Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: March 31, 2024

Citation: Messori, A., et al., 2024. Efficacy of ICD in ischemic cardiac disease determined by reconstructing patient-level data from Kaplan-Meier survival curves. Medical Research Archives, [online] 12(3). https://doi.org/10.18103/mra.v12i3.5211

DOI: https://doi.org/10.18103/mra.v12i3.5211

ISSN: 2375-1924

RESEARCH ARTICLE

Efficacy of ICD in ischemic cardiac disease determined by reconstructing patient-level data from Kaplan-Meier survival curves

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ABSTRACT

Background: Implantable cardioverter defibrillators (ICDs) are indicated for the prevention of sudden death in ischemic heart disease. Four randomized trials are the main source of efficacy data.

Aims and Methods: Reconstruction of patient-level data from survival curves is a new technique (called the Shiny method or IPDfromKM method) for studying effectiveness. We used this method to analyze the four afore-mentioned trials based on the endpoint of all-cause mortality. After reconstruction by the IPDfromKM method, patient-level data were pooled according to three therapeutic options: ICDs, medical therapy, and no active treatment. Standard statistical comparisons were then made between these three groups of patients. Time-to-event data for reconstructed patients were evaluated using standard Kaplan-Meier analysis. The hazard ratio was estimated to compare and interpret these survival data.

Results: A total of 4,621 patients were enrolled (follow-up, 60 months). Of these, 1,827 were treated with ICDs and 1,493 received medical therapy; the control group included 1,301 patients who received no active treatment. Our analysis, based on pooled Kaplan-Meier curves, showed that ICD was the most effective, followed by medical therapy and no active treatment. ICD was associated with significantly better survival compared with medical therapy (hazard ratio, 0.6523; 95% confidence interval [CI], 0.5580 to 0.7622; p<0.001) and no active treatment (hazard ratio, 0.6340; 95%CI, 0.5417 to 0.7424; p<0.001). In the subgroup of patients receiving an ICD, the heterogeneity between trials was negligible, whereas it was significant in the subgroups receiving medical therapy or no active treatment.

Conclusions: Our results provide original evidence on long-term survival in ischemic heart disease. Methodologically, our study confirmed the advantages of the Shiny method.

Keywords: meta-analysis; Kaplan-Meier curves; Shiny method; IPDFROMKM method; artificial intelligence; reconstructed individual patient data.

Introduction

Implantable cardioverter-defibrillators (ICDs) represent one of the most significant advances in cardiovascular medicine in 50 years[1]. The first approval by the U.S. Food and Drug Administration dates back to 1980. Then, the development of new technologies in this area has been constant leading to the sophisticated devices that are available today. In particular, transvenous lead systems converted ICDs from thoracotomy-based secondary prevention to primary prevention of sudden death in thousands patients worldwide. ICD acceptance was enhanced by prospective randomized controlled trials (RCTs) showing reduced mortality superior to antiarrhythmic drugs. At the same time, ICDs expanded from coronary disease to inherited arrhythmia conditions (such as hypertrophic cardiomyopathy). Thanks to progress in technology, subcutaneous ICDs were developed as an alternative to the traditional transvenous implantable cardioverter defibrillator. The subcutaneous ICD was designed to avoid complications related to the transvenous ICD lead by using an entirely extrathoracic placement[2,3]. Its advantages include easier implantation, fewer systemic infections, simplified detection algorithm of malignant ventricular arrhythmias and prevention from placing components in the cardiovascular system. Since the beginning, the subcutaneous ICD demonstrated high efficacy and safety, leading to market release after the first prospective multicentre trial[2]. In addition, while earlier studies focused on younger patients with higher ejection fraction, more recent studies showed favorable outcomes even in patients with comorbidities similar to those typically observed in patients receiving TV-ICD[1]. The development of second and third generation devices has contributed to reduce inappropriate shocks and overcome previous limitations[1,4].

Regarding the use in patients with coronary disease, four pivotal RCTs represent the reference in this area, namely MADIT-I[5], MUSTT[6], SCD-HeFT[7], and MADIT-II[8]. These are the studies reviewed by Hess et al. in their meta-analysis published in 2013[9]. On the other hand, a new original method (the IPDfromKM method[10], also called the Shiny method) has been used quite extensively in the last two years to pool the survival results reported in different controlled trials. The Shiny method was mainly developed for use in oncology[11], but recently its use in cardiology has become relevant[12].

In the present report, we used the Shiny method to pool the results of the four RCTs mentioned above, i.e., MADIT-I[5], MUSTT[6], SCD-HeFT[7], and MADIT-II[8].

