

Article

# Underutilization of Cardiac Resynchronization Therapy in Taiwanese Heart Failure Patients with Reduced Ejection Fraction

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Heart failure (HF) is a disease that consumes significant healthcare resources. It inflicts high morbidity and mortality, and has a great adverse impact on quality of life [1]. Cardiac resynchronization therapy (CRT) is considered as a second-line therapy based on guideline recommendation, and there has been numerous evidence demonstrating the benefits of CRT in HF patients with reduced ejection fraction (HFrEF) and wide QRS duration [2,3]. The COMPANION trial demonstrated that patients who received CRT implantation plus optimized medical therapy had significantly lower risks of all-cause mortality and hospitalization comparing to those who received optimized medical therapy alone [4]. Most studies of CRT have specified that the left ventricular ejection fraction (LVEF) should be <35%. In the MADIT-CRT and RAFT trials, patients with LVEF<30% who received cardiac resynchronization defibrillators (CRT-D) had significantly lower risks of HF hospitalization or all-cause mortality comparing to those only received implantable cardioverter defibrillator (ICD) [5,6]. Taiwan National Health Insurance Administration reimbursed the implantation of CRT since 2004 but the operation needs to meet the prior review criteria due to high costs of CRT device. The criteria for CRT implantation in Taiwan were that the symptomatic HF patients with NYHA functional class III-IV, LVEF  $\leq$ 35% despite guideline-advised medical therapy, plus (1) sinus rhythm, left bundle branch block (LBBB) pattern and QRS duration  $\geq$ 120ms, (2) permanent atrial fibrillation, LBBB pattern and QRS duration  $\geq$ 120ms, or (3) right ventricular pacing.

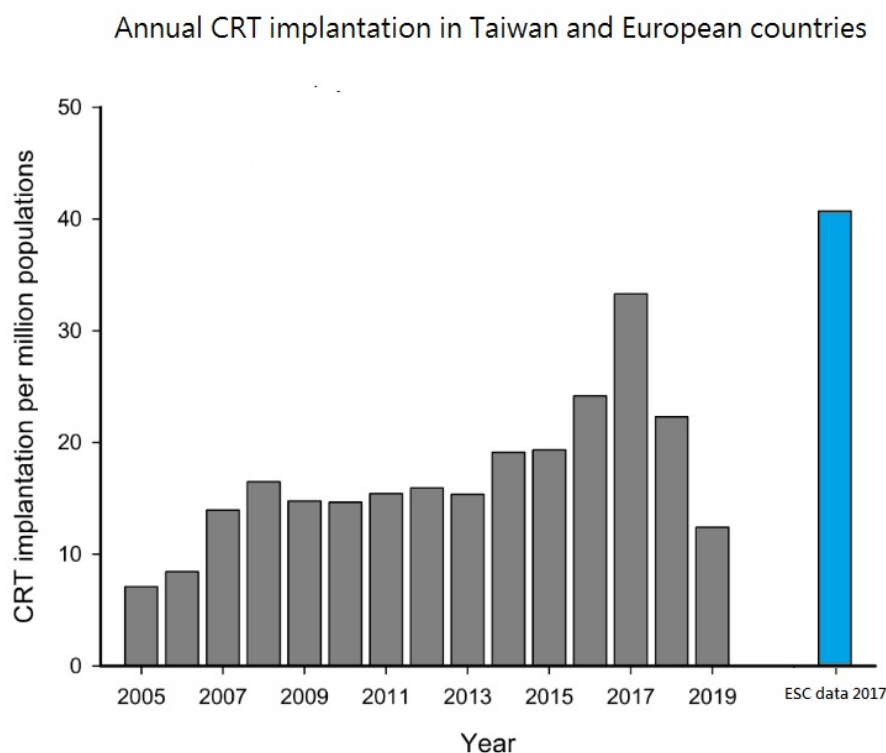
The Taiwan Society of Cardiology - Heart Failure with reduced Ejection Fraction (TSOC-HFrEF) registry was a prospective, multicenter, observational survey of patients presenting to 21 hospitals in Taiwan for acute decompensated systolic HF from May 2013 to October 2014. It showed that the guideline-recommended therapies were prescribed sub-optimally and both one-year mortality and re-hospitalization rates for HF were high in Taiwan [7,8]. This registry also demonstrated the implantation rate of CRT was only 1.9% in Taiwanese acute decompensated HF patients [7]. Another study including two large HF trials (PARADIGM-HF and ATOMSPHERE) showed that despite similar percentage of wide QRS (QRS duration  $\geq$ 120ms) among different countries, the utilization rates of CRT were significantly lower in patients lived in the countries with greater income inequality comparing to those who lived in the countries with lesser income inequality (Table. 1) [9]. It is worth noting that although Taiwan had less income inequality with Gini coefficient around 34%, the utilization rate of CRT was similar to or even lower than the countries with greatest inequality.

