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Contractibility sensor signal evolution predicts cardiovascular events in patients with cardiac resynchronization therapy

Abbreviated title: Contractibility sensor signal evolution and cardiovascular events in CRT

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Summary

Background. – While a multicentre trial has demonstrated that the SonR™ contractility sensor is as effective as echocardiography-guided optimization at improving response to cardiac resynchronization therapy, an association between SonR™ values and clinical endpoints has not been established.

Aims. – The primary objective was to assess the predictive value of SonR™ signal evolution regarding cardiovascular events in patients implanted with a cardiac resynchronization therapy device. The secondary objective was to evaluate whether SonR™ signal evolution was associated with cardiovascular death.

Methods. – All patients with a SonR™ system implanted between 2012 and 2016 were included in this retrospective study. SonR™ signal evolution was calculated over the first 6 months after implantation: $(\text{month 6 value} - \text{month 1 value}) / \text{month 1 value} * 100$. The primary endpoint (cardiovascular events) was a composite of cardiovascular death, hospitalization for acute heart failure or ventricular arrhythmia.

Results. – Seventy-four patients (median age 67 years; 81% men) were followed up over a median 20 (13; 29) months. Cumulative incidence function showed that SonR™ signal evolution was predictive of cardiovascular events (threshold < 10.70%; $P = 0.023$) and predictive of cardiovascular death ($P = 0.0018$). After multivariable analysis, SonR™ signal evolution was independently associated with the onset of cardiovascular events (hazard ratio 4.03, 95% confidence interval 1.31–12.43; $P = 0.015$), even after adjustment for left bundle branch block and chronic kidney disease.

Conclusions. – In this first study publishing data on SonR™ signals in a real-life setting, SonR™ signal evolution over the first 6 months after cardiac resynchronization implantation was an independent predictor of cardiovascular events at follow-up. This variable could be useful to identify patients at higher risk of further adverse events after cardiac resynchronization implantation.

Résumé

Contexte. – Une étude a démontré que le SonR™ était aussi efficace que l'optimisation échographique pour améliorer la réponse après resynchronisation cardiaque. Cependant, l'association entre les valeurs SonR™ et les événements cliniques n'a jamais été étudiée.

Objectifs. – L'objectif primaire était d'évaluer la valeur prédictive du signal SonR™ vis-à-vis d'événements cardiovasculaires chez les patients implantés d'une resynchronisation cardiaque.

L'objectif secondaire était d'évaluer l'association entre les valeurs SonR™ et la survenue de décès cardiovasculaires.

Méthodes. – Les patients implantés d'un système SonR™ entre 2012 et 2016 ont été inclus dans cette étude rétrospective. L'évolution du signal SonR™ pendant 6 mois après l'implantation a été calculée : $(\text{valeur M6} - \text{valeur M1})/\text{valeur M1} * 100$. Le critère de jugement principal (événements cardiovasculaires) associait décès cardiovasculaire, hospitalisation pour insuffisance cardiaque et arythmie ventriculaire.

Résultats. – Soixante-quatre patients (67 ans ; 81 % hommes) ont été suivis durant une médiane de 20 (13–29) mois. La fonction d'incidence cumulée a montré que l'évolution du signal SonR™ était prédictif d'évènements cardiovasculaires (seuil < 10,70 %; $P = 0,023$) et de décès cardiovasculaires ($P = 0,0018$). Après analyse multivariée, l'évolution du signal SonR™ était indépendamment associé avec la survenue d'évènements cardiovasculaires (HR 4,03, IC95 % 1,31–12,43 ; $P = 0,015$) même après ajustement sur le bloc de branche gauche et l'insuffisance rénale chronique.

Conclusion. – Cette étude, réalisée dans des conditions de vraie vie, a montré que l'évolution du signal SonR™ durant les 6 premiers mois après implantation d'une resynchronisation cardiaque était prédicteur de survenue d'évènements cardiovasculaires. Ce paramètre permettrait d'identifier les patients à haut risque d'évènements cardiovasculaire après implantation d'un resynchronisation cardiaque.

