

# Better outcome at lower costs after implementing a CRT-care pathway: comprehensive evaluation of real-world data

Antonius M.W. van Stipdonk<sup>1\*</sup>, Stijn Schretlen<sup>2</sup>, Wim Dohmen<sup>1</sup>, Christian Knackstedt<sup>1</sup>, Fabienne Beckers-Wesche<sup>1</sup>, Luuk Debie<sup>1</sup>, Hans-Peter Brunner-La Rocca<sup>1</sup> and Kevin Vernooy<sup>1,3</sup>

<sup>1</sup>Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, The Netherlands; <sup>2</sup>Medtronic Integrated Health Solutions, Eindhoven, The Netherlands; and <sup>3</sup>Cardiology Department, Radboud University Medical Center, Nijmegen, The Netherlands

## Abstract

**Aims** Cardiac resynchronization therapy (CRT) requires intensive, complex, and multidisciplinary care for heart failure (HF) patients. Due to limitations in time, resources, and coordination of care, in current practice, this is often incomplete. We evaluated the effect of the introduction of a CRT-care pathway (CRT-CPW) on clinical outcome and costs.

**Methods and results** The CRT-CPW focused on structuring CRT patient selection, implantation, and follow-up management. To facilitate and guarantee quality, checklists were introduced. The CRT-CPW was implemented in the Maastricht University Medical Centre in 2014. Physician-led usual care was restructured to a nurse-led care pathway. A retrospective comparison of data from CRT patients receiving usual care (2012–2014, 222 patients) and patients receiving care according to CRT-CPW (2015–2018, 241 patients) was performed. The primary outcome was the composite of all-cause mortality and HF hospitalization. Hospital-related costs of cardiovascular care after CRT implantation were analysed to address cost-effectiveness of the CRT-CPW. Demographics were comparable in the usual care and CRT-CPW groups. Kaplan–Meier estimates of the occurrence of the primary endpoint showed a significant improvement in the CRT-CPW group (25.7% vs. 34.7%, hazard ratio 0.56; confidence interval 0.40–0.78;  $P < 0.005$ ), at 36 months of follow-up. The total costs for cardiology-related hospitalizations were significantly reduced in the CRT-CPW group [€17 698 (14 192–21 195) vs. 19 933 (16 980–22 991),  $P < 0.001$ ]. Bootstrap cost-effectiveness analyses showed that implementation of CRT-CPW would be an economically dominant strategy in 90.7% of bootstrap samples.

**Conclusions** The introduction of a novel multidisciplinary, nurse-led care pathway for CRT patients resulted in significant reduction of the combination of all-cause mortality and HF hospitalizations, at reduced cardiovascular-related hospital costs.

**Keywords** Cardiac resynchronization therapy; Heart failure; Care pathway; Value-based health care; Cost-effectiveness

Received: 9 November 2021; Revised: 11 April 2022; Accepted: 19 April 2022

\*Correspondence to:

Antonius M. W. van Stipdonk, MD, PhD, Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, PO Box 5800, 6202 AZ Maastricht, The Netherlands.

Email: [twan.van.stipdonk@mumc.nl](mailto:twan.van.stipdonk@mumc.nl)

Antonius M. W. van Stipdonk and S. Schretlen contributed equally as the first authors.

## Introduction

Multiple randomized clinical trials have shown that cardiac resynchronization therapy (CRT) reduces symptoms of heart failure (HF), improves exercise capacity and quality of life, and reduces HF hospitalizations and mortality.<sup>1–6</sup> Clinical guidelines of the European Society of Cardiology and the American College of Cardiology Foundation/American Heart

Association endorse these results and recommend utilization of CRT in selected HF patients.<sup>7–10</sup>

Despite guidelines and experts' consensus, variability in patient selection, implantation techniques, in-hospital management, and follow-up is observed in clinical practice.<sup>11–13</sup> To optimize benefit from CRT, thorough selection, carefully planned implantation strategy, and a comprehensive follow-up including HF treatment and device management

should be reassured. Previously, a small number of studies introducing structured, comprehensive programmes to improve the use and outcomes of CRT in HF patients have shown promising results.<sup>14,15</sup> However, the widespread adaptation of such programmes requires it to improve outcomes without the use of extensive or highly specialized resources. Moreover, as recourses and costs are becoming more important with the expanding HF population,<sup>16</sup> evaluation of interventions should consider cost-effectiveness. In general HF care, the transition from physician-led to nurse-led care has been shown to result in a reduced risk of HF hospitalization and is a cost-effective intervention.<sup>16–20</sup> Moreover, studies have shown that structured aids in HF care programmes can lead to improved adherence to guidelines.<sup>14,21,22</sup> We therefore developed and implemented a multidisciplinary, nurse-led, structured CRT-care pathway (CRT-CPW), with protocolized aids and advanced planning, which aims to improve outcome at reduced costs.<sup>23</sup> This paper evaluates whether the implementation of the CRT-CPW improves outcome by reducing all-cause mortality and HF hospitalization, and whether the CRT-CPW is cost-effective.

