes vs. no)	—	—	Mineralocorticoid receptor antagonists (yes vs. no)	1.40 (1.08, 1.82)	0.012
ACE/ARB/ARNI (ACE/ARB alone vs. other)[a]	—	—	ACE/ARB/ARNI (ACE/ARB alone vs. other)[a]	1.29 (0.89, 1.86)	0.18
ACE/ARB/ARNI (ARNI alone vs. other)[a]	—	—	ACE/ARB/ARNI (ARNI alone vs. other)[a]	1.55 (1.01, 2.39)	0.044
Diuretics (yes vs. no)	—	—	Diuretics (yes vs. no)	0.79 (0.59, 1.06)	0.11
Clinical endpoint 2—Improved or stabilized CCS versus worsened CCS					
Multivariable modelling—*a priori analysis*	OR (95% CI)	*P* value	Multivariable modelling—*post-hoc analysis*	OR (95% CI)	*P* value
Ischaemic aetiology (ischaemic vs. non-ischaemic)	0.67 (0.49,0.91)	0.010	Ischaemic aetiology (ischaemic vs. non-ischaemic)	0.70 (0.51,0.95)	0.024
Left bundle branch block (LBBB vs. non-LBBB)	1.28 (0.95,1.74)	0.11	Left bundle branch block (LBBB vs. non-LBBB)	1.28 (0.94,1.75)	0.11
Atrial fibrillation (yes vs. no)	0.71 (0.52,0.97)	0.033	Atrial fibrillation (yes vs. no)	0.81 (0.59,1.11)	0.18
Renal dysfunction (yes vs. no)	0.67 (0.48,0.94)	0.021	Renal Dysfunction (yes vs. no)	0.73 (0.52,1.03)	0.076
Mineralocorticoid receptor antagonists (yes vs. no)	—	—	Mineralocorticoid receptor antagonists (yes vs. no)	1.55 (1.13,2.11)	0.006
ACE/ARB/ARNI (ACE/ARB alone vs. other)[a]	—	—	ACE/ARB/ARNI (ACE/ARB alone vs. other)[a]	1.42 (0.94,2.15)	0.094
ACE/ARB/ARNI (ARNI alone vs. other)[a]	—	—	ACE/ARB/ARNI (ARNI alone vs. other)[a]	1.30 (0.80,2.12)	0.28
Diuretics (yes vs. no)	—	—	Diuretics (yes vs. no)	0.61 (0.42,0.88)	0.009

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CCS, clinical composite score; CI, confidence interval; LBBB, left bundle branch block; NYHA, New York Heart Association; OR, odds ratio.

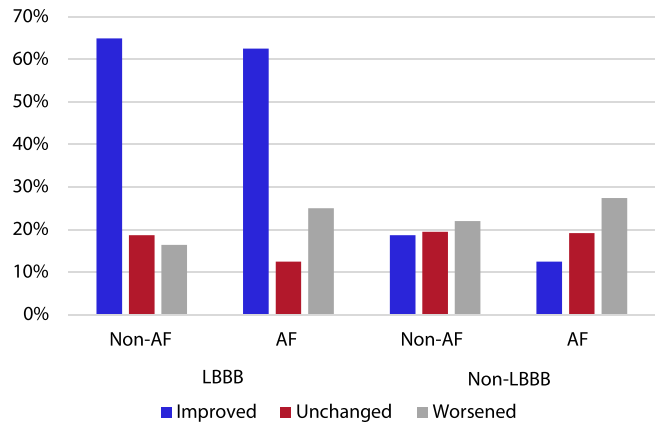
[a]Other represents subset of patients not prescribed ACE, ARB, and ARNI.

Table 3 Univariate factors associated with all-cause mortality survival rate and heart failure hospitalization free rate.