KEYWORDS

Cardiac resynchronization therapy;

Heart failure;

Mortality;

Cardiac contractility;

Ventricular tachycardia;

MOTS CLÉS

Resynchronisation cardiaque ;

Insuffisance cardiaque ;

Mortalité ;

Contractibilité cardiaque ;

Tachycardie ventriculaire ;

Abbreviations: CRT, cardiac resynchronization therapy; NYHA, New York Heart Association;
ROC, receiver operating characteristic; SSE, SonR™ signal evolution.

Background

Cardiac resynchronization therapy (CRT) is an effective treatment, but up to 30% of patients are non-responders [1]. Manufacturers have developed several techniques to try to improve response to CRT; one is the microaccelerometer sensor SonR™, which is located at the tip of the right atrial lead [2]. This device detects cardiac vibrations, reflecting left ventricle contractibility, and optimizes atrioventricular and interventricular delays according to the amplitude of SonR™ signal.

Clinical data on SonR™ technology are scarce. The efficacy of this technology was assessed in a multicentre non-inferiority randomized study including > 900 patients, proving that delay optimization by SonR™ was as effective as echocardiography-guided optimization [3]. The primary endpoint was a nesting of global death and New York Heart Association (NYHA) functional class or quality-of-life scale improvement 12 months after CRT implantation. More recently, a small-scale study analysing 25 patients questioned the reliability of SonR™ as a good surrogate for left ventricular contraction [4].

Response after CRT is commonly assessed but does not predict clinical outcomes [5]. So, rather than limiting our evaluation to rate of response to CRT and SonR™ reliability, reflecting left ventricular contractibility, we decided to study the association between SonR™ signal evolution (SSE) and the onset of cardiovascular events.

The primary objective of this study was to assess the predictive value of SSE regarding a composite criterion of cardiovascular events in a real-life cohort of patients implanted with a CRT device. The secondary objective was to assess the predictive value of SSE regarding the onset of cardiovascular death after CRT implantation.

Methods

Patients

All patients implanted with a resynchronization device using SonR™ technology at the Cardiology Department of Poitiers University Hospital between January 2012 and January 2016 were included retrospectively. The study was conducted according to the ethical principles stated in the Declaration of Helsinki and was approved by the hospital's ethics committee. All patients received an information letter. Patients were implanted if all the following criteria were present: New York Heart Association class II, III or IV; left ventricular ejection fraction $\leq 35\%$; QRS duration ≥ 120 ms with left bundle branch block morphology or QRS duration > 150 ms and no left bundle branch block morphology; and

optimal medical therapy, including beta-blockers and angiotensin-converting enzyme inhibitors. Patients aged < 18 years and those without interventricular and atrioventricular delay optimization according to the SonR™ signal were excluded. Sociodemographic and clinical characteristics and electrocardiogram intervals were collected at the time of CRT implantation. Renal dysfunction was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m², using the Modification of Diet in Renal Disease (MDRD) formula. Chronic obstructive pulmonary disease was defined as forced expiratory volume in 1 s/forced vital capacity < 0.70 at spirometry.

SonR™ signal

The SonR™ signal, which measures microaccelerations expressed in terms of gravitational acceleration (expressed in g), was collected from device files 6 months after CRT implantation. Automated extraction provided day-by-day SonR™ signal values, and the mean value of SonR™ over each month was taken into account. To analyse SonR™ signal evolution (SSE), we calculated evolution of SonR™ signal at 6 months (as a percentage): $([\text{month 6 value} - \text{month 1 value}]/\text{month 1 value}) * 100$.

Follow-up

Patients were followed up from the time of CRT implantation until 1 January 2017. The primary endpoint was cardiovascular events, which was a composite of cardiovascular death, ventricular arrhythmia requiring defibrillator therapy or hospitalization for heart failure. The secondary endpoint was cardiovascular death. Data were collected using hospital archives and hospital software that archived medical data. All the hospitalization and consultation reports were examined. If necessary, general practitioners and referring cardiologists were contacted to provide missing information. An independent cardiologist blinded to SonR™ evolution adjudicated all the events. Events that occurred within the first 6 months were not considered when the predictive value of SonR™ evolution during the first 6 months was assessed.

Statistical analysis

Categorical variables are expressed as numbers (percentages), and continuous variables as medians (interquartile ranges). Comparisons of groups were performed using the χ^2 test for categorical variables and Student's *t* test, or the Mann-Whitney test if appropriate, for quantitative variables.