## Methods

### Cardiac resynchronization therapy-care pathway

In 2013, three CRT expert centres experienced the need for a best practice care process design in order to accommodate the complex multidisciplinary care for these patients and therefore optimize outcomes. Incorporating local experiences and scientific evidence, a benchmark CRT-CPW design was designed. The design aimed to capture predictors of outcomes relevant to each individual process step, using checklists. The generic care pathway was then operationalized to fit the Maastricht University Medical Centre+ (MUMC+) organization, detailing structured planning of process steps with relevant resources needed, and responsibilities of contributors. The most important changes introduced compared with usual care at the MUMC+ were the structured planning of follow-up from implantation on and a transition of tasks from physicians to specialized HF nurses and device technicians, enabling one-stop-shop visits, to reduce unnecessary resource use and patient burden. Importantly, the care pathway did not focus on the implementation of novel tools for device implantation (e.g. quadripolar leads), enhanced patient monitoring (use of home monitoring), use of new device algorithms, or prescription of novel HF medication. The CRT-CPW involves a structured workflow with routine, pre-planned contacts led by trained HF nurses in collaboration with device technicians. Heterogeneity of care for HF patients treated with CRT was captured by the use of checklists at (1) patient referral, (2) pre-implant assessment, (3) device

implantation, and (4) follow-up, used at aforementioned prespecified one-stop-shop contact moments. The care pathway involved the implementation of a multidisciplinary (HF and electrophysiology) meeting discussing referrals, a one-stop-shop pre-assessment visit with an implanting physician and specialized device nurse, single-day admission for implantation, and 2 week, 3 month, 6 month, and 12 month pre-planned one-stop-shop follow-up contacts with HF nurses and device technicians. Each step was guided by the checklists to ensure dedicated optimization in each way possible. For detailed insight into the checklists and the care pathway design, we refer to a previously published evaluation of the CRT-CPW.<sup>23</sup>

The implementation of the care pathway took place from January 2014 to September 2014. During this time, all contributors to the different phases of the CRT-CPW were trained on the use of the checklists and on logistic and IT support changes relevant to their contributions to the CPW.

### Data collection and analysis

The study was performed according to the Declaration of Helsinki and was approved by the Medical Ethics Committee (METC). At the time of the METC approval of the CRT-CPW study, Dutch guidelines allowed the use of de-identified patient data acquired from routine clinical care, without prior individual patient consent.

All patients who underwent CRT device implantation or upgrade procedure (from any device vendor) and received follow-up care at the MUMC+ were included in the current analysis. Baseline characteristics were collected by extracting data from the MUMC+ (electronic) hospital information system. HF cause was deemed ischaemic when there was clear evidence of myocardial infarction or coronary artery bypass graft (CABG) in the medical history.

A retrospective data analysis of two CRT patient groups was conducted comparing the usual care group (2012–2014) with the CRT-CPW group (2015–2018). The primary outcome was the composite of all-cause mortality and HF hospitalizations. Secondary outcomes were the components of the primary outcome analysed separately and hospital-related costs of cardiovascular care after CRT implantation. Clinical outcome data were retrieved from the electronic hospital information system, linked to municipal registries on mortality. Hospitalizations were deemed HF-related when clearly described as such in discharge forms by responsible physicians.

Furthermore, total hospital-related costs of cardiovascular care from 6 months before and 12 months after CRT implantation were analysed to address cost-effectiveness. To calculate the cardiac care-related costs per CRT patient, all registered care activities related to the CRT-CPW per patient

such as diagnostics (echocardiography, electrocardiogram, and X-ray's), hospitalization days, cathlab procedure time, and consultations were multiplied with their respective hospital cost–price per activity. To define which care activities are CRT-CPW related, all care activities connected to cardiology DRG's within a time scope from 6 months prior to CRT device implant until 12 months after were included. These activities were retrieved from the electronic hospital information system. The hospital cost–price per care activity is based on annual activity-based costing methodology and were provided by hospital finance department.

## Statistical analysis

Categorical variables are summarized with counts and percentages and compared with Fisher's exact test for nominal variables and the Cochran–Mantel–Haenszel test for ordinal variables. Continuous variables are reported as mean (standard deviation), or median [interquartile range], as appropriate, and compared with Student's *t*-test or Wilcoxon rank sum test, respectively. Analyses were conducted in SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA). Incidence of death, HF hospitalization, and the composite of these events are estimated using the Kaplan–Meier method. The log-rank test is used to compare event incidence between groups. Univariable Cox regression is used to obtain estimates for the hazard ratio (HR) and its 95% confidence interval (CI).