Variable	All-cause mortality survival rate	HR (95% CI)	*P* value	HF hospitalization free rate	HR (95% CI)	*P* value
Age						
Age < 65 years	95.8%	0.54 (0.35, 0.81)	0.003	94.6%	0.53 (0.36, 0.76)	<0.001
Age ≥ 65 years	92.2%			90.0%		
Sex						
Female	95.9%	0.56 (0.34, 0.91)	0.018	93.2%	0.76 (0.52, 1.14)	0.19
Male	92.7%			91.2%		
NYHA class						
I–II	95.3%	0.53 (0.37, 0.76)	<0.001	94.6%	0.45 (0.33, 0.63)	<0.001
III–IV	91.3%			88.5%		
Diabetes						
Present	91.4%	1.62 (1.14, 2.29)	0.006	88.2%	1.81 (1.33, 2.46)	<0.001
Absent	94.6%			93.4%		
Ischaemic aetiology						
Ischaemic	91.8%	1.70 (1.19, 2.42)	0.003	90.3%	1.39 (1.02, 1.90)	0.036
Non-ischaemic	95.1%			93.0%		
QRS morphology						
LBBB	94.1%	0.88 (0.57, 1.36)	0.56	93.0%	0.62 (0.42, 0.90)	0.013
Non-LBBB	93.4%			89.1%		
AF						
Present	89.6%	2.48 (1.75, 3.52)	<0.001	87.7%	2.17 (1.59, 2.94)	<0.001
Absent	95.7%			93.4%		
QRS duration						
<150 ms	94.0%	0.77 (0.43, 1.37)	0.37	90.9%	0.88 (0.54, 1.44)	0.61
≥150 ms	92.2%			89.6%		
RV-LV duration						
<70 ms	92.9%	1.42 (0.73, 2.78)	0.31	89.8%	2.35 (1.23, 4.49)	0.009
≥70 ms	95.0%			95.5%		
LV lead position						
Apical	92.3%	1.20 (0.56, 1.20)	0.63	90.8%	1.14 (0.56, 2.33)	0.72
Non-apical	93.5%			92.0%		

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association; RV, right ventricular.

Figure 3 Clinical composite score stratified by bundle branch block and atrial fibrillation status. AF, atrial fibrillation; LBBB, left bundle branch block.

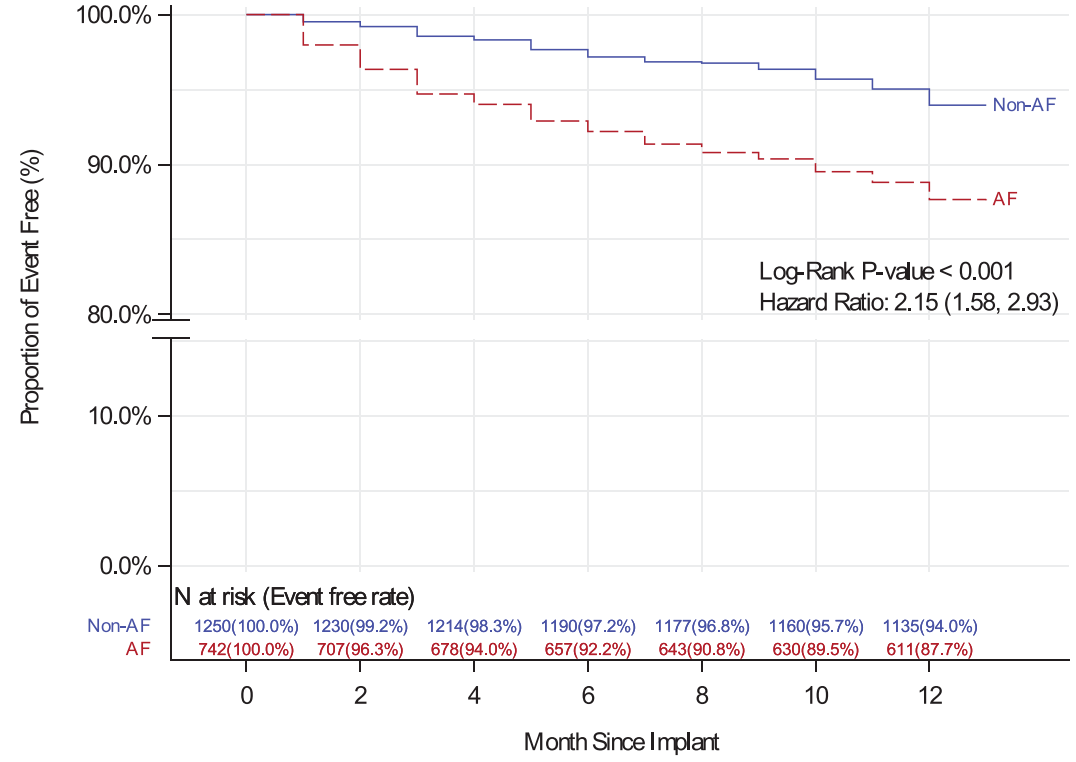


Discussion

The SMART registry was designed to determine the rate of response to CRT therapy in a real-world experience, in which the implanted population would more accurately represent CRT-D patients compared with what has been seen in clinical trials, providing insight into responder rates in under-represented individuals. The comparison of enrolment in the SMART registry to past CRT approval studies, along with the use of guideline recommended drug therapy, has been previously reported.[23] As intended, the SMART registry reflected a real-world population with a high prevalence of comorbidities including AF, renal dysfunction, diabetes mellitus and ischaemic heart disease.

