

Real-world outcomes in cardiac resynchronization therapy patients: design and baseline demographics of the SMART- Registry

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Abstract

Aims The SMART (Strategic MANagement to optimize response to cardiac Resynchronization Therapy) Registry was designed to assess real-world outcomes for patients receiving a cardiac resynchronization therapy defibrillator (CRT-D) and to better understand which programming and optimization techniques are used and how effective they are.

Methods and results The SMART Registry is a global, multicentre, prospective, observational, post-market CRT-D registry with a planned enrolment of 2000 subjects from a maximum of 200 sites in Europe, North America, and Asia-Pacific region. Each subject will be followed up for a minimum of 12 months. The primary endpoint of CRT response rate at 12 months is defined by a clinical composite score of all-cause mortality, heart failure events, New York Heart Association Class, and quality of life as assessed by a patient global assessment instrument. A subgroup composed of the first 103 consecutive European subjects implanted with an NG4 device will have left ventricular multisite pacing feature enabled at any time during the initial 12 months of follow-up. The primary endpoint for this sub-analysis will be the NG4 PG-related complication-free rate at 36 months.

Conclusions The SMART Registry achieved its recruitment target in August 2019, with 2014 patients enrolled. The baseline demographics demonstrated that patients were generally older, with greater co-morbidity, and on more contemporary medical therapy than in the key CRT trials. The results of the SMART Registry will determine which programming and optimization techniques are effective in this real-world population.

Keywords Heart failure; Left ventricular systolic dysfunction; CRT; Prognosis; Registry

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Introduction

Cardiac resynchronization therapy is a key guideline-recommended therapy for heart failure (HF) patients with severe left ventricular (LV) systolic dysfunction and broad QRS.^{1–3} However, it is recognized that response rates—measured by a myriad of clinical parameters—vary and that

the ‘typical’ HF patient is often unrepresented in clinical trials due to the presence of co-morbidities.⁴

The SMART (Strategic MANagement to optimize response to cardiac Resynchronization Therapy) Registry was designed to assess real-world outcomes for patients receiving a cardiac resynchronization therapy defibrillator (CRT-D) and to better understand which programming and optimization techniques are used and how effective they are over a 12 month period.

Study design

The SMART Registry is a global, multicentre, prospective, observational, post-market CRT-D study with a planned enrolment of 2000 subjects from a maximum of 200 sites in Europe, North America, and Asia-Pacific region. To reduce the impact of individual centre bias, each site was allowed to enrol up to a maximum of 200 subjects. The first enrolment for the study was April 2017, with each subject followed up for a minimum of 12 months. The last patient visit is expected to be September 2020 for the full registry, and December 2021 for the multisite pacing (MSP) subgroup.

All subjects were required to have been implanted with a Boston Scientific quadripolar NG3 or NG4 CRT-D device in conjunction with a quadripolar lead from any manufacturer and fulfil the inclusion/exclusion criteria. If deemed to be eligible for participation, the patient was asked to sign and date the informed consent form, and those who did so were considered enrolled in the study.

Inclusion criteria

All subjects were enrolled between 1 and 21 calendar days post implantation or upgrade to a Boston Scientific NG3 or NG4 CRT-D device, connected with any manufacturer's quadripolar LV lead. Subjects were required to be 18 years or older, or of legal age to give informed consent specific to each country and national laws, and willing and capable of complying with follow-up visits.

Exclusion criteria

Subjects with a documented life expectancy of less than 12 months, those on the active heart transplant list or with an LV assist device, or those who have had a pre-existing CRT device were not eligible to participate. Other key exclusion criteria include women of childbearing potential who were or might have been pregnant at time of study enrolment and those with any contraindication to receive a CRT-D device per local guidelines.

Devices used

The Boston Scientific quadripolar NG3/NG4 CRT-D devices used in the SMART Registry have a new suite of tools that allow for individualized patient therapy, with the goal of improving the management of HF patients. These include LV MSP, VectorGuide™, SmartDelay™, and HeartLogic™. Where these features are used, the SMART Registry will evaluate their utility and their impact on the clinical outcomes.