	Data from PARADIGM-HF & ATOMSPHERE studies			Data from TSOC HFReEF registry
	Gini Tertile 1 Less inequality N= 5,320	Gini Tertile 2 Intermediate group N= 6,124	Gini Tertile 3 Greatest inequality N= 3,772	N= 1,509
<b>Baseline characteristics</b>				
Gini coefficient	<33	33-41	>41	33.8
Number of countries	18	19	17	1
Age, yrs	66.3±10.3	62.8±11.6	61.0±12.2	64.0±15.8
Female	1,118 (21.0)	1,273 (20.8)	936 (24.8)	416 (27.6)
Per capita income, USD	31,582±18,675	20,714±17,704	9,980±5,706	25,026
Percentage of national GDP spent on health care, %	9.1±1.9	7.8±3.4	6.8±1.5	6.4
<b>ECG findings</b>				
QRS ≥120ms	1,624 (30.5)	1,783 (29.1)	1,220 (32.3)	439 (30.9)
LBBB	1,023 (19.2)	1,219 (19.9)	815 (21.6)	98 (6.9)
RBBB	601 (11.3)	564 (9.2)	405 (10.7)	NR
Non-LBBB	NR	NR	NR	275 (19.4)
Pacing	NR	NR	NR	66 (4.6)
QRS duration (ms)	119.9±34.7	114.9±35.5	116.5±36.7	112.9±29.6
<b>Drug and device</b>				
Diuretics	4,342 (81.6)	4,903 (80.1)	2,945 (78.1)	1,202 (82.2)
Digitalis	1,374 (25.8)	1,955 (31.9)	1,395 (37.0)	379 (25.9)
Beta-blocker	4,995 (93.9)	5,591 (91.3)	3,489 (92.5)	872 (59.6)
MRA	2,381 (44.8)	2,660 (43.4)	2,162 (57.3)	716 (49.0)
ACEi	4,772 (89.7)	5,434 (88.7)	3,191 (84.6)	402 (27.5)
ARB	621 (11.7)	717 (11.7)	590 (15.6)	506 (34.6)
Anti-coagulants	2,426 (45.6)	1,717 (28.0)	631 (16.7)	312 (21.3)
Anti-platelet	2,469 (46.4)	3,393 (55.4)	1,978 (52.4)	869 (59.4)
Conventional pacemaker	780 (14.7)	709 (11.6)	297 (7.9)	48 (3.2)
ICD or CRT-D	1,131 (21.3)	986 (16.1)	165 (4.4)	39 (2.6)
CRT-P or CRT-D	442 (8.3)	417 (6.8)	101 (2.7)	29 (1.9)

**Table 1.** Comparison of baseline characteristics and treatment between Taiwan and other countries according to income inequality

Many possible explanations may be pertinent. For example, physicians' unawareness of these beneficial device therapies and patients' wish of taking oral medications rather than receiving invasive procedures. Moreover, low implanting procedural rewards in Taiwan might also impair physicians' desires to implant CRT. Although the gross domestic product (GDP) per capita of Taiwan ranged between the countries with less inequality and intermediated group, the percentage of national GDP expenditure on healthcare was relatively low in Taiwan. The strained national healthcare budget may affect the approval rate of prior review for CRT. Data from TSOC-HFrEF registry enrolled patients with recently acute decompensated HF, including patients with de novo HF, whereas PARADIGM-HF and ATOMSPHERE enrolled patients with chronic HF, therefore we cannot directly compare these data. However, among the TSOC-HFrEF registry populations, 30.9% of them had QRS duration  $\geq 120$ ms at baseline, but only 20 patients received CRT implantation during index HF hospitalization (12 CRT-P, 8 CRT-D), and only 9 patients received CRT implantation during one-year follow-up period (8 CRT-P, 1 CRT-D). Taking all these together, at the end of follow-up, there was still minority of patients in the TSOC-HFrEF had received CRT implantation (approximate 4%).

From the National Health Insurance Database, the annual CRT implantations per million populations increased from 7.07 in 2005, 14.64 in 2010 to 19.33 in 2015 (Figure.1), which may reflect the increase of physicians' awareness of CRT implantation. However, comparing to the European



**Figure 1.** The annual CRT implantations in Taiwan and European countries

countries, the number of CRT implantation in Taiwan is still lower (The mean and median CRT implantations per million populations across the European countries were 40.7 and 27.7, respectively, by ESC HF Atlas) [10]. Noteworthy, the increasing trend of CRT implantations in Taiwan peaked in 2017 then fell in 2018 and 2019. This may be because the novel angiotensin receptor neprilysin inhibitor has been widely introduced since 2017. However, the effects of angiotensin receptor neprilysin inhibitor on the mechanical dyssynchrony in patients with LBBB remain unknown. Future clinical trials may be needed to clarify this issue.

In conclusion, among symptomatic HF patients with QRS duration  $\geq 120$  msec and depressed LV systolic function, CRT had been shown to improve LV function and reduce LV volume [4–6]. Nevertheless, the utilization rate of CRT in Taiwanese patients is low. A call to action to strengthen physicians' awareness of these beneficial device therapies so as to formulate health policy to advocate the adherence of HF treatment guideline should be emphasized.

#### Conflicts of Interest:

The authors declare no conflict of interest.

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