Detailed analysis of the CCS revealed patients that improved were more likely to be younger (i.e., <65 years of

Figure 4 (A) Kaplan–Meier for HF- associated hospitalizations across AF versus non-AF groups. (B) Kaplan–Meier for all-cause mortality across AF versus non-AF groups. (C) Kaplan–Meier for HF-associated hospitalizations across AF non-LBB versus non-AF LBBB groups. (D) Kaplan–Meier for all-cause mortality across AF versus non-AF groups. AF, atrial fibrillation; HF, heart failre; LBBB, left bundle branch block.



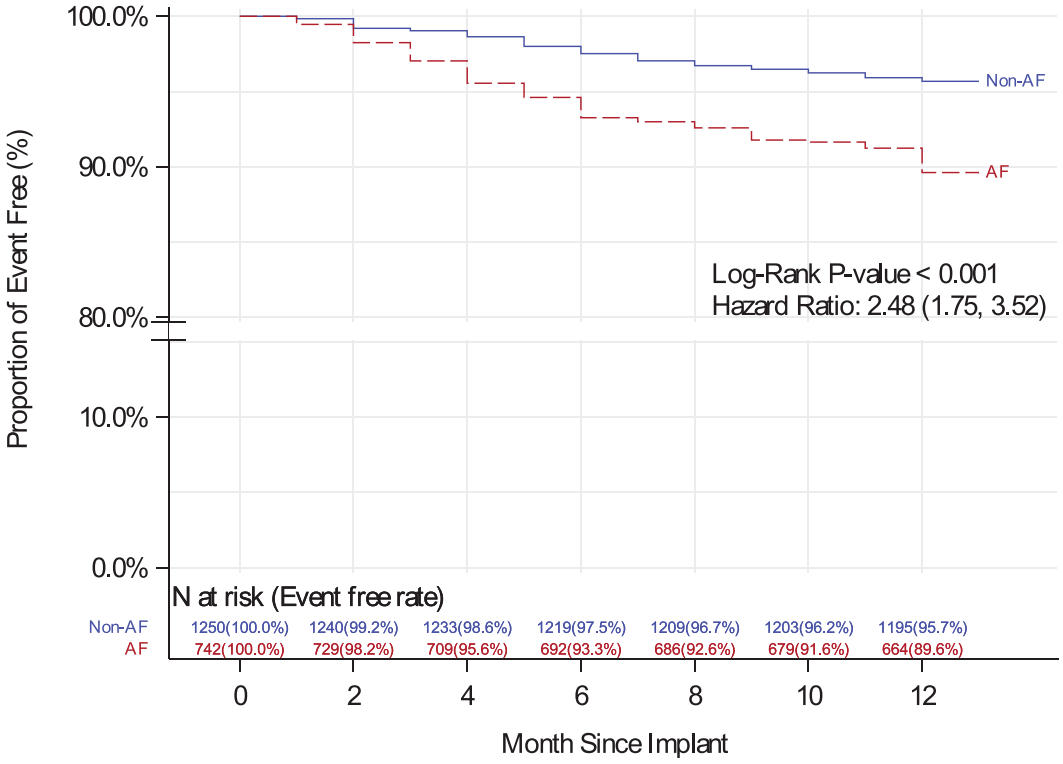


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Figure 4 Continued

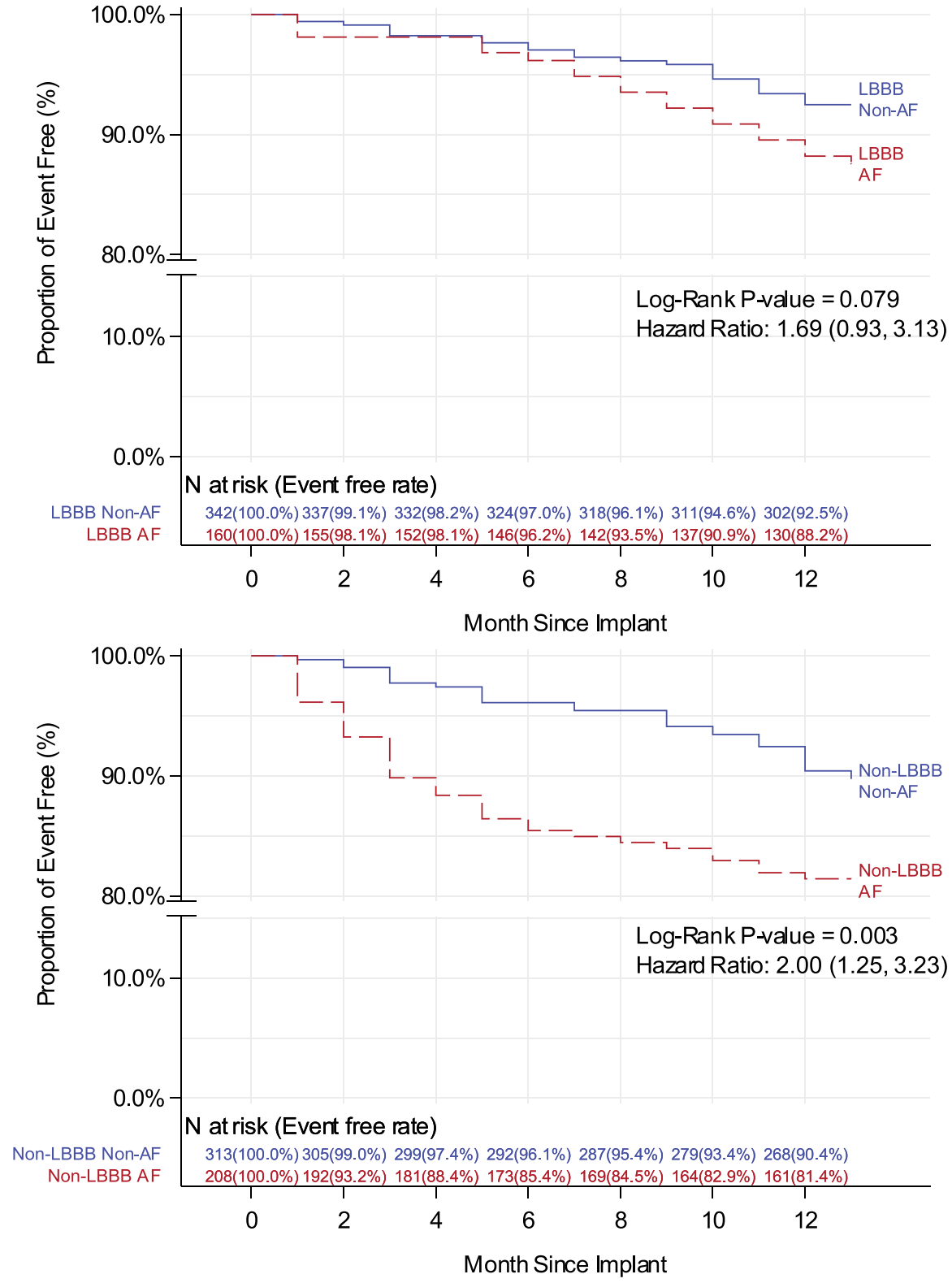
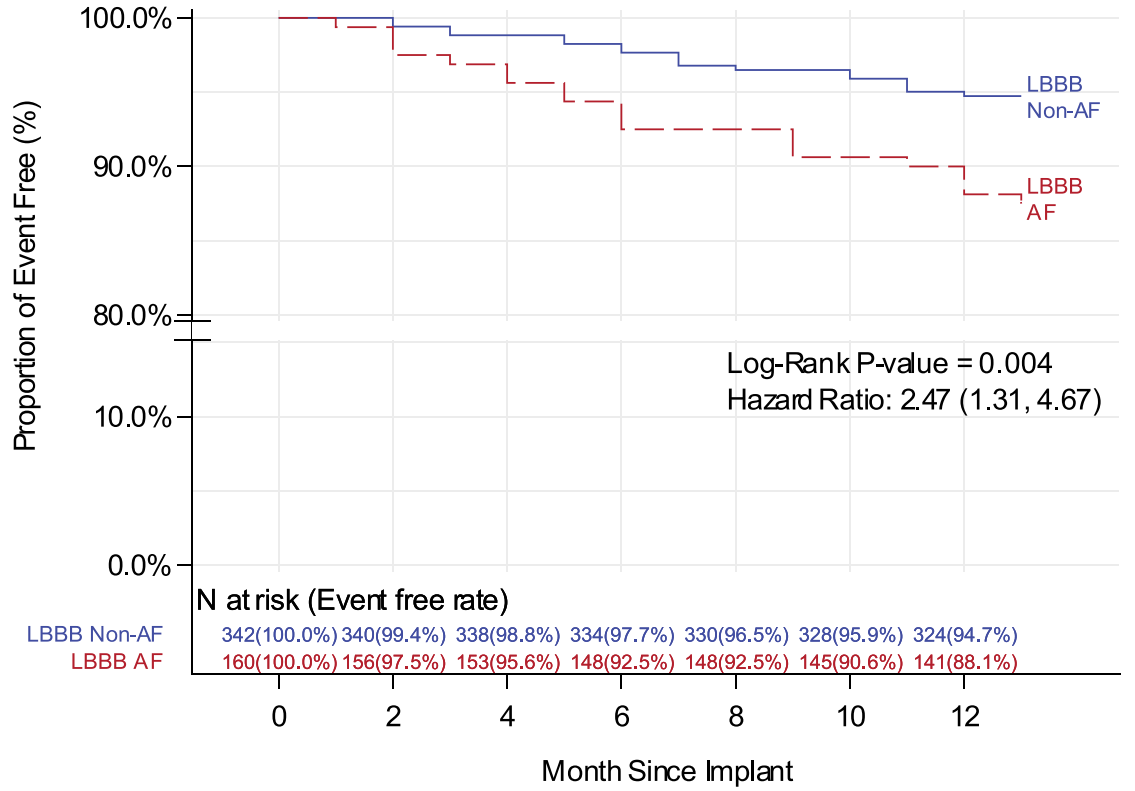