Left ventricular MSP is intended to improve the response to CRT by delivering two LV pulses per pacing cycle via different vectors from the quadripolar LV lead. Although it has been shown to be non-inferior to biventricular pacing and may improve symptoms and quality of life, mortality data are awaited.^{5,6} VectorGuide™ allows the clinician to quickly evaluate multiple quadripolar LV pacing vectors to identify the best configuration comparing the four cathodes' right ventricular (RV)–LV delay.^{7,8} RV–LV delay has been defined as the best predictor of CRT response in implanted HF patients.⁹ The SmartDelay™ optimization feature provides recommended settings for programming the paced and sensed atrioventricular (AV) delay based on the measurement of intrinsic AV intervals. The objective of the feature is to recommend AV delays that provide optimally timed CRT, which maximizes cardiac contractile function. Finally, the HeartLogic™ algorithm combines novel sensor parameters such as heart sounds and markers of ventilation, along with other measurements like thoracic impedance, heart rate, and activity into an index for the early detection of worsening HF.¹⁰ Following recent publications on this new and unique feature,^{11–16} the SMART Registry will provide data on relevant sample size in real-life scenario and may help in evaluating the relationship between sensor data and CRT response.

Primary endpoint

The primary endpoint of CRT response rate at 12 months will be defined by a clinical composite score (CCS)¹⁷ of all-cause mortality, HF events, New York Heart Association (NYHA) Class, and quality of life as assessed by a patient global assessment instrument, which is a brief quality of life self-reported assessment. Multivariate analyses will then be performed to determine which covariates and optimization methods are associated with response.

Multisite pacing sub-study

An MSP cohort is composed of a minimum of the first 103 consecutive European subjects implanted with an NG4 device and who had LV MSP feature enabled at any time during the initial 12 months of follow-up. Enrolment was completed in November 2018. These subjects will undergo additional follow-up at 24 and 36 months and then annually until the last of this cohort has 36 months of follow-up. The primary endpoint for this sub-analysis will be the NG4 pulse generator (PG)-related complication-free rate (CFR) at 36 months.

Statistics

The primary endpoint of the CRT response rate defined by the CCS will be calculated in the full SMART Registry patient

Table 1 Baseline characteristics of the SMART Registry, with key CRT trials for comparison

Characteristic	MUSTIC ³⁰	MIRACLE ³¹	CONTAK-CD ³²	MIRACLE-ICD ³³	COMPANION ³⁴	CARE-HF ³⁵	MADIT-CRT ³⁶	RAFT ²⁸	DANISH ³⁷	SMART Registry
Year of publication	2001	2002	2003	2003	2004	2005	2009	2010	2016	2020
N	131	453	490	369	1520	813	1820	1798	1116	2014
CRT-D or CRT-P	CRT-P	OMT vs. CRT-P	CRT-D (CRT on vs. off)	CRT-D (CRT on vs. off)	OMT vs. CRT-D vs. CRT-P (1:2:2)	OMT vs. CRT-P	ICD vs. CRT (2:3)	ICD vs. CRT-D	OMT vs. ICD (58% CRT)	CRT-D
Follow-up, mean (months)	12	6	6	6	15.7	29.4	28.8	40	68	12
Primary endpoint	QOL, 6MW, VO ₂	NYHA, QOL, 6MW	HF progression	QOL, 6MW, NYHA	ACM and ACH	ACM + CVH	ACM + HFE	AMC + HFH	ACM	CCS
CRT-D 1 year mortality (%)	—	—	15 ^a	—	12	—	—	4 ^b	4 ^c	— ^d
Demographics (CRT arm)										
Age, mean (years)	64	64	66	67	67	67	65	66	64	68
Male (%)	78	68	85	76	67	74	75	85	72	77
White (%)	—	90	—	—	—	—	90	—	—	92
NYHA Class	100% III	90% III	32% II, 60% III, 8% IV	88% III, 12% IV	86% III	93% III	14% I, 86% II	79% II, 21% III	53% II, 45% III	5% I, 46% II, 47% III, 2% IV
LVEF, mean (%)	24	22	21	24	21	25	24	23	25	29.8
Ischaemic (%)	32	50	67	64	55	40	55	69	0	50
QRS (ms)	196	167	160	165	160	160	158 ^e	157	146	151
LBBS (%)	87	—	54	75	71	90 ^g	70	73	—	50
AF (%)	50	—	—	—	—	—	11	13	24	37
Diabetes (%)	—	—	—	—	40	—	30	33	18	34
eGFR (mL/min/1.73 m ²)	—	—	62 ^h	—	—	—	—	45	—	—
eGFR (30–59 mL/min) (%)	—	—	—	—	—	—	—	6	—	—
eGFR (<30 mL/min) (%)	—	—	—	—	—	—	—	—	—	16 ⁱ
COPD (%)	—	—	—	—	—	—	—	—	—	23 ^j
Renal dysfunction	—	—	—	—	—	—	—	—	—	—
Medication at baseline (CRT arm)										
ACE inhibitor (%)	—	—	74 ^h	—	70	—	77	—	96	44
ARB (%)	—	—	16 ^h	—	20 ⁱ	—	21	—	—	31
ACE/ARB (%)	98	93	86	93	90	95	95	96	—	75
Sacubitril/valsartan (%)	—	—	—	—	—	—	—	—	—	21
Beta-blocker (%)	25	62	48 ^h	62	68 ⁱ	70	93	90	92	87
MRA (%)	18	—	18 ^h	54	54	54	32	42	59	49
Diuretic (%)	96	94	88	93	96	43 ('high dose')	76	85	—	70
Digoxin (%)	52	78	69	—	41 ^j	40	27	34	—	6