Methods

The studies supporting the effectiveness of ICDs in ischemic heart disease were identified by a standard PubMed search, which confirmed the four RCTs mentioned above[5-8]. The IPDfromKM method[10-12] was then used to examine the effectiveness data reported in these four studies. This method is an artificial intelligence technique designed for application to time-to-event clinical trials. Its application results in the reconstruction of an individual patient database from each survival curve included in the analysis. There are three main operational steps in the application of this method. In the first, the image of a Kaplan-Meier curve is digitized to generate

the y-vs-x coordinates of the curve; in the second, the published report of the clinical trial is carefully read by at least two investigators to determine the number of patients enrolled with specific reference to the Kaplan-Meier curves digitized in the first step; the third step is the most complex, because the information obtained from the first two steps is analyzed by an artificial intelligence algorithm that generates an individual patient database of "reconstructed" patients; this database includes the estimated length of survival and whether the patient experienced the endpoint at the end of follow-up or not (e.g. a patient who died or a censored case).

The randomized design of the trial was a prerequisite for our analysis. The endpoint was death from any cause during a follow-up period of up to 60 months. The four included trials evaluated the following three treatments: 1) treatment with an ICD; 2) medical therapy based on oral agents such as class I drugs or sotalol or amiodarone; and 3) no active treatment. The IPDfromKM method[10] was used to reconstruct individual patient data from the four trials and was applied separately within each trial for each treatment group evaluated. Finally, our comparisons of the efficacy of these three treatments were made by estimating medians and hazard ratios (HRs) with their 95% confidence intervals (CIs). The restricted mean survival time (RMST)[13] was estimated in cases where the median was not reached.

Two separate heterogeneity analyses were performed: the first was performed on the total patient population of the four trials, while the second was performed by examining each of the three treatments separately. Heterogeneity was assessed using two standard tests: the likelihood ratio test and the Wald test[14]. All these statistical analyses were performed under the R platform (R Core Team. Foundation for Statistical Computing, Vienna, Austria, 2021, url https://www.R-project.org/), using the following packages: "survRM2", "survival", "survminer" and "ggsurvplot". The "rmst2" function was used to estimate RMST.

Results

The main characteristics of the four RCTs included in our analysis are described in Table 1. To reconstruct individual patient data from Kaplan-Meier plots, the IPDfromKM method was applied 11 times, i.e., with application to each of the 11 patient groups listed in Table 1. Reconstructed patients were then grouped according to the three afore-mentioned treatments, i.e., ICD, medical therapy, and no active treatment.

Table 1. Main characteristics of the four randomized controlled trials included in our analysis, The endpoint of death from any cause was reported in each of these trials.

Trial name	First author and year of publication	Follow-up length (months)	No of patients in treatment arms*		
			ICD (n=1,827)	Medical therapy (n=1,003)	No active treatment (n=944)
MADIT-I[2]	Moss, 1996	60	n=95	-	n=101
SCD-HeFT[3]	Bardy, 2005	60	n=829	n=845§	n=847
MUSTT[4]	Buxton, 1999	60	n=161	n=158§§	n=353
MADIT-II[5]	Moss, 2002	48	n=742	n=490	-
Total			n=1,827	n=1,493	n=1,301

§Amiodarone3

§§Class I agents or amiodarone or sotalol5

*The crude event rates in the 4 trials were as follows: MADIT-I, 15/95 vs 39/101; SCD-HeFT, 182/829 vs 240/845 vs 244/847; MADIT-II, 105/742 vs 97/490; MUSTT, 35/161 vs 97/158 vs 158/353.

Our main analysis of the efficacy data comparing these three treatments examined survival data for a total of 4,621 reconstructed patients grouped according to the three treatments (Figure 1). ICD therapy was found to be significantly superior to both medical therapy (HR, 0.6523; 95% confidence interval [CI], 0.5580 to 0.7622) and no active treatment (HR, 0.6340; 95%CI, 0.5417 to 0.7424). In contrast, medical therapy and no active treatment showed an almost identical survival pattern (HR for medical therapy versus no active treatment, 1.029; 95%CI, 0.824 to 1.284). For these three treatments, we determined the values of RMST because all three survival curves were above 50% residual survival until the last time point of follow-up. The following values were estimated: RMST for ICD, 50.71 months (95%CI, 49.75 to 51.67) for ICD; RMST for medical therapy, 46.57 months (95%CI, 45.41 to 47.73); RMST for no active treatment, 46.25 months (95%CI, 45.03 to 47.46).