Multivariable modelling of death, HF hospitalization, and the composite event was done using Cox regression. The models include group (CRT-CPW vs. usual care), sex, age, body mass index, left ventricular ejection fraction (LVEF), QRS duration, New York Heart Association (NYHA) class, left bundle branch block (LBBB), ischaemic cardiomyopathy, hypertension, atrial fibrillation, chronic lung disease, diabetes, de novo implant, therapeutic vs. prophylactic, urgent vs. elective, and CRT-P vs. CRT-D device.

Multivariable modelling of cost was done using linear regression on the natural logarithm of cost. Parameter estimates are converted to cost scale and reported as a relative, per cent-wise change per unit change of the covariate.

Stratified bootstrap was used to assess robustness of and correlation between the reduction in mortality and reduction in cost associated with implementation of the CRT pathway. Five thousand samples with replacement were taken. For each sample, HR and  $\Delta$ cost were calculated. Results are reported with a scatter plot and summary statistics, identifying four quadrants defined by  $HR < 1$  vs.  $HR \geq 1$  and  $\Delta$ cost  $< 0$  vs.  $\Delta$ cost  $\geq 0$ .

Multiple imputation of missing values was performed using fully conditional specification to create 25 complete data sets.<sup>24</sup> Multivariable regression models are reported from the completed datasets, using Rubin's rule to combine the results.<sup>25</sup>

## Results

### Patient characteristics

The study cohort comprised a total of 463 patients available for analysis. Data collected from 222 patients referred for implantation of a CRT device before implementation of the CRT-CPW (usual care group) and data from 241 patients after introduction of the CRT-CPW (CRT-CPW group) were analysed.

The two groups reflect a typical real-world CRT population, with an average age of 68 years old; more than 80% of patients were in NYHA functional class II or III. The average baseline LVEF was 30%, with an ischaemic cause of HF present in 40% of patients. Over 85% of patients were treated with an angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker and beta-blocker, and over 50% with a mineralocorticoid receptor antagonist. Fourteen per cent of patients underwent an upgrade procedure from a previous device, and over 70% of patients received a CRT-ICD system. Baseline QRS duration was  $158 \pm 28$  ms, and 50% of patients showed a baseline LBBB QRS morphology. The baseline characteristics of the usual care and CRT-CPW group patients were largely comparable (see *Table 1*). In the CRT-CPW group, atrial fibrillation and previous myocardial infarction were more prevalent (see *Table 1*).

### Outcome

The mean follow-up time in the usual care group was  $62.8 \pm 30.2$  months, and  $37.7 \pm 14.9$  months in the CRT-CPW group. Death from any cause or admission for HF occurred in 127 patients (57.2%) in the usual care group and 64 patients (26.6%) in the CRT-CPW group. Kaplan–Meier estimates for incidence at 12, 24, and 36 months were 14.9%, 24.8%, and 34.7% in the usual care group and 11.2%, 18.8%, and 25.7% in the CRT-CPW group, respectively (*Figure 1A*).

Multivariable Cox regression model for the composite of all-cause mortality and HF hospitalization (Supporting Information, *Table S1*) shows a significant reduction of 44% (HR 0.56, CI 0.40–0.78,  $P = 0.0006$ ) in the CRT-CPW group. Other significant predictors of the occurrence of the primary outcome were increasing age, a history of atrial fibrillation, higher functional class, and ischaemic HF aetiology.

### All-cause mortality

Kaplan–Meier estimates for incidence of all-cause mortality at 12, 24, and 36 months were 8.1%, 17.6%, and 25.2% in the usual care group and 5.4%, 10.9%, and 18.4% in the CRT-CPW group, respectively (*Figure 1B*). Multivariable Cox regression model for mortality (Supporting Information, *Table S2*) shows that CRT-CPW group assignment was associ-