Figure 4 Continued



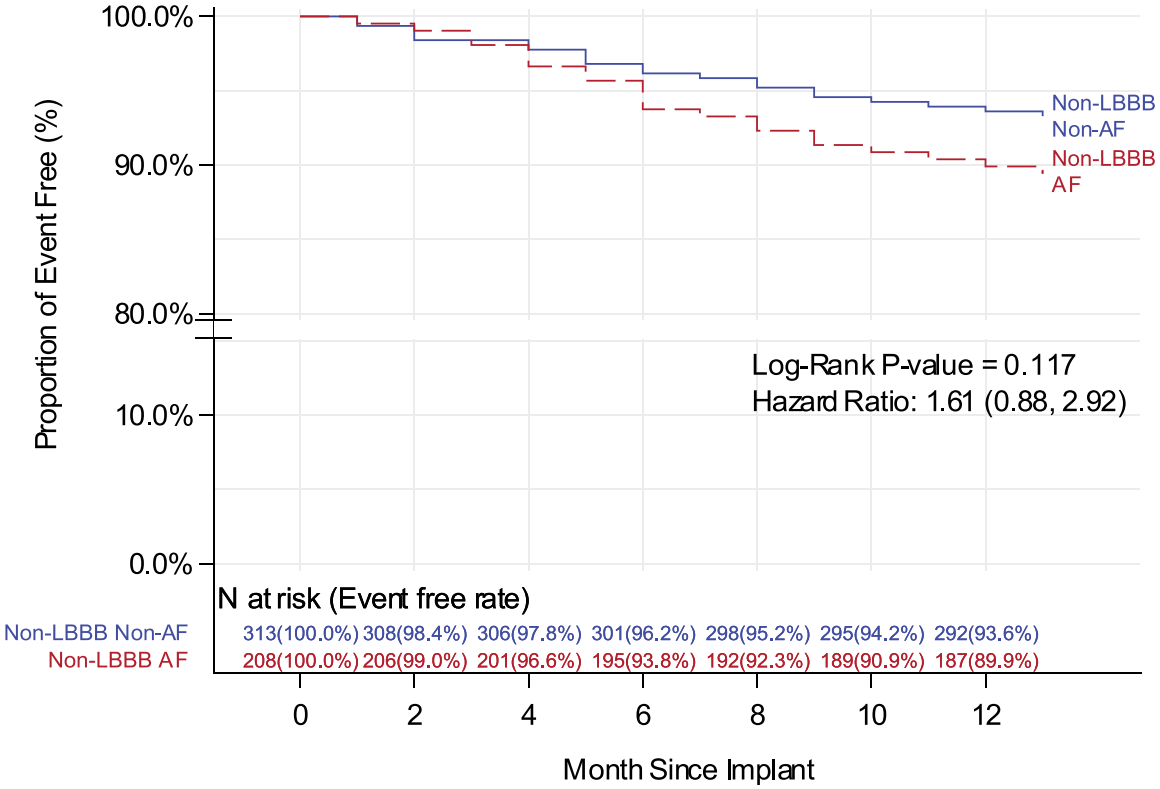
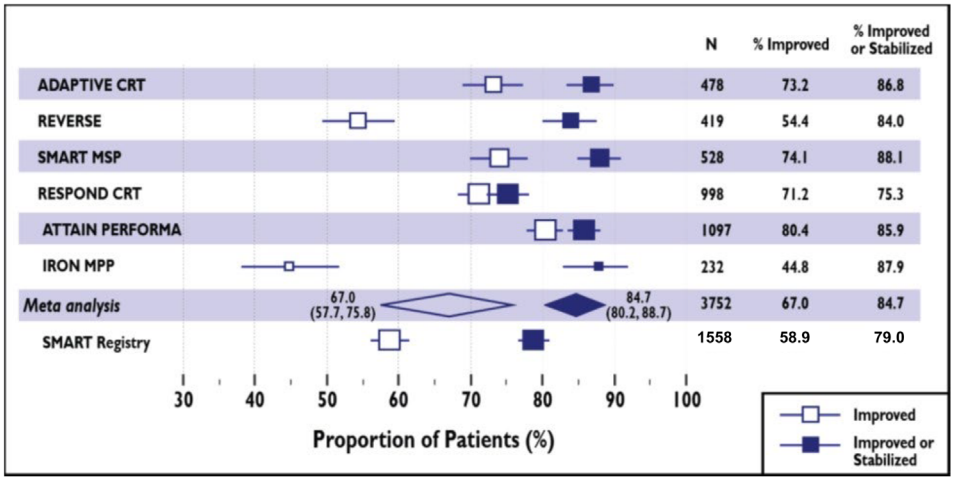