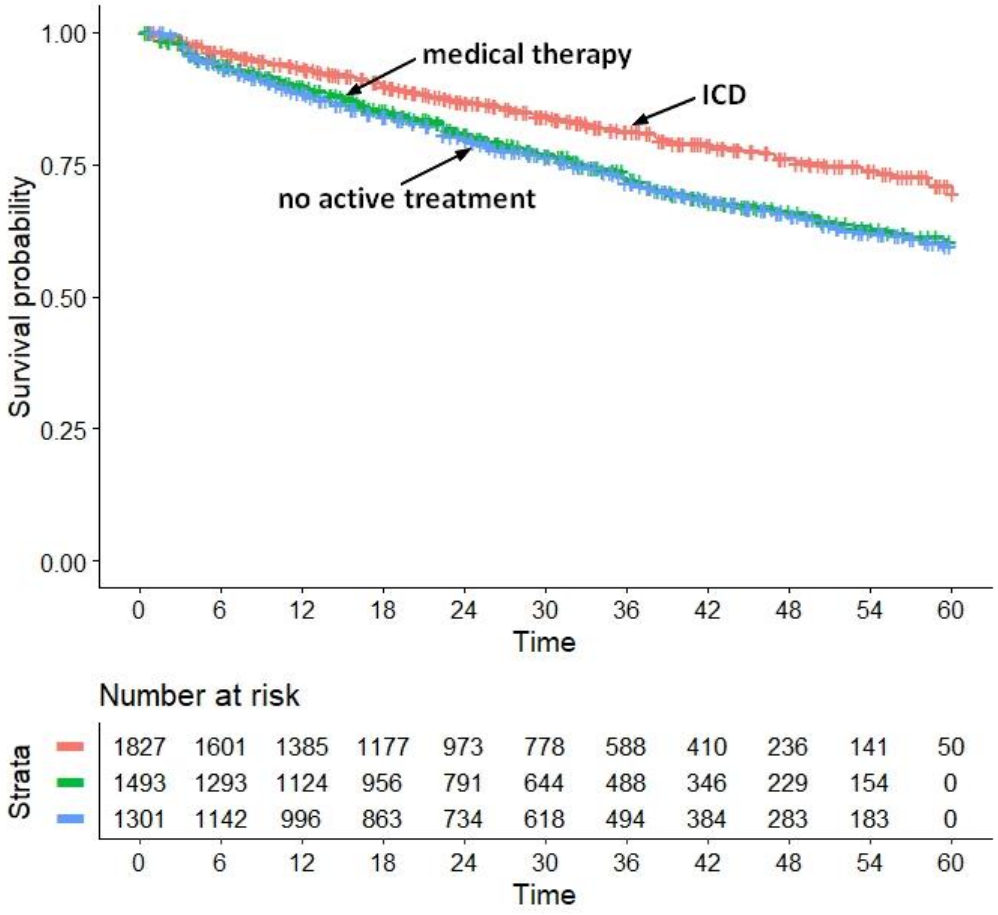

Figure 1. Application of the Shiny method: results of the primary analysis. Abbreviations: ICD, implantable cardioverter defibrillator.

In our main analysis based on the total group of 4,621 patients, the degree of heterogeneity was highly significant (likelihood ratio test, 41.55 on 2 df, p<0.001; Wald test, 39.31 on 2 df, p<0.001), which simply reflects the presence of significant differences among the three treatments. On the other hand, Figure 2 summarizes the results of the heterogeneity assessments performed separately for each of the three treatments. With respect to the ICD, the four trial-specific patient groups were extremely homogeneous and yielded very similar survival curves (panel A); accordingly, the likelihood ratio test and the Wald test did not reach statistical significance (likelihood ratio test, 5.7 on 3 df, p=0.10; Wald test, 5.74 on 3 df, p=0.10), and no difference between the four patient groups reached statistical significance. In contrast, there were two significant differences in the three trials that used medical therapy (Figure 2, panel B), in that patients in the MUSTT and the MADIT-II trials showed a worse survival pattern than those in the SCD-HeFT trial (HR, 2.010 with 95%CI of 1.521 to 2.657 and HR, 1.385 with 95%CI of 1.087 to 1.765, respectively). A possible explanation could simply be that the SCD-HeFT trial selected patients with less advanced disease than the other two trials. Finally, for the three trials that included patients not receiving active treatment, both the likelihood ratio test and the Wald test showed a significant degree of heterogeneity

(likelihood ratio test= 28.6 on 2 df, p<0.001; Wald test, 29.96 on 2 df, p<0.001); this finding can be explained by the fact that survival was significantly more favorable in the SCD-HeFT trial than in the MADIT-I trial (HR, 0.4623; 95%CI, 0.3270 to 0.6534; p<0.001).

