Primary Prevention with Implantable Cardioverter-Defibrillators after Myocardial Infarction: Variability of Outcomes Estimated From Four Controlled Studies

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Abstract

Background: A few studies have previously been focused on the sources of variability in patients receiving primary prevention with implantable cardioverter-defibrillators (ICDs) after myocardial infarction (MI). While time to implantation after MI showed no influence on outcomes, the extent of between-studies variability and the presence of any temporal trend across different calendar years have not been investigated thus far.

Methods: The clinical material was represented by 4 clinical trials comparing ICDs vs no ICDs (trials acronyms: MADIT-I, MUSTT, MADIT-II, SCD-HeFT). Our analysis was a meta-regression evaluating the data of these trials according to the end-point of all-cause mortality between ICD versus no-ICD. Three covariates were evaluated: time to implantation after MI; calendar year of the original trial; trial. Calendar year (or temporal trend) was defined as the mid-point of the enrolment interval of the trial. Our statistical model was random-effect.

Results: Among the three covariates examined, our meta-regression identified temporal trend as the only one that was retained in the model (p=0.004). Time from MI remained very far from statistical significance (p=0.986). The 4 study-specific covariates were in some cases close to the p=0.05 threshold, but none of these reached this limit. More importantly, our findings concerning temporal trend indicated that, in the comparison between ICD and no-ICD, the incremental benefit showed a statistically significant decline with time. According to our regression line, hazard ratio was 0.33 in 1993 (relative risk reduction=67%) versus 0.67 in 2000 (relative risk reduction=33%); regardless of its statistical significance, this difference clearly is clinically relevant.

Conclusion: Interpreting this trend of declining incremental benefit with time in patients receiving ICD is difficult and, at present, explanations are purely speculative. Irrespective of the reasons likely to explain these findings our results have both clinical relevance and statistical strength and should therefore be made available to the scientific community.

Keywords

Implantable cardioverter-defibrillators; Myocardial infarction; Mortality; Temporal trend; Meta-regression

Introduction

Pooling patient-level data from different clinical studies is becoming more and more frequent, and this offers new opportunities to the scientific community to better interpret the trials’ results. In studying primary prevention with implantable cardioverter-defibrillators (ICDs) after myocardial infarction (MI), a collaborative consortium involving the investigators of 9 clinical trials has recently produced a patient-level meta-analysis [1]. To establish whether time to implantation after MI had any influence on mortality, 4 trials were selected for their characteristics of homogeneity. While the analysis of these trials confirmed the superiority of outcomes for ICD vs no-ICD, time to implantation after MI was found to have an erratic effect with no significant influence on mortality.

In this area, the study of sources of variability is important, and two aspects in particular may merit further scrutiny. Firstly, since no specific analysis of between-study variability in this area has previously been done, this source of variability deserves to be studied in more detail. Secondly, it can be worthwhile to study the presence of a temporal trend of outcomes (i.e. variability of outcomes across different calendar years), particularly because the aforementioned trials were conducted in quite different periods spanning from 1990 to 2001.

The dataset published by Hess and co-workers is very detailed (with information on 2,388 patients from 4 trials). This allowed us to undertake a further analysis of the same data with the aim to clarify the two points mentioned-above.

Methods

Our analysis was a meta-regression in which the end-point was all-cause mortality [expressed as hazard ratio (HR) between ICD versus no-ICD]. Four trials were included (MADIT-I, MUSTT, MADIT-II, SCD-HeFT). Three covariates were evaluated: a) time to implantation after MI; b) calendar year of the original trial; c) trial (i.e. a covariate stratified on 4 levels corresponding to the 4 trials). As usual, this latter categorical covariate was handled after conversion into 4 dummy variables expressing a Yes-No criterion for each trial. Calendar year (denoted below as “temporal trend”) was defined as the mid-point of the enrolment interval of the trial. Our statistical model was random-effect. A stepwise approach was employed that retained in the model all covariates showing p<0.05. Further details on our meta-regression methods have been described previously [2,3].

Results

Our meta-regression identified temporal trend as the only covariate that was retained in the model because of its statistical significance (t=+3.18; p=0.004). Time from MI remained very far from statistical significance (t=-0.018; p=0.986). The 4 study-specific covariates were in some cases close to the p=0.05 threshold, but none of these reached this limit (t-values of +2.04, -2.05, -0.75, and +0.82 for MADIT-I, MUSTT, MADIT-II, and SCD-HeFT, respectively, with p-values of 0.054, 0.053, 0.46, and 0.42, respectively). Positive t-values imply a tendency towards increased all-cause mortality and vice versa.
Our findings concerning temporal trend indicate that, in the comparison between ICD and no-ICD, the incremental benefit showed a statistically significant decline with time (Figure 1). According to our regression line, HR was 0.33 in 1993 (relative risk reduction=67%) versus 0.67 in 2000 (relative risk reduction=33%); regardless of its statistical significance, this difference clearly is clinically relevant.

Discussion

Interpreting this trend of declining incremental benefit with time in patients receiving ICD is difficult. One explanation is that more recent trials have adopted slightly different enrolment patterns than earlier ones; however, Hess et al. [1] tried to actively control for potential between-study differences in enrolment criteria, and in fact they kept in their analysis only a select subgroup of the trials examined. Another explanation is that, even though the enrolment criteria were homogeneous, the subgroup distribution of enrolled patients across different risk categories was not the same between earlier and more recent trials. Alternatively, one should recall that, in other areas, early trials of potentially lower quality have yielded larger benefits than more recent ones [4].

Irrespective of which explanation is more likely, our results describe a finding that seems to have both clinical relevance and statistical strength and that should therefore be made available to the scientific community.

References