**Table 1** Baseline characteristics

Baseline characteristics <i>Presented as N (%) or mean ± standard deviation</i>	Usual care (N = 222)	CRT-care pathway (N = 241)	P-value <sup>a</sup>
Male	156 (70.3%)	174 (72.2%)	0.68
Age (years) <sup>b</sup>	68.1 ± 11.0	68.6 ± 10.3	0.66
BMI (kg/m <sup>2</sup> )	27.4 ± 5.0	27.5 ± 4.7	
NYHA class <sup>c</sup>			0.11
Class I	6 (2.9%)	15 (8.0%)	
Class II	124 (59.6%)	88 (46.8%)	
Class III	72 (34.6%)	63 (33.5%)	
Class IV	6 (2.9%)	22 (11.7%)	
Missing	14 (6.3%)	53 (22.0%)	
LBBB	117 (52.7%)	117 (48.5%)	0.51
QRS duration (ms)	157.6 ± 28.4	155.9 ± 31.0	0.54
LVEF (%)	28.9 ± 9.1	30.4 ± 10.1	0.089
LVESV (mL), mean ± standard deviation	133.2 ± 58.6	133.1 ± 58.2	0.99
Ischaemic cardiomyopathy	90 (40.5%)	95 (39.4%)	0.85
Hypertension	75 (33.8%)	86 (35.7%)	0.70
Myocardial infarction	52 (23.4%)	78 (32.4%)	0.038
Atrial fibrillation	73 (32.9%)	104 (43.2%)	0.028
Chronic lung disease	33 (14.9%)	35 (14.5%)	1.00
Diabetes	44 (19.8%)	56 (23.2%)	0.43
Kidney failure	2 (0.9%)	2 (0.8%)	1.00
NT-proBNP (pg/mL)	361 ± 621	354 ± 503	0.90
GFR (MDRD formula)	63.3 ± 28.6	59.8 ± 22.0	0.15
Beta-blocker	193 (86.9%)	205 (85.1%)	0.59
ACEi/ARB	200 (90.1%)	204 (84.6%)	0.094
MRA	107 (48.2%)	135 (56.0%)	0.095
ARNI	0 (0.0%)	5 (2.1%)	0.062
Upgrade from ICD/pacemaker	26 (11.7%)	40 (16.6%)	0.14
CRT-D <sup>c</sup>	172 (77.5%)	168 (69.7%)	0.073

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; GFR, glomerular filtration rate; ICD, implantable cardioverter-defibrillator; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association.

<sup>a</sup>P-value compares old and new pathways. Tests used are Student's *t*-test, Cochran–Mantel–Haenszel's test, and Fisher's exact test.

<sup>b</sup>Age is estimated from age ranges.

<sup>c</sup>Percentages exclude missing values from denominator.

ated with a significant 40% reduction (HR 0.60, CI 0.41–0.87, *P* = 0.007) in mortality.

## Heart failure hospitalizations

Kaplan–Meier estimates for incidence of HF hospitalizations at 12, 24, and 36 months were 8.7%, 12.7%, and 18.1% in the usual care group and 6.4%, 10.1%, and 11.2% in the CRT-CPW group, respectively (HR 0.57, CI 0.35–0.92, *P* = 0.021) (Figure 1C). Multivariable Cox regression model for incidence of HF hospitalizations (time to first) (Supporting Information, Table S3) showed that CRT-CPW treatment was associated with a significant 51% reduction (HR 0.49, CI 0.30–0.81, *P* = 0.005) in HF hospitalization rate.

## Hospital-related costs of cardiovascular care and cost-effectiveness

The total costs for cardiology-related hospital costs from 6 months before up to 12 months after CRT device

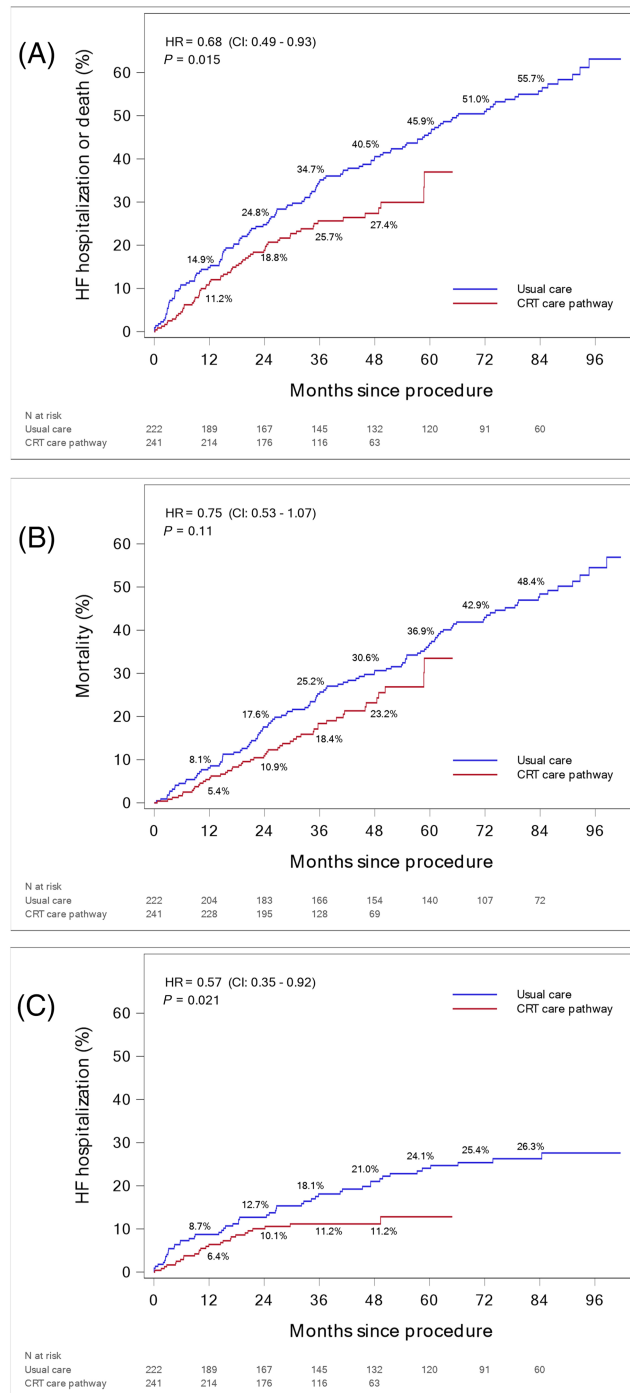
implantation reduced significantly in the CRT-CPW group [€17.698 (14 192–21 195) vs. 19.933 (16 980–22 991), *P* < 0.001]. Multivariable linear regression analysis showed an average 9.3% cost reduction (CI –13.8% to 4.5%, *P* < 0.005; Supporting Information, Table S4).