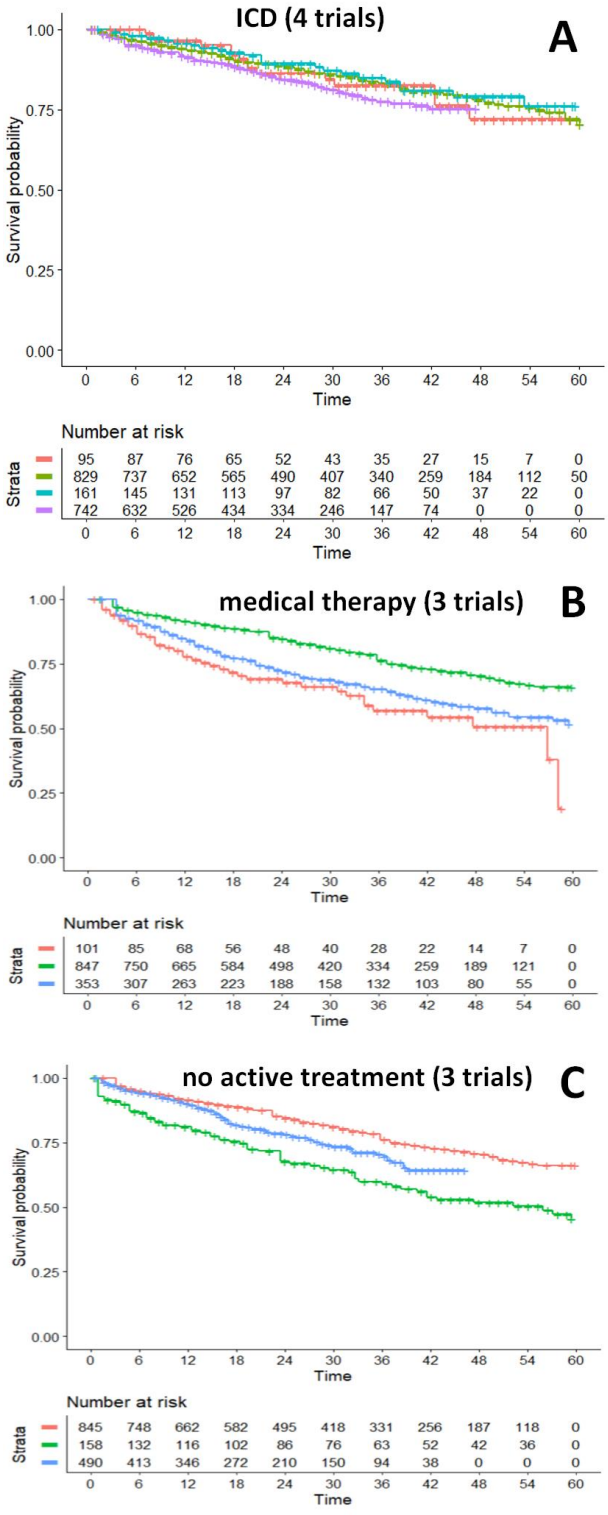

Figure 2. Assessment of heterogeneity for the datasets of ICD (Panel A, 4 trials), medical therapy (Panel B, 3 trials), and no active treatment (Panel C, 3 trials). See Table 1 for further details on individual trials. Abbreviations: ICD, implantable cardioverter defibrillator.

Discussion

Compared to a standard meta-analysis (e.g., a traditional binary meta-analysis or a network meta-analysis[9]), the Shiny method has several advantages. The most important is theoretical, since this method is able to handle censoring, whereas all types of meta-analyses of aggregate data are unable to adjust the results for censoring. Thus, a common approximation in current meta-analyses is to ignore censored patients and work with crude rates (i.e., numerator with the number of events over denominator with the total number of patients enrolled). As a result of this advantage, a Shiny analysis takes into account the follow-up length of the included studies, whereas a standard binary meta-analysis does not. Another advantage of the Shiny method is the graphical presentation of results, which allows the time course of events to be examined from randomization to the last time point of follow-up. This graphical approach is also useful for determining the degree of heterogeneity across pooled studies.

The main limitation of the Shiny method is that few people are familiar with the reconstruction of individual patient data from Kaplan-Meier curves. On the one hand, experiences like the one presented here (where the same dataset is examined in duplicate by the Shiny method and by a standard meta-analysis[1]) are important because they investigate the advantages and reliability of this new method. On the other hand, they are valuable because they simply increase the number of people familiar with the Shiny method. In this context, the present paper aims to stimulate more debate about the pros and cons of the Shiny method, beyond the considerations that have already been discussed among oncologists in recent years[11,14-18].

Conflict of Interest:

The authors declare no conflict of interest.

Funding:

No funding.

Acknowledgements

• data availability statement: all databases of reconstructed patients are available from the author upon request.

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