Test characteristics and accuracy of SSE to predict the primary endpoint were calculated. Univariate logistic regressions were used to calculate the areas under the receiver operating characteristic (ROC) curves; SonR™ cut-off values were chosen as the values maximizing the likelihood ratio. Cumulative incidence curves were built according to these cut-off values, and were compared using the Fine and Gray model because of competing risks related to non-cardiac death [6]. For analysis of the predictive value of SSE, the events that occurred within the first 6 months were not considered. The associations between SSE and cardiovascular events and deaths were evaluated in univariate and multivariable Fine and Gray regression analyses. The proportional hazards assumption was assessed using log-log plots. Multivariable analysis used a backward elimination procedure performed on an initial model, including every factor associated with prognosis at the $P < 0.20$ level in the univariate analysis.

Analyses were performed using SPSS 22 (SPSS, Inc., Chicago, IL, USA) and SAS 9.3 (SAS Institute, Inc., Cary, NC, USA) statistical software. Two-sided P values < 0.05 were considered statistically significant.

Results

Population characteristics

Of the 79 patients eligible to participate in the study, five were not included (two patients refused and three had a flat SonR™ signal after implantation). For the 74 patients included in the study, the median age was 67 years and 60 (81%) were men. Baseline characteristics of the patients are described in [Table 1](#). The aetiology of heart failure was idiopathic dilated cardiomyopathy in 39 (53%) patients, ischaemic cardiomyopathy in 34 (46%) patients and valvular cardiomyopathy in one (1%) patient. The median QRS duration on electrocardiogram was 160 (152; 180) ms at implantation, and 63 (85%) patients had left bundle branch block. With echocardiography, the median left ventricular ejection fraction was 28 (23; 33) %, the left ventricular end-diastolic diameter was 67 (58; 74) mm and the left ventricular end-systolic diameter was 54 (47; 62) mm. Median N-terminal pro B-type natriuretic peptide concentration was 1361 (518; 3166) pg/mL.

Follow-up and survival analysis

The median clinical follow-up was 20 (13; 29) months. During follow-up, no patient was lost and 13 (18%) deaths occurred, including nine (13%) cardiovascular deaths (heart failure, $n = 6$; sudden cardiac death, $n = 3$); 14 (19%) patients were hospitalized for heart failure, one (1%) was hospitalized for stroke and seven (10%) had at least one appropriate device therapy for life-threatening ventricular arrhythmia. During the blanking period of 6 months, two deaths occurred (one from septicaemia and one from heart failure), four patients were hospitalized for heart failure and three patients had appropriate device therapy for life-threatening ventricular arrhythmia.

Absolute SonR™ signal values from month 4 to month 6 were significantly lower in patients who experienced cardiovascular events compared with in patients who did not (Table 2). SSE was statistically different between patients in whom cardiovascular events occurred and those in whom they did not. Patients who died from a cardiovascular cause had significantly lower SonR™ values at month 6 compared with those who did not (median 0.40 [0.25; 0.49] vs 0.56 [0.38; 0.76], respectively; $P = 0.04$). The SSE was statistically lower in patients who died from cardiovascular causes compared with those who did not (median -25.73 [-45.50 ; -19.69] vs 9.74 [-10.51 ; 43.54], respectively; $P = 0.001$).

As two deaths occurred during the blanking period of 6 months, ROC curves, cumulative incidence function and multivariable analysis were performed in the 72 remaining patients, accounting for 20 cardiovascular events. The ROC curves analysing the ability of the SSE to predict cardiovascular events and cardiovascular death are given in Fig. 1. The area under the curve predicting cardiovascular death was greater than the area under the curve for predicting cardiovascular events. The cut-off values maximizing the likelihood ratio were 10.70% (sensitivity, 0.55; specificity, 0.81) to predict cardiovascular events and -18.55% (sensitivity, 0.86; specificity, 0.88) to predict cardiovascular death.

Using these cut-off values, cumulative incidence function showed that the probability of cardiovascular events was significantly higher in patients with $SSE < 10.70\%$ ($P = 0.023$), and that the probability of cardiovascular death was significantly higher in patients with $SSE < -18.55\%$ ($P = 0.0018$) (Fig. 2).