6MW, 6 min walk; ACE, angiotensin-converting enzyme; ACH, all-cause hospitalisation; ACM, all-cause mortality; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; CCS, clinical composite score at 12 months: all-cause mortality, heart failure events, NYHA Class, and patient quality of life questionnaire; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; CVH, cardiovascular hospitalisation; eGFR, estimated glomerular filtration rate; HF, heart failure; HFE, heart failure event; HFH, heart failure hospitalisation; ICD, implantable cardioverter defibrillator; LBBS, left bundle branch block; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OMT, optimal medical therapy; QOL, quality of life; SMART, Strategic Management to optimize response to cardiac resynchronization therapy.

High dose diuretics = ≥80 mg furosemide, ≥2 mg bumetanide, or ≥20 mg torsemide.

^aDe Marco T et al.: Baseline clinical characteristics associated with all-cause mortality in CRT-D patients: a ten-year retrospective analysis from the CONTAK CD Study (abstract). *J Am Coll Cardiol* 2009.

^bUS Food and Drug Administration: PMA P0100131/S232. RAFT. Summary of Safety and Effectiveness Data, 2011. https://www.accessdata.fda.gov/cdrh_docs/pdf/P0100131S232b.pdf.

^cLevy WC: Should non-ischemic CRT candidates receive CRT-P or CRT-D? (editorial) *J Am Coll Cardiol* 2017; 69: 1679–1682.

^dSMART Registry is in follow-up phase. CRT-D 1 year mortality (%) is part of primary endpoint analysis.

^eUS Food and Drug Administration: PMA P0100012/S230. MADIT-CRT. Summary of Safety and Effectiveness Data, 2010. https://www.accessdata.fda.gov/cdrh_docs/pdf/P0100012S230b.pdf.

^fUS Food and Drug Administration: PMA P0100131. INSYNCRD. Summary of Safety and Effectiveness Data, 2002. https://www.accessdata.fda.gov/cdrh_docs/pdf/P0100131b.pdf.

^gGervais R, Lederer C, Shankar A, et al.: Surface electrocardiogram to predict outcomes in candidates for cardiac resynchronization therapy: a sub-analysis of the CARE HF trial. *Eur J Heart Fail* 2009; 11: 699–705.

^hDe Marco T, Boehmer JP, Carlson MD, Jaski B, Schafer J, Yong P. Baseline factors influencing both early and long-term all-cause mortality in CRT-D patients: a seven-year retrospective analysis (abstract). *Heart Rhythm* 2005; 2 (5 Suppl): S321.

ⁱSMART Registry collected baseline data on chronic pulmonary disease.

^jBoston Scientific Corporation: COMPANION Data on file.

population as well as in selected subgroups. The CCS allows for three levels of CRT response: improved, unchanged, or worsened. The number and per cent of the SMART Registry subjects contributing to each level will be calculated. The CRT response will then be compared between selected subgroups using statistical tests accounting for the ordinality of the CCS response, when appropriate. In analyses comparing two subgroups, a Cochran–Armitage test for trend will be employed when appropriate. If more than two subgroups will be compared, a cumulative logit model or other appropriate test will be used. There are no formal hypotheses to be tested for this primary endpoint. The sample size was chosen mainly by considering the required number of subgroup analyses instead of traditional statistical powering calculations.

