Prevalence and Predictors of Appropriate Implantable Cardioverter Defibrillator Therapy in Chronic Left Ventricular Dysfunction Patients for Primary Prevention of Sudden Cardiac Death in Siriraj Hospital

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Objective: *The purpose of the present study was to identify the prevalence and predictors of first appropriate implantable cardioverter defibrillator (ICD) therapy in patients with chronic LV dysfunction after placement of ICD for primary prevention.*
Material and Method: *Retrospective design was used. Patients (n = 115) from Siriraj Hospitals with ischemic or non-ischemic cardiomyopathy who underwent ICD implantation for primary prevention were studied. Clinical data and ICD therapy data were obtained from medical records and ICD interrogation reports.*
Results: *First appropriate ICD therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF) were seen in 22 patients (19%) of whom 11 (9.5%) received ICD shock and 11 patients (9.5%) received anti-tachycardic pacing. Lack of beta-blocker use and lack of aldosterone antagonist use were identified as significant predictors of appropriate therapy. There was no difference in prevalence of appropriate ICD therapy between ischemic and non-ischemic groups. The freedom from first appropriate therapy at 1, 2 and 3 years was 88%, 80% and 78%. The freedom rate was constant after the third year*
Conclusion: *Nearly one-fifth of chronic LV dysfunction patients with primary prevention ICD implantation experience appropriate ICD therapy. Most first appropriate ICD therapy occurs within 2 years after implantation. Lack of beta-blocker use and lack of aldosterone antagonist use were significant predictors of appropriate therapy.*

Keywords: *Implantable cardioverter defibrillator, Sudden cardiac death, Primary prevention, Predictors*

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Cardiac arrhythmia is a common cause of sudden cardiac death in the chronic heart failure patient. Sudden cardiac death (SCD) from arrhythmia may account for one-half of overall mortality in this group of patients[1]. Implantable cardioverter defibrillator (ICD) is currently recommended by guidelines as an effective tool for primary and secondary prevention of sudden cardiac death in several cardiovascular diseases, particularly in-patient with chronic left ventricular (LV) dysfunction[2]. Effectiveness was confirmed by several studies[3]. In real life practice, there are variations in characteristics of patient and disease severity[4]. Several studies in Western countries determine clinical predictors of ICD therapy in primary prevention of sudden cardiac death. Prevalence of ICD therapy in primary prevention was 19% and was predicted by non-sustained ventricular tachycardia and lack of beta-blocker use in one study[5]. However, prevalence was 44% in another study and was predicted by high body mass index, chronic kidney disease, poor LV function and metabolic syndrome[6]. Appropriate ICD therapy was associated with higher cardiovascular mortality. The purpose of the present study was to evaluate the predictors of first ICD therapy in chronically LV dysfunctional patient.

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Material and Method

Study design

The study was retrospective and was supported by routine to research unit of Siriraj Hospital. The study protocol was approved by Ethics Committee of Siriraj Hospital, Mahidol University.

Study population

Between January 2005 and January 2013, 419 patients underwent ICD or cardiac resynchronization therapy with defibrillator (CRT-D) implantation at Siriraj Hospital. The study flow chart is shown in Fig. 1. The patients with ICD implantation for secondary prevention of SCD and patient without chronic LV dysfunction were excluded from study. Six patients who were not followed-up by our center after ICD implantation were excluded. We retrospectively studied 115 patients with both ischemic and non-ischemic cardiomyopathy who underwent ICD implantation for primary prevention of SCD as per 2008 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines. The indications were one of the following: [1] left ventricular ejection fraction (LVEF) less than or equal to 35% due to prior myocardial infarction, at least 40 days post-myocardial infarction and New York Heart Association (NYHA) functional class II or III; [2] Non-ischemic cardiomyopathy with LVEF less than or equal to 35% with NYHA functional class II or III; [3] LVEF less than or equal to 30% due to prior myocardial infarction, at least 40 days post-myocardial infarction and NYHA functional class I. Ischemic cardiomyopathy (ICM) was defined as a reduced LVEF (less than or equal to 35%) associated with any one of the following: 1) History of myocardial infarction; 2) A history of coronary artery bypass surgery or percutaneous coronary intervention; 3) Significant coronary artery stenosis documented by conventional coronary angiography. Non-ischemic cardiomyopathy