According to the results of the multivariable Fine and Gray analysis, SSE < 10.70% was associated with the occurrence of cardiovascular events (hazard ratio [HR] 4.03, 95% confidence interval [CI] 1.31–12.43; $P = 0.015$), even after adjustment for left bundle branch block and renal dysfunction (Table 3). Multivariable analysis regarding cardiovascular death could not be carried out because of the small number of cardiovascular deaths, which would have rendered the results unreliable. Nevertheless, in the univariate analysis, SSE < –18.55% was associated with an increased risk of cardiovascular death (HR 28.08, 95% CI 3.45–228.05; $P = 0.002$).

Discussion

To our knowledge, this is the first study assessing the association between SonR™ values and the onset of major cardiovascular events in patients treated in everyday clinical practice. Our main finding is that evolution of SonR™ signal during the first 6 months after implantation is predictive of cardiovascular events and death at follow-up. Indeed, with cumulative incidence function, the probability of cardiovascular events was significantly greater when SSE was < 10.70%. Moreover, SSE was an independent factor predicting cardiovascular events after multivariable analysis.

SonR™ signal evolution over time

After CRT implantation, SonR™ signal absolute values increased from month 1 to month 6 in patients who did not experience cardiovascular events, whereas they tended to decrease from month 3 to month 6 in patients who experienced cardiovascular outcomes. These trends might be related to the reverse remodelling occurring during the first months after CRT implantation [7]. Indeed, studies have demonstrated that echocardiographic variables improve from 3 months after implantation [8]. The SonR™ decrease might be a result of the overwhelming reverse remodelling by heart failure progression. Evolution between repeated echocardiography variables and the SonR™ signal should be investigated to confirm that hypothesis.

Response to CRT

While definition of response to CRT is not standardized across studies, it is generally defined by symptoms (NYHA scale or quality-of-life scale), cardiac imaging variables (left ventricular ejection fraction or left ventricular diameters), clinical outcomes (cardiac mortality, heart failure episodes) or a

combination of these variables. Studies have demonstrated that symptom improvement after CRT was not necessarily associated with better clinical outcomes, and was consequently a poor surrogate for harder endpoints [2]. Imaging, especially echocardiographic variables, may not have reliable reproducibility [9]. These are the reasons why we did not choose variables that would have been controversial, but only assessed clinical outcomes in our composite primary endpoint, whatever the improvement in symptoms or imaging results.

Prediction of events

The most striking differences between groups were obtained when SonR™ evolution and not absolute values were considered. Indeed, SonR™ measures left ventricular acceleration, which has interindividual variations as a result of left ventricular mass, fibrosis, calcification or lead position [10]. With Fine and Gray regression analysis, SonR™ relative evolution was a predictor of cardiovascular events, even after adjustment for renal dysfunction and left bundle branch block. Left bundle branch block is a well-known variable predicting more favourable outcomes after CRT – specifically, fewer cardiac deaths and hospitalizations for heart failure [11, 12]. Indeed, pacing the inferolateral left ventricular region, the activation of which is delayed during left bundle branch block, reverses electrical dyssynchrony [13]. Renal dysfunction has been described as being associated with higher mortality after CRT [14, 15]. In contrast, the RESPOND study demonstrated that the SonR™ system could be of particular interest in patients with renal dysfunction, because in subgroup analysis, patients optimized with SonR™ were better responders than patients optimized with echocardiography [3].

SonR™ signal in daily settings

Despite good patient selection before implantation, some patients will still have cardiovascular outcomes. Thus, SonR™ evolution could be used as a simple tool to identify patients at high cardiovascular risk 6 months after CRT implantation, as suggested in a small-scale case-series study [16]. The SonR™ signal is easy to interpret and can be monitored remotely, as it is available with telemonitoring. SonR™ could also be of particular interest in the early management of end-stage heart failure, by prioritizing patients on the cardiac transplantation waiting list or screening for left ventricular assistance device implantation [17].

Study limitations

One major limitation was the small sample size resulting from this being a single-centre study. Despite the statistical significance of our results, because of the small number of events we were unable to perform a Fine and Gray multivariable analysis of cardiovascular death. The second limitation was the difference in baseline characteristics between our patients and those in larger randomized trials. Patients more often had atrial fibrillation, chronic kidney disease and ischaemic cardiomyopathy than those included in large randomized clinical trials [18, 19]. Nevertheless, the baseline characteristics of our patients were closer to those of large registries [20]. The increased rate of comorbidity characteristics may explain the high rate of death in our cohort, which was around 18%.