Figure 5 Comparison of response rates, defined by improved or improved/stabilized clinical composite score, across landmark cardiac resynchronization therapy trials and registries.



age) and to have LBBB QRS morphology. In contrast, those that tended to worsen were more likely to be men or have comorbidities such as diabetes mellitus, AF and renal dysfunction, as well as have HF of an ischaemic aetiology (*Figure* 2A,B). *Figure* 5 presents a comparison of CRT response, as defined by both improved or improved/stabilized CCS outcomes, in the SMART registry and across landmark clinical trials and registries. Lower clinical response rates in SMART registry are attributed to differences in patient demographics from the foundational clinical trials, which collectively excluded either persistent/permanent atrial arrhythmias.[14,25,26] The prognostic importance of comorbidities in CRT patients is established in the literature.[27,28] Patients with comorbidities are perhaps unsurprisingly less likely to have robust responses to CRT than patients without comorbidities. As this was a non-interventional study, the association can thus be noted, but not further explained, and its main significance is the finding that additional research must continue to be performed to accurately determine evidence-based recommendations for management of these patients.

Current CRT guidelines are largely based on the results of randomized clinical trials that predominately enrolled a patient population in sinus rhythm with LBBB conduction, and this is reflected in the strongest weighting of recommendation in those with the broadest LBBB.[7] In particular, the percentage of LBBB conduction was 77%, 81%, 86% and 72% in ADAPTIVE,[29] SMART MSP,[26] RESPOND-CRT[14] and ATTAIN PERFORMA,[30] respectively. Only 62% of the enrolled patients had LBBB conduction in SMART registry. IRON-MPP[31] was an observational Italian registry; the lower rates of improved CCS outcomes, relative to the randomized clinical trials, could be traced to the inclusion of AF (23% of enrolled patients) and NYHA class II–IV patients. The 37% of enrolled patients in SMART registry with AF is similar to what is observed in other large, contemporary registries.[20,31,32] With the recent reporting of increased incidence of comorbidities (particularly AF) in HF patients,[20,33] the SMART registry expands upon the real-world clinical practice findings by providing 12 months of follow-up and clinical outcomes on CRT-D recipients, and also by enrolling an older patient population with comorbidities, such as diabetes mellitus, renal dysfunction and AF, that would have otherwise been excluded from the aforementioned randomized trials.[23]