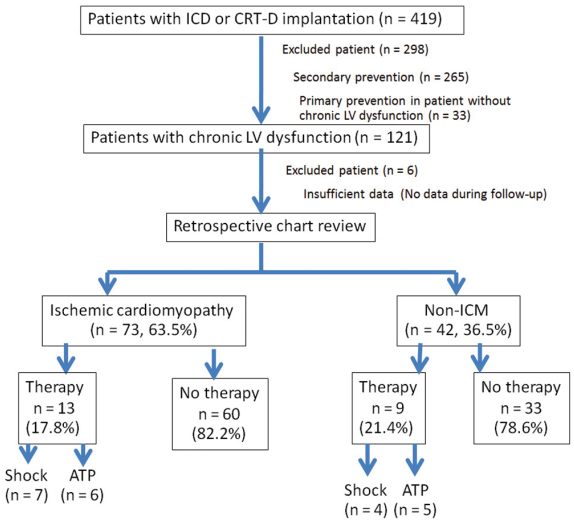

Fig. 1 Study flow chart.

was defined as a reduced LVEF (less than or equal to 35%) with a lack of coronary artery disease (as defined by above). Patient's underlying disease (such as hypertension, diabetes and atrial fibrillation), echocardiographic parameter prior to implantation and ICD interrogation data were collected from the medical record.

Medical treatment and serum creatinine data were collected at the day of first appropriate ICD therapy in the group of patients with first appropriate therapy. In the group without first appropriate therapy, these data were collected at the day of last available device interrogation prior to either patient death or last follow-up.

Endpoint

The endpoint was first appropriate ICD therapy either anti-tachycardic pacing (ATP) or shock for ventricular arrhythmia (including monomorphic ventricular tachycardia, polymorphic ventricular tachycardia and ventricular fibrillation). Monomorphic ventricular tachycardia (VT) was defined as tachycardia with abrupt onset, AV dissociation, change in morphology on ventricular electrogram compared to baseline, cycle length 200-500 millisecond and less than 30 millisecond of beat-to-beat variation. Polymorphic ventricular tachycardia was defined as tachycardia with abrupt onset, AV dissociation, change in morphology on ventricular electrogram compared to baseline, cycle length 200-500 millisecond and morphology change over time with more than 30 millisecond beat-to-beat variation. Ventricular fibrillation was defined as same as polymorphic VT except for cycle length of less than 200 millisecond.

Statistical analysis

Data are reported as percentage of subjects for categorical variables. Continuous variables are reported as mean ± standard deviation (SD) or median and range. Univariate and multivariate analysis were performed to identify the predictors of first appropriate ICD therapy. In univariate analysis, Chi-square or Fischer's exact test was used for categorical variables and independent t-test or Mann-Whitney U test was used for continuous variables. All variables with *p*-value less than 0.05 in the univariate analysis were included for multivariate analysis using multiple logistic regression with adjusted odds ratio and 95% confidence interval (CI). Time-to-event curves in the group with first appropriate ICD therapy were

calculated by method of Kaplan-Meier. SPSS software version 16.0 was used for analysis.

Results

One hundred fifteen patients (mean age 63.39±11.69 years, 75.7% male) were included for analysis. Sixty-four patients (55.7%) received ICD implantation and another fifty-one patients (44.3%) received CRT-D implantation for primary prevention. Characteristic of patients are shown in Table 1. Of 115 patients, 63.5% had ischemic cardiomyopathy, 61.7% had hypertension, 42.6% had diabetes and 14.8% had atrial fibrillation. The average LV ejection fraction and LV diastolic diameter were 24.34% and 69.29 mm respectively. The median serum creatinine level was 1.23 mg/dL.

Appropriate ICD therapy occurred in 22 patients (19%). Eleven patients received ICD shock as first appropriate therapy. Another 11 patients received ATP as first appropriate therapy.

Univariate analysis

Univariate predictors of first appropriate ICD therapy are shown in Table 1. There was no difference in prevalence of first appropriate ICD therapy between ischemic and non-ischemic group. There was no difference in hypertension, diabetes and atrial fibrillation between two groups also. The prevalence of beta-blocker use was significantly lower in patients who received appropriate therapy compared to patient who received no therapy (72.7% vs. 92.5%, $p = 0.017$) in both ischemic and non-ischemic group. Prevalence of aldosterone antagonist use was also significantly lower in patients who received appropriate therapy (22.7% vs. 48.4%, $p = 0.03$). LVEF, left ventricular diastolic dimension (LVDD), serum creatinine, use of angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), diuretic, amiodarone, antiplatelet and statin use were not significantly different between the therapy group and no-therapy group.