A bootstrap analysis of cost-effectiveness showed 90.7% of the bootstrap samples was in the dominant quadrant (Figure 2), indicating simultaneous clinical benefit and cost reduction for the CRT-CPW.

## Discussion

The main finding of the current study is that the implementation of a multidisciplinary, nurse-led care pathway for CRT patients is associated with a significant reduction in the incidence of the composite endpoint of death and HF hospitalization. Furthermore, the implementation of the care pathway is associated with a reduction of care-related costs, resulting in dominant cost-effectiveness.

**Figure 1** (A) Composite of death and HF hospitalization. Figure 1A shows the Kaplan–Meier estimates for the composite of all-cause mortality and HF hospitalization. (B) Mortality. Figure 1B shows the Kaplan–Meier estimates for all-cause mortality. The hazard ratio with 95% confidence interval with estimated mortality at selected time points, and number of patients at risk. (C) Incidence of HF hospitalizations. Figure 1C shows the Kaplan–Meier estimates for incidence of HF hospitalizations. CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; HR, hazard ratio.



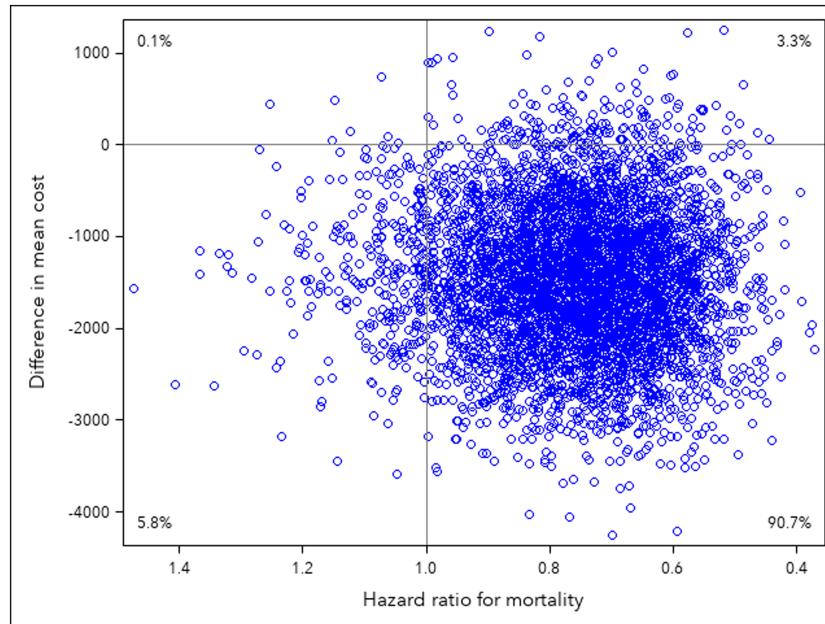
## Clinical outcomes

The incidence of all-cause mortality and HF hospitalization in this study resembles that of earlier CRT studies. Patients in

the CRT arm of the Resynchronization-Defibrillation for Ambulatory Heart Failure Trial (RAFT) randomized CRT trial<sup>4</sup> experienced equal event rates at 2 or 3 years of follow-up, compared with the CRT-CPW patients in the current study.



**Figure 2** Five thousand bootstrap estimates of the hazard ratio for mortality and the difference in mean costs between conventional and cardiac resynchronization therapy-care pathway.



However, usual care patients experienced a significantly higher event rate. The RAFT cohort, however, included 80% of patients in HF functional class II, whereas the current cohort included ~40% of patients with functional class III or IV. Of note, baseline functional class was missing in a substantial number of patients in both usual care and CRT-CPW patient groups; this is due to the retrospective nature of the current study.

