Primary Prevention of Sudden Cardiac Death in Patients with Ischemic Heart Disease —Possible Role of the Shock Device in the Asia—

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Recently several randomized trials have demonstrated the excellent role of the implantable cardioverter-defibrillator (ICD) in improving the mortality rate in patients with a high risk of sudden cardiac death regardless of its purpose or the underlying heart disease. However, because such large clinical trials have only been carried out in Western countries, those results may not be fully applicable to Japanese or other Asian patient populations.

According to a Japanese study, the total mortality in the patients was approximately 20% during 5 years of follow up, which was comparable to, or slightly better than that in the MADIT-II patients with ICDs. In such a patient population with an excellent prognosis, the MADIT-II criteria can not easily be applied. Therefore, we should strengthen the criteria, i.e. from an EF ≤ 35% to 25% or adopt the usage of additional examinations (e.g. signal averaging ECG, micro-volt T wave alternance or EPS).

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Key words: Primary prevention, Sudden cardiac death, Myocardial infarction, Implantable cardioverter defibrillator

Introduction

Recently several randomized trials have demonstrated the excellent role of the ICD in improving the mortality rate in patients with a high risk of sudden cardiac death regardless of its purpose (primary or secondary prevention) or the underlying heart disease (ischemic or non-ischemic). However, because such large clinical trials have only been carried out in Western countries, those results may not be fully applicable to Japanese or other Asian patient populations. In 2006, ICDs with the capability of cardiac resynchronization (CRT-D) were approved in Japan. The newest devices are expected to provide further improvement in the mortality and/or quality of life (QOL) in patients with heart failure. However, their high cost may impose a burden on our limited resources if they are used without careful consideration.

The purpose of this article was to review the various large randomized trials that used ICDs, and to discuss a more effective usage of ICDs for primary prevention in Japanese or other Asian patients with a prior myocardial infarction (MI) based on the proper interpretation of the evidence gained from the Western countries.

1. MADIT1)

MADIT was the first clinical trial which demon-
strated the efficacy of the ICD for primary prevention in patients with ischemic heart disease. The study included very high risk patients for sudden cardiac death (non-sustained VT, prior Q wave MI, EF ≤ 35%, or inducible sustained VT not suppressed by propranolol at the electrophysiologic study), and compared the total mortality between the patients treated with only antiarrhythmic drugs (mainly amiodarone) and those with ICDs. The study showed that the ICD decreased the total mortality by 54%.

2. MUSTT

MUSTT tested the hypothesis that an electrophysiologic study (EPS)-guided antiarrhythmic therapy (antiarrhythmic drugs and/or ICD) would reduce the risk of arrhythmic death in patients with MI and non-sustained VT. The inclusion criteria were an EF ≤ 40%, >1 week post-MI and inducible sustained VT by EPS. However, ultimately the study reached the main conclusion that ICD therapy alone improved the mortality rather than proving the original hypothesis of the study which was to demonstrate the superiority of the EPS-guided antiarrhythmic therapy. The ICD reduced the total mortality by 50% compared to the non-EPS-guided group.

3. MADIT-II

Following the very encouraging results from MADIT, MADIT-II was conducted to evaluate the efficacy of the ICD in lower-risk patients with MI. A total of 1,232 MI patients with an EF ≤ 30% were randomly assigned at a ration of 3:2 to ICD and conventional therapy groups. The documentation of non-sustained VT and inducibility of sustained VT/VF were not required. The study demonstrated a 31% reduction in the total mortality with ICD therapy.

4. SCDHeFT

SCDHeFT was designed to evaluate the efficacy of ICD therapy and amiodarone in patients with heart failure due to ischemic or non-ischemic causes. A total of 2,521 patients with a New York Heart Association (NYHA) class II or III and an EF ≤ 35% were evenly assigned to placebo, amiodarone or ICD groups. All patients received conventional therapy for their heart failure. As compared to the placebo group, the ICD therapy group was associated with a 23% decreased risk of sudden death in the overall patients and 21% in the patients with ischemic heart disease. Amiodarone did not improve the patient outcome.

5. Comparison of the Four Randomized Studies

Figure 1 shows the improvement in the total mortality achieved by ICD therapy in each study. The MADIT and MUSTT studies which enrolled more risky patients for sudden cardiac death (documentation of non-sustained VT and induction of sustained VT/VF by EPS) demonstrated more than a 50% reduction in the total mortality. On the other hand, MADIT-II and SCDHeFT, which expanded the inclusion criteria to patients with a lower risk, reduced the mortality by 20–30%. That difference might be due to the level of the risk for arrhythmic death in the enrolled patients. Therefore, it could be interpreted that the recognition of non-sustained VT and induction of VT/VF by EPS are effective methods for risk stratification and may result in the effective usage of ICDs in patients with MI. However, in 2005, the AHA/JACC task force accepted MADIT-II criteria as a class I indication for an ICD implantation. That decision may have been based on the high incidence of sudden cardiac death of MI patients in North American people and on the limitations (high false negative values) of the EPS. According to a MUSTT sub-study, EPS was “statistically” effective in predicting the occurrence of sustained VT/VF episodes in patients with MI, but false negative values of the EPS (20% during 5 years of follow up) were too high to ignore (Figure 2). For example, when we are faced with a certain fatal but almost curative disease being treated properly, which is very representative of ICD therapy in VT/VF patients, we should expend maximum effort to avoid any false negative results when predicting the patient outcome. If we fail to select an appropriate therapy for such patients, the result could be very serious.