Multivariate analysis

Multivariate analysis is shown in Table 2. Beta-blocker therapy was associated with less ICD therapy (adjusted odds ratio 0.23, 95% CI 0.07-0.82). Aldosterone antagonist therapy was also associated

Table 1. Characteristics of primary prevention ICD population and univariate predictors of first appropriate ICD therapy

Characteristics	Overall (n = 121)	No therapy (n = 93)	Therapy (n = 22)	*p*-value
Male sex	75.7%	74.2%	81.8%	0.45
ICM	63.5%	64.5%	59.1%	0.64
Hypertension	61.7%	64.5%	50.0%	0.21
Diabetes	42.6%	43.0%	40.9%	0.86
Atrial fibrillation	14.8%	12.9%	22.7%	0.243
Beta-blocker	88.7%	92.5%	72.7%	0.017
ACEI/ARB	72.7%	71.0%	72.7%	0.87
Diuretic	63.6%	62.4%	63.6%	0.91
Aldosterone antagonist	22.7%	48.4%	22.7%	0.03
Digoxin	31.8%	29.0%	31.8%	0.80
Amiodarone	4.5%	8.6%	4.5%	1.0
Aspirin	69.6%	67.7%	77.3%	0.38
Clopidogrel	18.3%	17.2%	22.7%	0.55
Statin	74.8%	73.1%	81.8%	0.40
Age (year)	63.39±11.69	63.34±12.21	63.59±9.43	0.93
LVDD (mm)	69.29±10.11	68.74±10.30	71.62±9.11	0.25
LVEF (%)	24.34 (10-37)	24.05 (10-37)	25.64 (13.65-35)	0.35
Creatinine (mg/dL)	1.23 (0.7-9.8)	1.55 (0.7-7.08)	1.86 (0.7-9.8)	0.99

ICM = ischemic cardiomyopathy; ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; LVDD = left ventricular diastolic diameter; LVEF = left ventricular ejection fraction

Table 2. Multivariate predictors of first appropriate ICD therapy

Characteristics	Odds ratio	95% CI	*p*-value
Beta-blocker	0.23	0.07-0.82	0.023
Aldosterone antagonist	0.33	0.11-0.99	0.049

with less ICD therapy (adjusted odds ratio 0.33, 95% CI 0.11-0.99). Lack of beta-blocker use and lack of aldosterone antagonist use were significant predictors of first appropriate ICD therapy in patient with chronic LV dysfunction underwent ICD implantation for primary prevention.

Survival curves depicting the freedom from first appropriate ICD therapy for both ischemic and non-ischemic cardiomyopathy are shown in Fig. 2. The freedom from first appropriate therapy at 1, 2 and 3 years was 88%, 80% and 78%. The freedom rate was constant after third year. Survival curves depicting freedom from first appropriate therapy in patients with or without beta-blocker therapy are shown in Fig. 4. Survival curves depicting freedom from first appropriate therapy in patients with or without aldosterone antagonist are shown in Fig. 5. There was clear difference in freedom from the first appropriate ICD therapy after first year of follow-up period.

Discussion

The benefit of secondary prophylactic ICD implantation in chronic LV dysfunction patient is obvious. The appropriate ICD therapy rates were reported ranging from 54% during 45 months of follow-up to 64% during 36 months of follow-up in

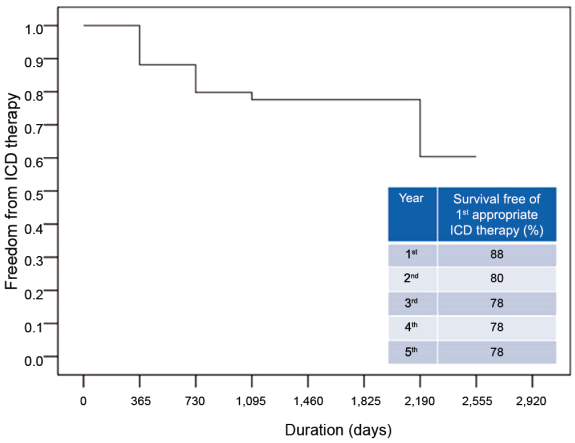

Fig. 2 Survival curve depicting freedom from first appropriate ICD therapy in both ischemic and non-ischemic cardiomyopathy.