Conclusions

This study is the first to analyse the relationship between SonR™ signal values and clinical outcomes in everyday clinical practice conditions after CRT implantation. The evolution between SonR™ signal value at month 1 and month 6 was an independent predictor of cardiovascular events in the multivariable analysis. SonR™ evolution might be helpful as a means of identifying patients at high risk of adverse events, especially through remote monitoring of the signal.

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Disclosure of interest

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The other authors declare that they have no conflict of interest concerning this article.

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Figure legends

Figure 1. Receiver-operating characteristic (ROC) curves analysing the ability of SonR™ signal evolution to predict (A) cardiovascular events and (B) cardiovascular death. AUC: area under the curve; Se: sensitivity; Spe: specificity.

Figure 2. Cumulated incidence function probabilities. A. Cumulated incidence function of cardiovascular events according to SonR™ signal evolution of 10.70%. B. Cumulated incidence function of cardiovascular death according to SonR™ signal evolution of –18.55%.

Table 1 Baseline characteristics.

Clinical and demographic characteristics	
Age (years)	67 (56; 75)
Men	60 (81)
Body mass index (kg/m ²)	26.7 (23.9; 31)
Systolic blood pressure (mmHg)	120 (107; 134)
Diastolic blood pressure (mmHg)	69 (60; 73)
New York Heart Association functional class	
II	32 (43)
III	42 (57)
IV	0 (0)
Medical history	
Diabetes	15 (20)
Current smoker	23 (31)
Dyslipidaemia	38 (51)
Systemic hypertension	32 (43)
Atrial fibrillation	24 (32)
Renal dysfunction	36 (49)
Chronic obstructive pulmonary disease	10 (14)
Stroke	3 (4)
Aetiology of heart failure	
Ischaemic cardiomyopathy	34 (46)
Idiopathic dilated cardiomyopathy	39 (53)
Valvular cardiomyopathy	1 (1)
Medication	
ACE inhibitors/ARBs	68 (92)
Beta-blockers	66 (89)
Diuretics	58 (78)
Antialdosterone drugs	34 (46)

Electrocardiography

Heart rate (beats per minute)	67 (60; 75)
PR interval (ms)	200 (177; 220)
QRS duration (ms)	160 (152; 180)
Left bundle branch block	63 (85)
No left bundle branch block	11 (15)

Echocardiography

Left ventricular ejection fraction (%)	28 (23; 33)
Left ventricular end-diastolic diameter (mm)	67 (58; 74)
Left ventricular end-systolic diameter (mm)	54 (47; 62)

Biological data

N-terminal pro-B-type natriuretic peptide (pg/mL)	1361 (518; 3166)
Creatinine ($\mu\text{mol/L}$)	93 (84; 119)
Haemoglobin (dg/L)	13.8 (12.9; 15.2)
C-reactive protein (mg/L)	3 (1; 11)

Data are expressed as median (first quartile; third quartile) or number (%). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker

Table 2 SonR™ signal values according to cardiovascular events and cardiovascular deaths.

	Cardiovascular events						Cardiovascular deaths					
	No			Yes			No			Yes		
	<i>n</i>	Median (Q1; Q3)	<i>n</i>	Median (Q1; Q3)	<i>n</i>	Median (Q1; Q3)	<i>n</i>	Median (Q1; Q3)	<i>n</i>	Median (Q1; Q3)	<i>n</i>	Median (Q1; Q3)
SonR™ value												
Month 1 (g)	49	0.46 (0.39; 0.64)	25	0.42 (0.33; 0.65)	0.37	65	0.44 (0.38; 0.62)	9	0.48 (0.31; 0.74)	0.84		
Month 2 (g)	49	0.50 (0.41; 0.69)	25	0.47 (0.29; 0.74)	0.43	65	0.50 (0.36; 0.68)	9	0.61 (0.29; 0.86)	0.80		
Month 3 (g)	49	0.57 (0.39; 0.72)	25	0.44 (0.31; 0.64)	0.16	65	0.54 (0.34; 0.70)	9	0.47 (0.29; 0.68)	0.79		
Month 4 (g)	49	0.57 (0.35; 0.79)	25	0.40 (0.30; 0.55)	0.02	65	0.54 (0.33; 0.75)	9	0.46 (0.29; 0.49)	0.26		
Month 5 (g)	49	0.61 (0.38; 0.79)	25	0.43 (0.31; 0.56)	0.006	65	0.54 (0.35; 0.75)	9	0.47 (0.27; 0.57)	0.15		
Month 6 (g)	48	0.61 (0.39; 0.79)	24	0.41 (0.30; 0.52)	0.002	64	0.56 (0.38; 0.76)	8	0.40 (0.25; 0.49)	0.04		
SSE (%)	48	19.92 (-10.47; 54.02)	24	-8.54 (-27.80; 8.12)	0.002	64	9.74 (-10.51; 43.54)	8	-25.73 (-45.50; -19.69)	0.001		