Expanding the indications of ICDs in patient populations with a very high risk for sudden death (such as in North American MI patients) is thought to be reasonable.

6. Prognosis of MI Patients in Japan

Many Japanese medical doctors who are coronary interventional specialists may feel that the prognosis of Japanese MI patients is much better than that in MADIT-II. The total mortality in the control group of the MADIT-II trial reached more than 30% during 5 years of follow up. Furthermore, approximately half of the patients died suddenly. Tanno et al.
(Showa University) retrospectively investigated the prognosis of Japanese patients who met the criteria of MADIT-II.\(^7\) Figure 3 shows the Kaplan–Meier curves plotted with the data from their series and from MADIT-II. Surprisingly, the total mortality in the patients from Showa University (approximately 20% during 5 years of follow up) was comparable to, or slightly better than that in the MADIT-II patients with ICDs. Furthermore, they described that sudden cardiac death was observed in only 2 out of 9 deaths (22%). A large prospective cohort study in the Osaka area (OACIS) also demonstrated similar results.\(^8\) In such a patient population with an excellent prognosis, the MADIT-II criteria cannot easily be applied.

### 7. Relationship between the Incidence of Events and the Diagnostic Criteria

A perfect clinical examination which completely predicts the patient outcome never occurs. All examinations always produce both false positive and false negative results. Figure 4A demonstrates a certain examination with a 1:3 ratio of the probability of false negative and false positive results by assuming an incidence of 50%. In that case, the degree of false negative results, indicated by the closed area, were thought to be acceptable. Assuming there was a 10% incidence (Figure 4B), the false negative area would become very small and could be ignored. On the contrary, the false positive area (the dotted area) greatly expands, which may lead to an inappropriate indication for therapy in many patients. This could be applied to the low incidence of sudden cardiac death in Japanese MI patients. A criteria which had been adequate for a population with a high incidence of events (e.g. an EF < 35\% and sudden cardiac death in North American MI patients) could not directly be used in those with better outcomes. Therefore, we should strengthen the criteria, i.e. shift the cut-off line to the right (e.g. from an EF ≤ 35\% to 25\%) or adopt additional examinations (e.g. the signal averaging ECG, microvolt T wave alternance or an EPS).\(^6,9\)

![Figure 1](image.png) Improvement in total mortality in the ICD group as compared with the control (non-ICD) group in each randomized study. The MADIT and MUSTT studies which enrolled more risky patients for sudden cardiac death (documentation of non-sustained VT and induction of sustained VT/VF by EPS) demonstrated more than a 50% reduction in the total mortality. On the other hand, MADIT-II and SCDHeFT, which expanded the inclusion criteria to patients with a lower risk, reduced the mortality by 20–30%.

![Figure 2](image.png) The role of the electrophysiologic study (EPS) in post-MI patients. EPS was statistically effective in predicting the occurrence of sustained VT/VF episodes in patients with an MI, but false negative values from the EPS (a VT/VF incidence in the non-inducible group, the registry, of 20% during 5 years of follow up) were still too high to ignore.
Figure 3  The total mortality in Japanese patients who met the MADIT-II criteria. Tanno et al. (Showa University) retrospectively investigated the prognosis in Japanese patients who met the criteria for MADIT-II. This Figure shows the Kaplan-Meier curves plotted with the data from their series (our series are in the figure) and from MADIT-II. Surprisingly, the total mortality in the patients from Showa University (approximately 20% during 5 years of follow up) was comparable to, or slightly better than, that in the MADIT-II patients with ICDs. Furthermore, they described that sudden cardiac death was observed in only 2 out of 9 deaths (22%).

Figure 4  Relationship between the incidence of events and the diagnostic criteria.
A: Demonstrates a certain examination with a 1:3 ratio of the probability of false negative and false positive results by assuming a 50% incidence. In this case the degree of false negative results, indicated by the closed area, was thought to be acceptably small.
B: Describes how the examination works when the incidence is assumed to be 10%. The false negative area becomes very small and can be ignored. On the contrary, the false positive area (dotted area) greatly expands, which may lead to an inappropriate indication for therapy in many patients. This situation could be applied to the low incidence of sudden cardiac death in Japanese MI patients. We should therefore strengthen the criteria.

References


8) Personal communication