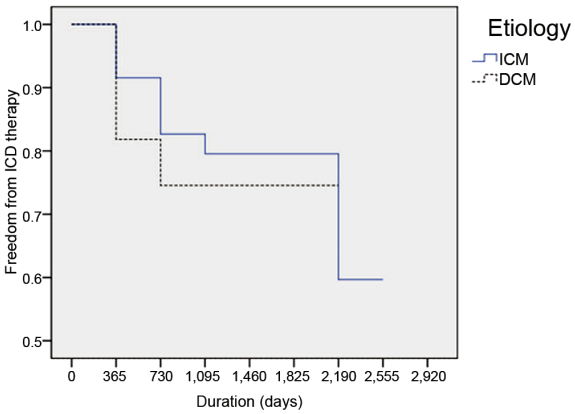

Fig. 3 Survival curve depicting freedom from first appropriate ICD therapy (ICM = ischemic cardiomyopathy; DCM = dilated cardiomyopathy).

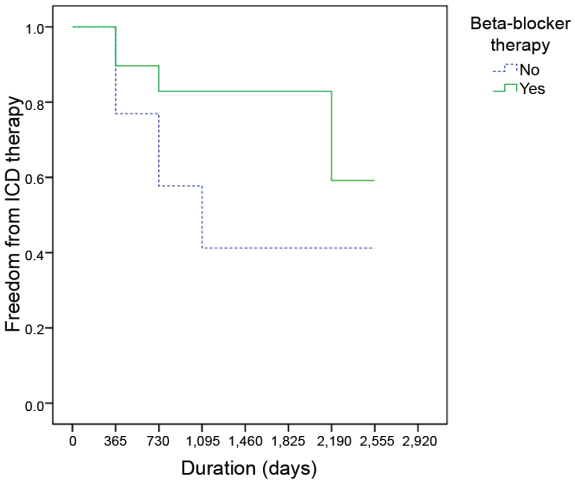

Fig. 4 Survival curves depicting freedom from first appropriate ICD therapy in patient with or without beta-blocker therapy.

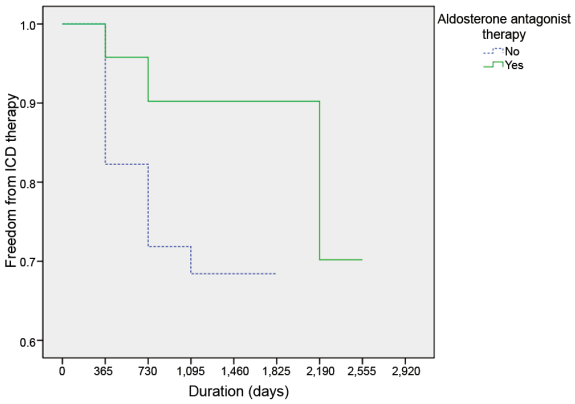

Fig. 5 Survival curve depicting freedom from first appropriate ICD therapy in patient with or without aldosterone antagonist therapy.

major secondary prevention trials[7]. However, the benefit of primary prophylactic ICD implantation in these patients has been debated in several studies due to the lower incidence of appropriate ICD therapy compared with secondary prevention trials. One study reported only 20% to 25% of primary prevention ICD patients receive appropriate shocks within 5 years of implantation[8].

The prevalence of primary prophylactic ICD implantation in Thai population is not known. The present study is the first study to determine prevalence and predictors of appropriate ICD therapy in Thai population. In Major primary prevention trials in Western world, incidences were reported ranging from 17% over 29 months to 31% over 24 months[7]. Prevalence in Siriraj Hospital is 19% with median follow-up duration of 1.85 years, which is comparable with the study of Verma et al[5].