In contrast to functional class, average baseline ejection fraction was higher in the current analyses (30% vs. 23%) than in the aforementioned RAFT trial. As the current analysis included patients with brady-pacing indications like high-degree AVB and ablate-and-pace strategy for atrial fibrillation, this included patients with baseline ejection fraction above 35%. A recent large, real-world, CRT cohort study from the UK<sup>26</sup> included over 50 000 patients implanted with a CRT device between 2009 and 2017. Even though extensive baseline data on the English CRT cohort are lacking, the real-world character likely makes it resemble the current cohort more than the RAFT trial population. All-cause mortality in this UK cohort was even slightly higher than in the usual care group in the present evaluation (28% vs. 25% at 3 years of follow-up). The higher mortality rates can be explained by a difference in inclusion period and setting, as the current analysis included patients implanted with a CRT device between 2012 and 2018 and the CRT-CPW was implemented in a tertiary referral centre in the current analyses, compared with a wide variety of centres in England.

Baseline differences between the two groups of CRT patients in the current analyses showed a higher percentage of patients with a history of atrial fibrillation and myocardial infarction in the CRT-CPW group. As recognized by guidelines, these differences are expected to reduce the effect of CRT in the CRT-CPW group.<sup>27–29</sup> Multivariable corrections of our results show that there is no significant effect of the baseline differences on the overall effect on clinical outcomes in CRT patients. However, multivariable correction of the Cox regression analyses on all-cause mortality revealed a significant association of CRT-CPW treatment and this endpoint.

The convincing association of CRT-CPW implementation with improved clinical outcomes is likely the effect of the sum of a complete, comprehensive evaluation for both CRT device-related and HF-related opportunities for treatment optimization, at each patient contact from patient selection up to long-term follow-up. These results confirm the observed potential for optimization in an intensive optimization programme proposed by Mullens *et al.*<sup>14</sup> As the checklists used for post-implantation optimization of patient management were based on the programme described by Mullens *et al.*, these results extend their results to the overall CRT patient population and, moreover, establish its superiority compared with routine follow-up in these patients. The CRT-CPW however differs from the programme described by Mullens *et al.* with respect to two very important aspects. Whereas Mullens *et al.* included non-responders to CRT referred to the clinic, evaluated at a single moment in time, the

CRT-CPW structurally optimizes treatment in any patient treated with CRT. Furthermore, the CRT-CPW aims to optimize treatment at each visit, from patient selection and device implantation to each contact during (long-term) follow-up.

The introduction of checklist-based interventions has been shown effective in the increasing guideline adherence in HF before. Fonarow *et al.* have implemented a guideline-based clinical decision support tool kit in 167 US outpatient cardiology practices in their IMPROVE HF trial.<sup>21</sup> The introduction of the structured support resulted in a significant increase in guideline adherence.<sup>21</sup> A consideration with respect to the results of the current study is that guidelines for HF treatment were updated during the conduction of this study. The adaptations of recommendations, especially with respect to general HF treatment, may confound the presented results. Even though baseline HF medical treatment did not significantly differ, optimization during follow-up should involve the updated medical treatment as well and may hence play a role in the improved clinical outcomes.

Altman *et al.* described an optimization programme similar to the currently described CRT-CPW.<sup>15</sup> The programme constituted of a three-visit (6 month) optimization service, providing multidisciplinary, specialized evaluation and intervention, after which patients were referred back to conventional care, unless refractory symptoms or non-response persisted. After a median follow-up of 24 months, patients evaluated in this optimization programme showed similar reductions in event rates (all-cause mortality, transplantation, or HF hospitalization) as in the current evaluation. Unfortunately, the content of the intervention(s) used in the optimization programme group was at the physician's discretion, and not described in detail. The multidisciplinary team consisted of dedicated HF and EP specialists, using echocardiographic optimization. It is not clear whether dedicated protocols were used and whether specialized nurses were involved. The lack of a clear optimization protocol limits the reproducibility of these results. Moreover, the use of multiple specialists during the visits precludes its implementation in many CRT clinics. In contrast, the proposed structured CRT-CPW included protocolled optimization, guided by checklists, substituting expert experience in CRT care to ensure all possible opportunities for optimization are taken without undue burden to specialists. This enables any CRT clinic to implement the CRT-CPW using current staff and resources, or even substituting physician care by nurse-led care, as shown in the current analysis.

## Cost-effectiveness

Incidence and prevalence of HF are increasing rapidly, with health care programmes needing to adapt to this increased need for care and expected increase in health care costs.<sup>16</sup>

Cardiac resynchronization therapy optimization programmes described before did not evaluate effects on costs.<sup>14,15</sup> However, the use of specialized physicians and resources (e.g. echocardiographic optimization) most likely result in additional costs, with the need of a cost-effectiveness analysis to be able to assess whether clinical results are worth the investment. In contrast, the currently evaluated CRT-CPW was not only introduced to ensure better outcomes by multidisciplinary management of HF patients eligible and treated with CRT but also to reduce the need of highly specialized care, resources, and as a consequence cost. The introduction of the CRT-CPW process improvement was associated with a shorter time-to-implant, shorter procedure-related length of stay, and a successful transition from a physician-led to a nurse-led care process, as was previously described in detail.<sup>23</sup> These process-related changes resulted in a significant reduction of costs, as shown in the current evaluation.