The SMART registry confirms that HF patients with AF have worse clinical outcomes, including higher mortality and hospitalization rates. Although AF necessitates patient-specific strategies to ensure adequate biventricular pacing through CRT device programming/optimizing, rate control via drug management, and/or rate/rhythm control using interventions such as AF catheter ablation, the percentage of ventricular pacing in the AF patients in this study was significantly suboptimal.[34] Inadequate biventricular pacing has been well-established as a causative factor that undermines CRT efficacy in the context of permanent AF. As documented in RAFT, only 34.3% and 47.1% of CRT patients with AF received ≥95% and ≥90% of ventricular pacing, respectively.[35] Atrioventricular ablation, yielding nearly 100% ventricular pacing and regular ventricular rhythm by complete atrioventricular block, is currently suggested as option to be considered in the guidelines (class IIa evidence level) for the management of severely symptomatic AF in HF patients.[7,36] The mortality benefit of atrioventricular node ablation in patients with CRT and AF has been previously demonstrated in two separate meta-analyses.[37,38] Superiority of atrioventricular node ablation and CRT, as compared with pharmacology therapy alone, was recently demonstrated to reduce all-cause mortality in symptomatic patients with permanent AF and narrow QRS duration in APAF-CRT.[39] Still, AV node ablation procedures are

limited by their irreversible nature and the potential long-term consequences remain to be fully established.

Limitations

There are limitations that should be considered in the interpretation of these results. The registry lacked a control group for comparing clinical outcomes and did not require several important parameters. For example, echocardiogram data were only obtained if required by standard of care and no biochemical measurements such as N-terminal pro-B-type natriuretic peptide levels were collected. Some values were also missing from the dataset, including a number of patients that did not have information on ventricular pacing. Similar to other large randomized clinical trials of CRT, patients in the SMART registry were predominately male, and the majority of the patients were either White or did not disclose their race, which might limit the generalizability of these findings to different populations. In addition, only devices from one manufacturer were used; thus, the findings may not be applicable to devices from other manufacturers. Further analysis of AF was hampered by the lower number of patients with pacing percentage data. Another limitation is that we are not able to evaluate the association between improvements in ventricular pacing, as achieved by optimized rate control medications and/or atrioventricular node ablation procedures, on clinical outcomes in AF patients.

Conclusions

Strengths of this large, contemporary registry include its global enrolment of CRT-D recipients with comorbidities that have been traditionally under-represented in the landmark randomized clinical trials, providing for an evaluation of clinical outcomes and clinical responder rates in a real-world standard of care setting. In the SMART registry, CRT response defined by CCS showed that 79% of patients either improved or stabilized over 12 months of follow-up. Clinical worsening was associated with non-LBBB QRS morphology, older age, renal dysfunction, AF and diabetes mellitus at baseline. Patients with AF had particularly worse clinical outcomes, including higher HF-associated hospitalization and all-cause mortality rates, during the follow-up period. It is postulated this could be partly attributable to the lower post-implant percentages of ventricular pacing as compared with patients in sinus rhythm.

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Conflict of interest

This trial was sponsored by Boston Scientific Corporation. I. G. B. received consultancy/proctoring fees from Boston Scientific, Abbott and Biosense Webster. R. S. G. received consultancy fees from Abbott, Anacardio, Astra Zeneca, Boehringer Ingelheim, Boston Scientific, Novartis, Pharmacosmos and Vifor. D. G. received consultancy fees from Abbott, Biotronik, Boston Scientific, St. Jude Medical and Zoll. G. M. received consultancy fees from Boston Scientific and Abbott. D. N. received consultancy fees from Abbott, Biosense Webster, Boston Scientific and Medtronic. N. L. received consultancy fees from Bayer, Bristol-Meyer Squibb and Pfizer. D. W. received consultancy fees from Boston Scientific, iRhythm Technologies and Medtronic and research grants from Boston Scientific. Five authors (S. V., M. H., E. M., P. Y. and K. S.) are employees of Boston Scientific.

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Supporting information

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

Table S1. Baseline and 12 month Ventricular Pacing percentages stratified by CCS outcome.
Table S2. Comparison of baseline and 12 month ventricular pacing percentages in sinus rhythm patients versus AF patients.
Table S3. Clinical composite score stratified by bundle branch block and atrial fibrillation status.

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