Certainly, appropriate ICD shock was associated with a significant increase in the risk of death from all causes. The present study also demonstrates some predictors of appropriate ICD therapy in chronic left ventricular dysfunction patients in which these predictors could be the target to maximize the benefit of ICD therapy. After multivariate analysis, lack of beta-blocker use was a significant predictor of therapy. This finding is consistent with other studies. The prevalence of beta-blocker use (88.7% in both ischemic and non-ischemic group) is very impressive in our center.

Interestingly, lack of aldosterone antagonist use was also found to be another significant predictor of first appropriate ICD therapy. Miner alocorticoid receptor activation results in negative effect on myocardium and pro arrhythmic effect. Several mechanisms by which miner alocorticoid receptor reduces sudden cardiac death have been proposed, such as improving the uptake of norepinephrine into myocardium and decrease in ventricular arrhythmias, improving parasympathetic activity as indicated by improved heart rate variability, QT dispersion and baroreceptor function[9]. Unsurprisingly, several trials show the positive effect of aldosterone antagonist in SCD prevention. In Randomized Aldactone Evaluation Study (RALES), spironolactone 12.5 to 50 mg/day was associated with SCD and total mortality reduction in ischemic or idiopathic dilated cardiomyopathy with severe left ventricular dysfunction[10]. The consistent effect of aldosterone antagonist in post-acute myocardial infarction heart failure patient was also shown[11].

A further well-designed study is needed to confirm our finding and may encourage the physician to engage in early use of aldosterone antagonist in this group of patients. Unfortunately, LVEF and serum creatinine level are not significant predictors of therapy in our studies.

Most first appropriate therapy occurred within 2 years of follow-up. The freedom from first appropriate ICD therapy was constant after third year of follow-up. Clear difference in freedom from first appropriate therapy was demonstrated after first year of follow-up in patients who received beta-blocker therapy or aldosterone antagonist therapy.

The retrospective nature of this study is an important limitation. Some potential factors in other studies such as non-sustained VT, NYHA functional class, body mass indexes and metabolic syndrome were not included in data collection and analysis. Our studies did not evaluate the potential effect of beta-blocker dosage and type to appropriate ICD therapy. However, the result of this study, which demonstrates the magnitude of the problem and, additionally, a promising new predictor of ICD therapy, may lead to other well-designed studies in the future to confirm the previous findings and maximize the benefit of ICD therapy in our country.

Conclusion

First appropriate ICD therapy was found in 19% of both ischemic and non-ischemic cardiomyopathy patients who underwent ICD implantation for primary prevention. Lack of beta-blocker use and lack of aldosterone antagonist use are significant predictors. Most first, appropriate therapy occurred within 2 years of follow-up.

What is already known on this topic?

ICD therapy is indicated for secondary prevention for sudden cardiac death as well as primary prevention. Prevalence of appropriate ICD shock in patient with secondary prevention is higher than primary prevention.

What this study adds?

We reported prevalence of appropriate ICD shock in patient with primary prevention. This data is important for selection of appropriate patient for ICD therapy especially in Asian population.

Potential conflicts of interest

None.

References

1. Uretsky BF, Sheahan RG. Primary prevention of sudden cardiac death in heart failure: will the solution be shocking? J Am Coll Cardiol 1997; 30: 1589-97.
2. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2008; 117: e350-e408.
3. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 2004; 44: 2166-72.
4. Goldenberg I, Vyas AK, Hall WJ, Moss AJ, Wang H, He H, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008; 51: 288-96.
5. Verma A, Sarak B, Kaplan AJ, Oosthuizen R, Beardsall M, Wulffhart Z, et al. Predictors of appropriate implantable cardioverter defibrillator (ICD) therapy in primary prevention patients with ischemic and nonischemic cardiomyopathy. Pacing Clin Electrophysiol 2010; 33: 320-9.
6. Ahmed I, Nelson WB, House CM, Zhu DW. Predictors of appropriate therapy in patients with implantable cardioverter-defibrillator for primary prevention of sudden cardiac death. Heart Int 2010; 5: e4.
7. Germano JJ, Reynolds M, Essebag V, Josephson ME. Frequency and causes of implantable cardioverter-defibrillator therapies: is device therapy proarrhythmic? Am J Cardiol 2006; 97: 1255-61.
8. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005; 352: 225-37.
9. Pitt B, Pitt GS. Added benefit of mineralocorticoid receptor blockade in the primary prevention of sudden cardiac death. Circulation 2007; 115: 2976-82.
10. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341: 709-17.
11. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348: 1309-21.