Additional secondary analyses may be performed, including CRT response in the overall cohort and in subgroups using groupings of the three levels of CCS: improved vs. unchanged/worsened, and improved/unchanged vs. worsened; and evaluation of the components of the CCS in the overall cohort and in subgroups (all-cause mortality, HF events, NYHA Class, and patient global assessment). In addition, utilization patterns of device features and diagnostics will also be calculated if available, including MSP, HeartLogic™, SmartDelay™, VectorGuide™, and programming of pacing vectors.

The MSP sub-study primary endpoint of NG4 PG-related CFR at 36 months will be defined as those adverse events that resulted in death, serious injury, correction of PG failure requiring invasive intervention, or permanent loss of PG device function. Complications related to the LV, RV, or right atrial leads will be reported but not counted against the endpoint. The following hypotheses will be evaluated to determine the safety of the NG4 device:

- H_0 : PG-related CFR at 36 months \leq 88.5%
- H_A : PG-related CFR at 36 months $>$ 88.5%

This performance goal of 88.5% was based on the observed safety rate of prior approved Boston Scientific devices and corresponding variabilities. The CFR will be calculated using Kaplan–Meier methodology, and the 95% one-sided pointwise log–log confidence limit of the CFR at 36 months will be compared with the performance goal of 88.5%; if the lower confidence limit exceeds 88.5%, the null hypothesis will be rejected.

Discussion

The SMART Registry is a large and contemporary study of 2014 CRT-D recipients that aims to evaluate outcomes in a ‘real-world’ population. The baseline characteristics are shown in *Table 1*, with those of key clinical trials illustrated for comparison.

As would be expected, the population in SMART is older than the device trials with a mean age of 68 years; 93% were in NYHA Class II or III at baseline. Half of patients had HF of an ischaemic aetiology, similar to the findings of Conrad *et al.*⁴ Similarly, co-morbidities were common with 34% having diabetes mellitus, 16% chronic obstructive pulmonary disease, and 23% renal dysfunction (with 1.2% on dialysis) at baseline. Atrial fibrillation (AF) was also common, with 37% of individuals having this at baseline, and much more common than in the main CRT trials.

Advances in medical and device therapy have dramatically improved the outlook for people with HF. Since the publication of the CONSENSUS study in 1987,¹⁸ we have gathered a wealth of evidence demonstrating a reduction in morbidity and mortality for patients with HF using angiotensin-converting enzyme inhibitors,¹⁸ beta-blockers,^{19,20} mineralocorticoid receptor antagonists,^{21,22} and, more recently, sacubitril/valsartan²³ and SGLT2 inhibitors.^{24,25} The population in SMART were well treated with 96% on an angiotensin-converting enzyme inhibitor/angiotensin receptor antagonist/sacubitril–valsartan and 87% on a beta-blocker. However, only 49% were treated with a mineralocorticoid receptor antagonist at baseline—an unfortunately similar real-world finding to other registries.²⁶ However, reflecting the contemporary nature of this registry, 21% of patients were treated with sacubitril/valsartan at baseline; more than were found in the DAPA-HF study (11%),²⁴ and similar to the proportion in the recently published EMPEROR-Reduced trial.²⁵

Large CRT trials generally excluded patients in AF, with only MADIT-CRT²⁷ and RAFT²⁸ recruiting 11% and 13% of such patients, respectively. In comparison, 37% of patients in the SMART Registry were in AF at baseline, very similar to the 40% of subjects described in a large contemporary cohort of HF patients.⁴ Also under-represented in clinical trials of CRT are patients without left bundle branch block. There is significant debate as to whether QRS width or morphology is more important in predicting response to CRT.²⁹ In this registry, 50% of participants did not have left bundle branch block, a much greater proportion than in the key CRT trials.

It is hoped that this large, contemporary registry will provide insight into the outcomes for the large number of individuals who are under-represented in our current evidence base and clarify which methods of programming appear to offer the best response to CRT.

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Conflict of interest

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