Q1: first quartile; Q3: third quartile; SSE: SonR™ signal evolution.

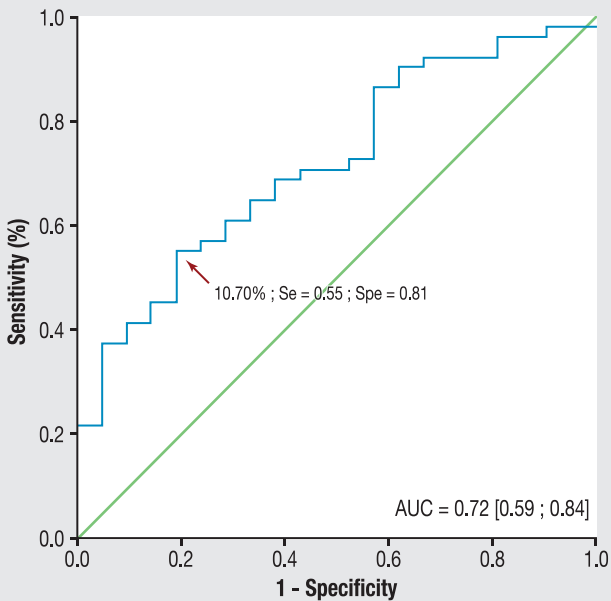
Table 3 Univariate and multivariable Fine and Gray regression analyses for cardiovascular events.

	Univariate analysis					Multivariable analysis				
	Beta	SE	HR	95% CI	P ^a	Beta	SE	HR	95% CI	P ^a
Male	0.31	0.59	1.36	0.43–4.30	0.60					
Ischaemic cardiomyopathy	-0.07	0.44	0.93	0.39–2.22	0.87					
Dilated cardiomyopathy	0.25	0.45	1.29	0.53–3.09	0.58					
Chronic obstructive pulmonary disease	0.75	0.55	2.12	0.73–6.20	0.17					
Atrial fibrillation	0.75	0.44	2.12	0.89–5.03	0.09					
Renal dysfunction	0.79	0.47	2.21	0.89–5.53	0.09	1.32	0.57	3.73	1.24–11.36	0.020
Diabetes	-0.30	0.61	0.74	0.23–2.43	0.62					
Hypertension	-0.47	0.43	0.63	0.27–1.46	0.28					
Left bundle branch block	-1.13	0.48	0.32	0.13–0.83	0.02	-1.61	0.55	0.20	0.07–0.59	0.003
SSE < 10.70%	1.26	0.55	3.52	1.19–10.38	0.02	1.39	0.57	4.03	1.31–12.43	0.015
Age	0.02	0.02	1.02	0.98–1.07	0.25					
Body mass index	-0.01	0.05	0.99	0.90–1.09	0.80					
N-terminal pro-B-type natriuretic peptide	0.08	0.06	1.08	0.96–1.21	0.20					
Haemoglobin	-0.05	0.15	0.95	0.70–1.27	0.72					
QRS width	-0.02	0.01	0.98	0.96–1.00	0.12					

Left ventricular end-diastolic diameter	-0.02	0.02	0.98	0.95-1.02	0.35
Left ventricular ejection fraction	0.04	0.04	1.04	0.97-1.12	0.29
PR interval	0.01	0.01	1.010	0.99-1.02	0.08

CI: confidence interval; HR: hazard ratio; SE: standard error; SSE: SonR™ signal evolution .

^a Fine and Gray model.

A**B**