S-ICD in Chinese population with primary prevention indication (SCOPE trial)

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Background

Subcutaneous implantable cardioverter defibrillator (S-ICD) is an important alternative to traditional intravenous ICD, especially for patients who are not suitable for implanting defibrillator wires via vein. In addition, it also has obvious advantages for young patients with long expected survival and who may need to replace defibrillation leads repeatedly. Therefore, its status in the prevention of sudden cardiac death (SCD) has been continuously improved, and it is more and more used in the primary prevention and secondary prevention of SCD in the world. With lots of multicenter studies laying the foundation for the effectiveness and safety of S-ICD, more than 90000 S-ICD have been implanted in European and American countries, but very few have been implanted in China, which shows a huge difference in clinical application. The feasibility and long-term safety of S-ICD and its data evaluation with TV-ICD in Chinese population are not clear. Therefore, multi- center clinical studies are urgently needed in China to provide scientific basis for S-ICD to provide further, localized high-level evidence to better apply S-ICD as a new technology and device in clinical practice.

Design

A prospective multicenter cohort study.

Objective

1. The primary objective: To determine the occurrence of inappropriate shock at 18 months after S-ICD implantation in Chinese population with primary prevention indication.

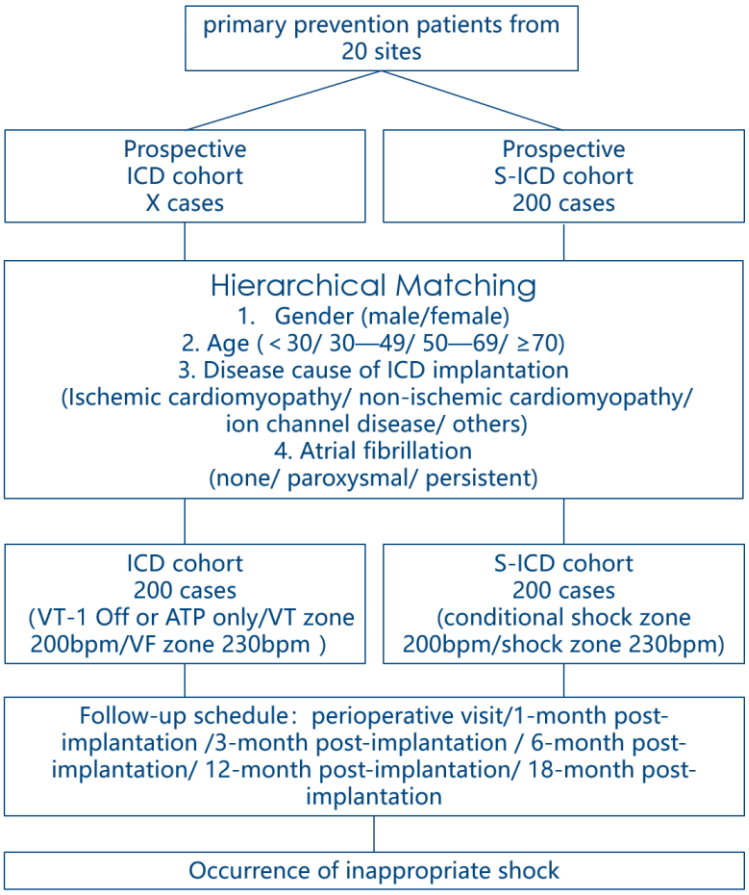
2.The secondary objective: To observe the tendency of difference between the long-term efficacy and safety of S-ICD and TV-ICD in Chinese population with primary prevention indication at the present level.

Rationale

Subcutaneous implantable cardioverter defibrillator (S-ICD) is an important alternative treatment for traditional intravenous ICD, especially for patients who are not suitable for implanting defibrillator wires via vein (such as deep vein anatomical abnormalities, after mechanical tricuspid valve replacement, high risk of infection). In addition, it also has obvious advantages for young patients with long expected survival and who may need to replace defibrillation leads repeatedly. Currently, there are lots of studies indicating the comparable effectiveness and safety of S-ICD to TV-ICD in patients with primary or secondary prevention indication, but few of them involve Chinese population. S-ICD has limited clinical data in Chinese population. At the same time, China lacks a multi-center follow-up platform no matter for S-ICD or TV-ICD to fill the gap of long-term follow-up data.This study aims to observe the performance of S-ICD in Chinese population with primary prevention indication.

Briefly, a prospective S-ICD cohort will involve 200 patients with primary prevention indication with the same prespecified programming (conditional shock zone 200 bpm/ shock zone 230bpm; Intermuscular implantation; SmartPass ON; Irritability test) from 20 Chinese sites. All the patients will be followed up for 18 months to observe the occurrence of inappropriate shock, which will be compared with a performance goal of 90.3%. At the same time, the results from subjects implanted with S-ICD will be compared with these from 200 patients implanted with TV-ICD with the same prespecified programming (VT-1 Off or ATP only/ VT zone 200bpm/ VF zone 230bpm) enrolled at the same period by a hierarchical matching method (gender/age/ disease cause of ICD implantation/ atrial fibrillation) to

explore whether there is any tendency of difference. All inappropriate shocks and appropriate shocks will be defined by no less than 3 professors.