The current evaluation of costs involved a direct calculation of local cardiology-related costs related to resource use and health care consultations. These costs are centre-specific and translation to patient-specific or societal costs may be dependent on the country-specific reimbursement systems. However, as it was associated with a significant reduction of hospitalizations, the intervention will result in reduced costs in most, if not all, health care systems. The difference in first-year HF hospitalizations accounts for the largest part of total cost savings in the current evaluation. However, as this cost evaluation was only possible for the period of 6 months before up to 12 months after CRT device implantation, the impact of the reduction of HF hospitalizations on costs in the current evaluation is limited. As HF hospitalizations were significantly reduced also beyond the first year after implantation, even larger cost reduction can be expected long term.

## Future outlook

The presented CRT-CPW implementation, in contrast to previous CRT optimization programmes, allows for copying in any setting as it specifically aimed to reduce resource use and transfer care from physicians to nurses. This offers opportunity for any clinic involved in care for CRT patients to adopt the presented programme to improve their CRT patient management.

## Limitations

Even though the current evaluation of the introduced CRT-CPW provides very hopeful results, the results were derived from a single-centre implementation, and the historical comparison design does not allow for definite conclusions on

superiority. As CRT and general HF therapy have evolved over time (e.g. the introduction of quadripolar leads and sacubitril/valsartan), changes in availability of HF or device therapy may have influenced results, even though adjustment for these factors in multivariable analysis did not show any significant impact on results. Still, complete adjustment is not possible. In addition, the results need confirmation in other centres to prove reproducibility. Lastly, the use of real-world data limits data completeness. Even though endpoint collection was complete, baseline data were not available in all patients, possibly influencing baseline comparability of treatment groups.

Hence, prospective, multicentre evaluation, in a (clustered) randomized controlled trial, is needed to provide definitive evidence that a structured CRT-CPW significantly improves outcomes of CRT-treated HF patients in any setting.

## Conclusions

The introduction of a structured nurse-led, multidisciplinary CRT-CPW may result in significantly better clinical outcome at lower costs. As this pathway does not require any highly specialized resources or physicians, it may be introduced in any clinic involved in CRT patient care. Still, prospective validation, ideally in a randomized controlled trial, is needed.

## Acknowledgements

Bart Gerritse, Richard N. Cornelussen, and Sandra Jacobs are acknowledged for the data analysis (BG), comments,

suggestions, and edits to the manuscript (BG, RC, SJ, Medtronic plc.).

## Conflict of interest

A.V.S., W.D., C.K., L.D., F.B.-W., and K.V. have nothing to disclose; S.S. is employee of Medtronic; and H.P.B.-L. reports grants from Vifor, Novartis, and Roche Diagnostics, outside the submitted work.

## Funding

This project was funded by a research grant from Medtronic plc.

## Supporting information

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

**Table S1.** Multivariable Cox regression model for the composite of all-cause mortality and HF hospitalization

**Table S2.** Multivariable Cox regression model for all-cause mortality

**Table S3.** Multivariable Cox regression model for HF hospitalizations

**Table S4.** Multivariable model for cardiology cost

## References

- Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy P, Defibrillation in Heart Failure I. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004; **350**: 2140–2150.
- Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure Study I. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med.* 2005; **352**: 1539–1549.
- Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CS, Sato N, Shah AN, Gheorghiuade M. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol.* 2014; **63**: 1123–1133.
- Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial I. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* 2010; **363**: 2385–2395.
- Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, Investigators M-CT. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med.* 2009; **361**: 1329–1338.
- Linde C, Abraham WT, Gold MR, Daubert C, Group RS. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERSE (REsynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction) study. *J Am Coll Cardiol.* 2010; **56**: 1826–1831.
- McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA,