การศึกษาความชุกและปัจจัยที่มีผลต่อการเกิดการรักษาด้วยเครื่องกระตุกหัวใจอัตโนมัติชนิดฝังในร่างกายอย่างเหมาะสมในผู้ป่วยที่มีการทำงานของหัวใจห้องซ้ายลดลงอย่างเรื้อรังที่ได้รับการใส่เครื่องเพื่อป้องกันการเสียชีวิตเฉียบพลันจากหัวใจระดับปฐมภูมิในโรงพยาบาลศิริราช

พลาย ชี้เจริญ, รุ่งโรจน์ กฤตยพงษ์, อาทิตย์ ยินดีงาม

วัตถุประสงค์: *เพื่อศึกษาความชุกและปัจจัยที่มีผลต่อการเกิดการรักษาอย่างเหมาะสมด้วยเครื่องกระตุกหัวใจอัตโนมัติชนิดฝังในร่างกาย ในผู้ป่วยโรคกล้ามเนื้อหัวใจห้องซ้ายทำงานลดลงชนิดขาดเลือดและไม่ขาดเลือดที่ได้รับการใส่เครื่องเพื่อการป้องกันแบบปฐมภูมิต่อการเกิดการเสียชีวิตเฉียบพลันจากหัวใจห้องล่างซ้ายเต้นผิดจังหวะ*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลังในผู้ป่วย 115 ราย ในผู้ป่วยที่มีการทำงานของหัวใจห้องล่างซ้ายลดลงอย่างเรื้อรังที่ได้รับการใส่เครื่องเพื่อป้องกันการเสียชีวิตเฉียบพลันจากหัวใจระดับปฐมภูมิในโรงพยาบาลศิริราช โดยการเก็บข้อมูลจากเวชระเบียนผู้ป่วยและแบบบันทึกการตรวจการทำงานของเครื่องกระตุกหัวใจอัตโนมัติ*

ผลการศึกษา: *การเกิดการรักษาหัวใจห้องล่างเต้นผิดจังหวะด้วยเครื่องกระตุกหัวใจอัตโนมัติชนิดฝังในร่างกายอย่างเหมาะสมในครั้งแรก พบในผู้ป่วย 22 ราย คิดเป็นร้อยละ 19 โดย 11 ราย เป็นการรักษาด้วย shock และผู้ป่วย 11 ราย เป็นการรักษาด้วย ATP การไม่ได้รับการรักษาด้วยยา beta-blocker และการไม่ได้รับการรักษาด้วยยา aldosterone antagonist เป็นปัจจัยสำคัญที่มีผลต่อการเกิดการรักษาด้วยเครื่องกระตุกหัวใจอัตโนมัติชนิดฝังในร่างกายอย่างเหมาะสมในผู้ป่วยกลุ่มนี้ จากผลการศึกษาไม่พบความแตกต่างในแง่ของความชุกของการเกิดการรักษาระหว่างกลุ่มผู้ป่วยโรคกล้ามเนื้อหัวใจห้องซ้ายทำงานลดลงชนิดขาดเลือดและไม่ขาดเลือด อัตราการปลอดการเกิดการรักษาที่ปีที่ 1 ถึงปีที่ 3 คือ ร้อยละ 88, 80, 78 ตามลำดับ และพบว่าอัตราการปลอดการเกิดการรักษาจะคงที่หลังปีที่สาม*

สรุป: *ผู้ป่วยที่มีการทำงานของหัวใจห้องซ้ายลดลงอย่างเรื้อรังที่ได้รับการใส่เครื่องเพื่อป้องกันการเสียชีวิตเฉียบพลันจากหัวใจระดับปฐมภูมิจำนวนเกือบหนึ่งในห้าเกิดการรักษาอย่างเหมาะสมเป็นครั้งแรกด้วยเครื่องกระตุกหัวใจอัตโนมัติชนิดฝังในร่างกาย โดยส่วนใหญ่พบว่าการเกิดการรักษาเกิดภายใน 2 ปีแรก ปัจจัยที่มีผลต่อการเกิดการรักษาได้แก่ การไม่ได้รับการรักษาด้วยยา beta-blocker และการไม่ได้รับการรักษาด้วยยา aldosterone antagonist*