Primary Endpoint

1. The proportion of subjects implanted with S-ICD that free from inappropriate shock at 18 months after the procedure.

Secondary Endpoint

1. The proportion of subjects implanted with TV-ICD that free from inappropriate shock at 18 months after the procedure.
2. Occurrence of appropriate shock at 18 months after implantation in both groups.
3. First and final successful conversion rate at 18 months after implantation in both groups.
4. Incidence of sudden cardiac death
5. Incidence of device or procedure related complication.

Planned Timelines

The recruitment period is estimated be 18 months and every subject will be followed up for 18 months.

Inclusion criteria

1) Age > 18 years old;
2) The subjects met the class I or class II indications of the current S-ICD for primary prevention of sudden cardiac death;

3) Subjects can be screened by S-ICD ECG;
4) The subjects are willing and able to sign informed consent and attend all relevant visits on time.

Exclusion criteria

1) Pregnant;
2) Subjects are participating in other clinical trials, which may affect this study;
3) The researchers determined that the subjects were not suitable for S-ICD implantation, such as patients need or will need pacing therapy for bradycardia; Subjects with known ventricular tachycardia at a rate below 170 beats per minute or with refractory recurrent monomorphic ventricular tachycardia that could not be managed with medication or ablation therapy;
4) Subjects implanted with a transvenous CRT-D or with history of pacemaker;
5) Subjects with paced rhythms at baseline or post-implant of TV-ICD;
6) Life expectancy < 18 months.

Sample size

1. The primary objective

A one-sample t-test will be used to test the one-sided hypothesis:
H0: FR ≥ PG
H1: FR < PG
Where FR is the lower limit of 95% confidence interval of the proportion of subjects that free from inappropriate shock at 18 months after S-ICD implantation and PGL is the performance goal.

Performance goal	Expected rate	Significance level (one-sided)	Power	Attrition	Sample size
90.3%	96.8%	0.025	0.8	0.15	181

The final sample size will be 200 cases.

The Performance goal is based on a meta-analysis, in which the incidence of inappropriate shock after TV-ICD implantation was 5.3% per year. The proportion of subjects that free from inappropriate shock at 18 months will be 1 - (5.3%*1.5) = 92.1%. The lower limit of 95% confidence interval will be 91.3%, and 90.3% will be used as the performance goal by adding a clinical non-inferiority threshold of 1% in this study.
The expected rate is estimated from the subgroup with all SmartPass ON in the UNTOUCHED trial, in which the incidence of inappropriate shock was 2.2%, and the higher limit of 95%CI was 3.2%, thus the proportion of subjects that free from inappropriate shock at 18 months in this study is expected at 1-3.2%=96.8%.

2. The secondary objective

Since head-to-head comparative trial needs a too large sample size (*detail calculation for sample size as below*), this study is designed as an observational study to indicate the safety and effectiveness of S-ICD and TV-ICD system in Chinese population with primary prevention indication. 200 patients implanted with S-ICD and 200 patients implanted with TV-ICD will be enrolled.
For ICD cohort, inappropriate shock is assumed as 5.83% at 18 months based on Chinese previous data, then the 95%CI will be 3.13%-10.25% (exact binormal test) for 200 cases. For S-ICD cohort, since there

is limited follow-up data about S-ICD, the inappropriate shock rate is assumed as 6.35% at 18 months based on previous meta-analysis comparing performance of ICD and S-ICD (HR=1.09, 5.83%*1.09=6.35%), then the 95%CI will be 3.51%-10.86% (exact binormal test) for 200 cases.
Since there is limited data about long-term complication about ICD or S-ICD in Chinese population, these results will be observational data. However, the results from PRAETORIAN or meta-analysis showed that there is no significance between these two cohorts in complication in population with primary prevention or secondary prevention population involved.

For non-inferiority trial design:

H0: $a > \delta$

H1: $a \leq \delta$

Where a is the HR of the occurrence of inappropriate shocks and complications at 18 months after the procedure of S-ICD and TV-ICD. δ is the non-inferior HR. Non-inferior HR is assumed as 1.45 as PRAETORIAN trial.

PASS 2020 non-inferior Log-rank test

Alpha: 0.025

Group Allocation: Enter percentage in Group 1, solve for N1 and N2

Percent in Group 1: 50

HR0 (Non-Inferiority Hazard Ratio): 1.45

h1 (Hazard Rate of Reference Group): 0.0807 (mortality until T0 assumed as 11.4%)

Accrual Time (Integers Only): 2

Accrual Pattern: Uniform or Equal

Total Time (Integers Only): 3.5

References Lost: 0.1

References Switch to Treatment: 0.0

Treatments Lost: 0.1

Treatments Switch to Reference: 0.0

N= 617 for each group

Statistical Analyses/Assumptions

1. Statistical assumptions

The lower limit of 95% confidence interval of the proportion of subjects implanted with S-ICD that free from inappropriate shock at 18 months after the implantation will be higher than the performance goal of 90.3%.

2. Statistical analysis

A one-sample t-test will be used to test the one-sided hypothesis of the primary objective. When the continuous variable obeys the normal distribution, it is expressed by means ± standard deviation, the comparison between groups is expressed by t-test, otherwise it is expressed by quartile spacing, and the rank sum test is used. Chi square test was used to compare the constituent ratio or rate. We will use the survival curve including Kaplan Meier method to estimate the event rate over time, log rank test to compare the event rate between groups and subgroups, and Cox proportional hazards model to analyse the related influencing factors in S-ICD cohort. In this study, $\alpha = 0.05$ was used as the statistical test level.

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