- Zannad F, Zeiher A, Task Force for the D, Treatment of A, Chronic Heart Failure of the European Society of C, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, Guidelines ESCCfP. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012; **14**: 803–869.
8. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Guidelines ESCCfP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerstrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J.* 2013; **34**: 2281–2329.
  9. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA 3rd, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD, Ellenbogen KA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hayes DL, Page RL, Stevenson LW, Sweeney MO, American College of Cardiology F, American Heart Association Task Force on Practice G, Heart Rhythm S. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. [corrected]. *Circulation.* 2012; **126**: 1784–1800.
  10. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2013; **128**: 1810–1852.
  11. Bogale N, Priori S, Gitt A, Alings M, Linde C, Dickstein K, Scientific Committee Nc, investigators. The European cardiac resynchronization therapy survey: patient selection and implantation practice vary according to centre volume. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2011; **13**: 1445–1453.
  12. Marinakis G, van Erven L, Bongioni MG, Lip GY, Pison L, Blomstrom-Lundqvist C, Scientific Initiative Committee EHRA. Practices of cardiac implantable electronic device follow-up: results of the European Heart Rhythm Association survey. *Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2012; **14**: 423–425.
  13. Curtis AB, Yancy CW, Albert NM, Stough WG, Gheorghiadu M, Heywood JT, McBride ML, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Fonarow GC. Cardiac resynchronization therapy utilization for heart failure: findings from IMPROVE HF. *Am Heart J.* 2009; **158**: 956–964.
  14. Mullens W, Grimm RA, Verga T, Dressing T, Starling RC, Wilkoff BL, Tang WH. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. *J Am Coll Cardiol.* 2009; **53**: 765–773.
  15. Altman RK, Parks KA, Schlett CL, Orencole M, Park MY, Truong QA, Deeprasertkul P, Moore SA, Barrett CD, Lewis GD, Das S, Upadhyay GA, Heist EK, Picard MH, Singh JP. Multidisciplinary care of patients receiving cardiac resynchronization therapy is associated with improved clinical outcomes. *Eur Heart J.* 2012; **33**: 2181–2188.
  16. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016; **37**: 2129–2200.
  17. Rich MW, Beckham V, Wittenberg C, Leven CL, Freedland KE, Carney RM. A multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure. *New England Journal of Medicine.* 1995; **333**: 1190–1195.
  18. Blue L, Lang E, McMurray JJV, Davie AP, McDonagh TA, Murdoch DR, Petrie MC, Connolly E, Norrie J, Round CE, Ford I, Morrison CE. Randomised controlled trial of specialist nurse intervention in heart failure. *BMJ.* 2001; **323**: 715–718.
  19. McDonagh TA, Blue L, Clark AL, Dahlström U, Ekman I, Lainscak M, McDonald K, Ryder M, Strömberg A, Jaarsma T, Care oboHFACoP. European Society of Cardiology Heart Failure Association Standards for delivering heart failure care. *Eur J Heart Fail.* 2011; **13**: 235–241.
  20. Strömberg A, Mårtensson J, Fridlund B, Levin L-Å, Karlsson J-E, Dahlström U. Nurse-led heart failure clinics improve survival and self-care behaviour in patients with heart failure: results from a prospective, randomised trial. *Eur Heart J.* 2003; **24**: 1014–1023.
  21. Fonarow GC, Albert NM, Curtis AB, Stough WG, Gheorghiadu M, Heywood JT, McBride ML, Inge PJ, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW. Improving evidence-based care for heart failure in outpatient cardiology practices: primary results of the Registry to Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting (IMPROVE HF). *Circulation.* 2010; **122**: 585–596.
  22. Fonarow GC, Abraham WT, Albert NM, Gattis Stough W, Gheorghiadu M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy CW, Young JB, Investigators O-H, Hospitals. Influence of a performance-improvement initiative on quality of care for patients hospitalized with heart failure: results of the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF). *Arch Intern Med.* 2007; **167**: 1493–1502.
  23. van Stipdonk AMW, Schretlen S, Dohmen W, Brunner-LaRocca HP, Knackstedt C, Vernooy K. Development and implementation of a cardiac resynchronisation therapy care pathway: improved process and reduced resource use. *BMJ Open Qual.* 2021; **10**.

24. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res.* 2007; **16**: 219–242.
25. Rubin DB. *Multiple Imputation for Non-response in Surveys.* New York: John Wiley & Sons; 1987.
26. Leyva F, Zegard A, Okafor O, de Bono J, McNulty D, Ahmed A, Marshall H, Ray D, Qiu T. Survival after cardiac resynchronization therapy: results from 50 084 implantations. *Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology.* 2019; **21**: 754–762.
27. Ousdigian KT, Borek PP, Koehler JL, Heywood JT, Ziegler PD, Wilkoff BL. The epidemic of inadequate biventricular pacing in patients with persistent or permanent atrial fibrillation and its association with mortality. *Circ Arrhythm Electrophysiol.* 2014; **7**: 370–376.
28. Kloosterman M, van Stipdonk AMW, Ter Horst I, Rienstra M, Van Gelder IC, Vos MA, Prinzen FW, Meine M, Vernooij K, Maass AH. Association between heart failure aetiology and magnitude of echocardiographic remodelling and outcome of cardiac resynchronization therapy. *ESC Heart Fail.* 2020; **7**: 645–653.
29. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elvik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol.* 2012; **59**: 1509–1518.